

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Late-stage assessment

[GID-HTE10041] - Topical antimicrobial dressings for infected leg ulcers in people and 16 and over

External Assessment Group report

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Purpose of the assessment report

Antimicrobial dressings (AMDs) used to treat infected leg ulcers have been identified by NICE for late-stage assessment (LSA). As described in the [NICE scope](#), the aim of this LSA is to assess whether price variations between AMDs using different agents are justified by their incremental differences, in order to understand which technologies represent value for money.

Declared interests of the authors

Description of any declared interests with related companies, and the matter under consideration. See [NICE's Policy on managing interests for board members and employees](#).

None.

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Responsibility for report

The views expressed in report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

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Abbreviations

Term	Definition
AE	Adverse event
AMD	Antimicrobial dressing
ANOVA	Analysis of variance
CEAC	Cost-effectiveness acceptability curve
CEAP	Clinical, etiological, anatomical, and pathophysiological
CI	Confidence interval
COVID	Coronavirus disease
CPRD	Clinical practice research datalink
DACC	Dialkylcarbamoyl chloride
DFU	Diabetic foot ulcer
DSA	Deterministic sensitivity analysis
EAG	External assessment group
GWC	Good-wound-care
HA	Hyaluronic acid
ICER	Incremental cost-effectiveness ratio
IQR	Interquartile range
ITT	Intention-to-treat
IWII	International wound infection institute
LOCF	Last observation carried forward
LSA	Late-stage assessment
NA	Not applicable
NBS	Numerical box scale
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NMB	Net monetary benefit
NR	Not reported
NRS	Numeric rating scale
NWCSP	National wound care strategy programme
OHP	Octenidine dihydrochloride/phenoxyethanol
PCMP	Polyhexamethylene biguanide antimicrobial
PHMB	Polyhexamethylene biguanide
PICO	Population, intervention, comparator, outcome
PP	Per protocol
PRISMA	Preferred reporting items for systematic review and meta-analysis

Term	Definition
PSA	Probabilistic sensitivity analysis
PSSRU	Personal social services research unit
PUSH	Pressure ulcer scale for healing
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SEM	Standard error of the mean
SOC	Standard of care
THIN	The Health Improvement Network Database
TRAE	Treatment related adverse events
VAS	Visual analogue scale
VLU	Venous leg ulcer
WHO	World Health Organization

Executive summary

Background

This late-stage assessment (LSA) has reviewed evidence and developed an economic model to evaluate the clinical- and cost-effectiveness of antimicrobial dressings (AMDs) to treat infected leg ulcers in adults. The LSA was designed to evaluate a variety of AMDs and establish whether different AMDs are associated with changes in clinical outcomes and value for money. A protocol for this work was developed based on the NICE scope. Clinical and economic evidence were identified through systematic literature searching and evidence submitted by companies.

Quality and relevance of the clinical evidence

The clinical review included a heterogeneous evidence base, evaluating 9 different agents and 11 different sub-agents for silver, iodine and honey AMDs. 12 of the 34 included studies were comparative, but only 4 compared eligible AMDs to each other. 21 of the 34 fully met the NICE scope, while the other 13 met a broader scope. These 13 studies were included because evidence fully meeting the scope was lacking for some AMDs, and so evaluate wound types and populations that may not be generalisable to a population with infected lower leg ulcers. No evidence was identified for 1 of the agents and 3 of the sub-agents.

Included studies were heterogeneous in the AMDs and sub-agents they evaluated, and consequently, the evidence base for each specific AMD is small. In addition, studies were predominantly non-comparative with small sample sizes, did not often report statistical significance, were largely considered at high risk of bias and varied in their populations, outcome definitions and timepoints of measurement. The EAG therefore considers the evidence base to be uncertain.

Comparative evidence generally favours silver agents for achieving complete healing. However, comparisons between silver sub-agents are inconsistent and this observation may be due to the higher number of studies assessing silver than other agents. Interpretation of other efficacy outcomes is more difficult due to the variation in outcome definitions and smaller number of studies reporting them. Adverse events across the different antimicrobial agents and dressing types were minimal.

Generalisability to the UK NHS setting was poor, with only 7 of the 34 studies being conducted in the UK. Generalisability to the population of interest was limited due to the variation in patient populations assessed within the included studies.

The evidence base identified does not allow a clear assessment of the relative efficacy of different AMDs to treat infected leg ulcers, and so does not provide conclusions on the validity of price variability.

Quality and relevance of the economic evidence

The EAG identified 6 economic evaluations of AMD agents to help inform the development of a de novo model. 6 of the 10 scoped agents of interest were evaluated by the selected studies, and the time horizon ranged from 4 weeks to 1 year. The generalisability of the economic evidence to the treatment of patients with infected leg ulcers within a UK health-care setting was poor, with only 1 of the 6 studies conducted in the UK.

The EAG de novo model was developed to assess the cost-effectiveness of AMDs. The model used a Markov structure with 4 health states: Infected unhealed, uninfected unhealed, healed, and dead. The outcomes from the clinical review informed clinical evidence, namely, the percentage 100% healed at 4 weeks or 12 weeks (depending on prescription time). Simplifying assumptions were required to inform the time at which infections resolved. Several sources were used to parameterise the cost and resource use data. Where possible, these were published UK databases; where not possible, high level, pragmatic searches were used to find appropriate publications to parameterise the model. In accordance with NICE methods guidance, the base case cost-effectiveness results were derived from a probabilistic sensitivity analysis to account for second order uncertainty around parameter values. Deterministic sensitivity analysis was conducted by varying key input parameters and areas of uncertainty were explored in the scenario analysis.

The probabilistic analysis showed a large overlap between confidence intervals, which demonstrates the available evidence cannot conclude whether there are clinically meaningful differences between the cost and quality adjusted life years of the agents. Key drivers of cost-effectiveness (with the potential to change the cost-effectiveness conclusion) were prescription time, efficacy and cost of AMDs. The

quality of the evidence informing the cost-effectiveness analysis was limited, with data particularly lacking on the rate of infection resolution; infection reoccurrence, and treatment-related adverse events leading to discontinuation.

Generalisability of the review evidence base for using AMDs to treat infected leg ulcers in a UK NHS setting was considered to be generally poor, with heterogeneity in the populations, outcomes and study designs of the studies further contributing to uncertainty. Results of the economic modelling demonstrated that the available evidence cannot conclude whether there are significant differences between the cost-effectiveness of the agents.

Recommendations for future evidence generation

The current evidence base does not allow a clear assessment of the relative merits of different types of AMDs in UK patients with infected leg ulcers, so no conclusions about the price variability were drawn. Further evidence should be collected to compare the performance of different agents and sub-agents within AMDs.

Observational designs using hospital data may provide pragmatic means of evaluation. These should focus on UK NHS patient populations with infected leg ulcers and clearly report the infection status of leg ulcers at baseline as well as how this was determined. Where possible, patients should be matched for key baseline characteristics that are likely to affect treatment outcomes including healing.

Any future studies should gather data on the use of AMDs in clinical practice, including the treatment sequencing effects of secondary and tertiary products, and the number of dressing changes determined by nursing staff to be required.

Outcomes should focus on those known to be of clinical value to patients and users (nursing staff), including those assessed in the user preference workshop which are currently not well represented in the evidence base. Outcome data should be gathered over a sufficiently long term (informed by clinical input) to capture all instances of infection resolution, reinfection, and complete healing.

1 Decision problem

The decision problem is described in the scope (NICE 2024b) and EAG comments are included in the protocol (YHEC 2024). Additional changes and comments are summarised in Table 1.1.

Table 1.1: Summary of decision problem

Aspect of the decision problem	LSA decision problem	EAG comments, including variation to the decision problem and rationale
Population	People aged 16 and over with a leg ulcer that shows signs and symptoms of local wound infection as per the IWII continuum	Evidence relating to diabetic foot ulcers and wounds of other types: Diabetic foot ulcers were not included in the economic model. However, where the review did not identify evidence for any of the listed agents, the records retrieved by the original searches (no additional searches were conducted) and relating to infected diabetic foot ulcers or leg ulcers of other types were re-assessed to include those with data relating to agents with no or insufficient evidence. If no evidence in infected leg ulcers was available, records relating to infected wounds elsewhere on the body were re-assessed. If no evidence in infected wounds was available, records relating to non-infected leg ulcers were re-assessed.
Healthcare setting	Primary and community care settings in the UK. If there is no evidence in these settings, relevant evidence in other healthcare settings or outside the UK may be considered where appropriate.	No change.
Intervention	Antimicrobial dressings available to the NHS on Part IX of the Drug Tariff. Interventions will include dressings using an active antimicrobial or bacterial-binding agent: Honey Iodine Silver Chlorhexidine Copper PHMB Octenidine Enzyme alginogel	Interventions were further categorised by antimicrobial sub-agent and dressing type as follows: Sub-agent: Honey (Manuka, monofloral and polyfloral) Iodine (cadexomer iodine and povidone iodine) Silver (ionic silver, ionic silver complex, ionic silver with antibiofilm agents, nanoparticulate silver, silver sulphate, silver sulphadiazine, metallic/elemental silver, silver oxysalts) Copper (cupric oxide) Dressing type:

Aspect of the decision problem	LSA decision problem	EAG comments, including variation to the decision problem and rationale
	DACC Chitosan	1. Alginate, gelling fibre, absorbent fibre 2. Foams, absorbent pads 3. Wound contact layers, gauze, 4. Ointments, gels, hydrogels 5. Hydrocolloid
Comparator(s)	An antimicrobial dressing that is considered current standard of care in the NHS (for example, based on clinical expert advice and clinical evidence). In most cases the comparator will not feature the additional agent included in the intervention. The comparator may differ between subgroups.	The comparator is the referent agent (the agent that is the most cost-effective compared to the others).
Outcomes	As listed in the final scope: Healing (wound healing and infection resolution) Pain Quality of Life Resource Use Adverse events and safety	No change.
Economic analysis	A health economic model will be developed, where possible, comprising a cost-comparison or cost utility analysis. Costs will be considered from an NHS and Personal Social Services perspective. Sensitivity and scenario analysis should be undertaken to address the relative effect of parameter or structural uncertainty on results. The time horizon should be long enough to reflect all important differences in costs or outcomes between the technologies being compared.	In the final protocol , it was planned that subgroups would be explored indirectly using categories of dressing, for example hydrocolloid compared with foams and absorbent pads. However, following publication of the protocol, the EAG was made aware that the required assumption that all silvers and all honeys could be grouped was not reflective of clinical practice. Therefore, the EAG revised their approach with sub-agents aligning with the International Wound Infection Institute (IWII) principals of best practice (2022) (International Wound Infection Institute (IWII) 2022). There was a paucity of evidence to allow for further disaggregation of the sub-agents into the categories defined in the scope without introducing additional uncertainty into the analysis. Therefore, the final model consisted of a principal analysis, grouping all agents and a secondary analysis of sub-agents.
Other issues for consideration	There is known variation in practice across local formularies and care pathways in the NHS. There are varied active components across the	No change.

Aspect of the decision problem	LSA decision problem	EAG comments, including variation to the decision problem and rationale
	antimicrobial dressings included in this scope and some may be contraindicated in certain groups (such as those with known sensitivities or people who are breastfeeding). The assessment will not be including evidence on leg ulcers at risk of infection because outcome measures would be different.	

Abbreviations: LSA – Late-stage assessment; EAG – External assessment group; IWII – International wound infection institute; UK – United Kingdom; NHS – National Health Service; PHMB – Polyhexamethylene biguanide; DACC – Dialkylcarbamoyl chloride; AMD – Antimicrobial dressing.

2 Technologies

2.1 *Antimicrobial dressings*

Topical antimicrobial dressings (AMDs) are dressings that contain an antimicrobial agent or deliver an antimicrobial agent directly to the wound/wound bed. AMDs can be used to reduce the level of bacteria at the surface of the wound, although they will not eliminate a spreading infection (BMJ Publishing Group Ltd and the Royal Pharmaceutical Society of Great Britain 2024). Therefore, AMDs can be considered in the treatment of local wound infections (BMJ Publishing Group Ltd and the Royal Pharmaceutical Society of Great Britain 2024, International Wound Infection Institute (IWII) 2022).

2.2 *Categorisation of AMDs*

2.2.1 *Summary of terms*

AMDs differ in the “category” and “type” of the dressing (Section 2.2, NICE 2024b). Dressing “categories” are based on clinical indication, while dressing “type” refers to the dressing medium. The categories and types of dressings considered in this assessment are set out in Table 2.1.

Table 2.1: Categories and types of dressing

Category of dressing	Dressing types included

(based on clinical indication)	
Dressings for exuding wounds, to absorb whilst maintaining a moist environment	Alginate, gelling fibre, absorbent fibre
Dressings for moderate to high exuding wounds	Foams, absorbent pads
Dressings for superficial or partial thickness wounds	Wound contact layers, e.g. gauze
Dressings for deeper wounds and wounds requiring debridement of thick slough	Ointments, hydrogels, gels or pastes containing the antimicrobial agent, or ribbons made from one of the materials from another category
Dressings to aid debridement of devitalised tissue	Hydrocolloid

AMDs differ in the active ingredient they contain (Section 2.2, NICE 2024b). Throughout this report, the term “agent” refers to the active ingredient in the dressing. During this assessment, stakeholder input highlighted the importance of considering the specific formulation of some agents. This formulation detail is defined as the “sub-agent” throughout this report. Sub-agents were identified for silver, iodine, honey and copper AMDs informed by stakeholder input, discussion with the Surgical Dressings Manufacturers Association, and input from professional experts. The expert opinions provided during these discussions informed the categorization of honey, iodine and PHMB, as shown in Table 2.2. The categorisation of silver into 3 sub-agents aligns with the 2022 consensus update of the International Wound Infection Institute (International Wound Infection Institute (IWII) 2022). Consideration of sub-agents was added to the assessment after finalisation of the scope. As such, evidence searches were designed to identify evidence specific to agents, rather than sub-agents. Table 2.2 details the agents and sub-agents considered in this assessment.

Table 2.2: Agents and sub-agents considered within the assessment.

Agent	Sub-agents
Copper	Cupric oxide
Chitosan	NA
Chlorhexidine	NA
Dialkylcarboamoyl chloride (DACC)	NA
Enzyme alginogel	NA
Honey	Manuka honey Monofloral honey Polyfloral honey
Iodine	Cadexomer iodine Povidone iodine
Octenidine	NA
PHMB	NA
Silver	Silver salts and compounds (this group includes silver oxides, phosphate, sulphates, chlorites and sulphadiazine). Elemental silver (this group includes metal and nano-crystalline silver). Silver with anti-biofilm mechanisms (this group includes silver with additional anti-biofilm mechanisms)(International Wound Infection Institute (IWII) 2022).

Abbreviations: DACC - Dialkylcarboamoyl chloride; NA – Not applicable; PHMB - Polyhexamethylene biguanide.

2.3 *Use of AMDs in community care*

There are many AMDs available to the NHS (Section 2.3, NICE 2024b). AMDs that have been approved by NHS Prescription Services for prescribing at NHS expense by an appropriate primary or community care practitioner are listed as ‘appliances’ in Part IX of the Drug Tariff (NHS Business Services Authority 2024).

The use of AMDs has increased since 1997 (Hussey et al. 2019). Analysis of data from the UK NHS Prescribing Cost Analysis has showed an increase in both the quantity of AMDs prescribed and the annual total net ingredient cost (excluding dispensing costs, fees or discounts) of AMDs, between 1997 to 2016 (Hussey et al. 2019). In 1997, the only agents of AMDs included in the Prescribing Cost Analysis were iodine and chlorhexidine (Hussey et al. 2019). The Prescribing Cost Analysis included silver-containing AMDs from 1998, and honey-containing AMDs from 2004

(Hussey et al. 2019). In 2016, AMDs comprised approximately 12.5% of all wound dressings prescribed in the community, and approximately 21% of expenditure on the same. Data supplied to NICE estimated an annual spend on antimicrobial dressings via NHS Supply Chain of more than £16 million (Section 2.3, NICE 2024b).

Clinical Practice Research Datalink (CPRD) data from 1st October 2018 to 31st March 2024 was evaluated to determine the most commonly prescribed AMDs for leg ulcers (Clinical Practice Research Datalink 2024). This evaluation found that dressings containing iodine were the most frequently issued (31.6% of total AMDs issued), followed by silver (27.1% of total AMDs issued). These 2 agents accounted for over half of the AMDs, though several agents included in this assessment (copper, chitosan and enzyme alginogel) were not represented in the CPRD data. Between 2018 and 2023, the agent with the greatest percentage of prescriptions has consistently been iodine (30.3% in 2018 to 32.2% in 2023), followed by silver and honey (silver: 29.8% in 2018 to 24.4% in 2023, honey: 15.3% in 2018 to 13.6% in 2023). The proportion of all AMDs that were octenidine dressings increased over this period (from 4.1% in 2018 to 11.0% in 2023). This appears to be stabilizing, with partial-year data of 11.2% in 2024. The proportion of AMDs represented by DACC and PHMB dressings has fallen slightly (DACC: 11.0% in 2018 to 6.8% in 2023, PHMB: 3.9% in 2018 to 2.3% in 2023). Chlorhexidine dressing use remained stable at less than 1% over this period.

2.4 *AMDs considered within this assessment*

A list of technologies to be included in this assessment was compiled using Part IX of the Drug Tariff and data from the CPRD provided to the EAG by NICE ([Clinical Practice Research Datalink 2024, NHS Business Services Authority 2024](#)). This was supplemented with information from stakeholder responses to a request for information. These sources informed the company name, technology name, agent type and number of sizes available, as displayed in Table 2.3. Sub-agent categorisation was performed by the EAG then reviewed and agreed by NICE after input from professional experts. Sub-agents were assigned by either:

- Information from the virtual medicinal product or actual medicinal product name in Part IX of the Drug Tariff (for example, where a PHMB dressing had a virtual medicinal product name of “bio-cellulose dressing,” the dressing was categorised as ‘PHMB in hydrated biocellulose’).
- Information available online about each technology, preferentially sourced from the manufacturer’s website, but from alternative sources if the information was not available on the manufacturer’s website.
- Information provided in industry responses to a request for information.
- Published literature, where the previous approaches did not provide sufficient information to determine a sub-agent. References are included in Table 2.3, where applicable.
- Consulting with professional experts.

A brief overview of the technologies as described by the companies can be found in Table 2.3. The list of technologies included in this assessment is complete as of August 2024, as this was the most recently published version of the Drug Tariff at the time of compilation. However, other technologies may be available to the NHS currently or in the future (NICE 2024b). Please see the [scope](#) for further details.

Table 2.3: Description of technologies included in the assessment

Company	Technology	Sizes available	Sub-agent
Copper dressings			
Edge Medical Ltd	MedCu dressing	3	NA
	MedCu dressing with adhesive border	2	
Chitosan dressings			
Axio Biosolutions Private Ltd	MaxioCel dressing	6	NA
Creed Medical Ltd	KytoCel dressing	7	
Chlorhexidine dressings			
Generic Supplier	Chlorhexidine gauze dressing BP	2	NA
DACC dressings			
BSN Medical Ltd	Cutimed Siltec Sorbact B dressing	5	NA
	Cutimed Sorbact dressing pad	3	
	Cutimed Sorbact Gel dressing	2	
	Cutimed Sorbact Hydroactive B dressing	4	
	Cutimed Sorbact Hydroactive dressing	5	
	Cutimed Sorbact swab	2	
	Cutimed Sorbion Sorbact dressing	4	
Enzyme alginogel dressings			
Flen Health UK Ltd	Flaminal Forte gel dressing	2	NA
	Flaminal Hydro gel dressing	2	
Honey dressings			
Advancis Medical	Algivon dressing	2	Manuka

Company	Technology	Sizes available	Sub-agent
	Algivon Plus dressing	2	
	Activon Medical Grade Manuka Honey dressing	2	
	Actilite gauze dressing	6	
	Activon Tulle gauze dressing	2	
H & R Healthcare Ltd	L-Mesitran ointment dressing	2	Polyfloral (Naskar et al. 2024, L-Mesitran 2021)
	L-Mesitran SOFT ointment dressing	1	
	SurgihoneyRO dressing	2	
	L-Mesitran Border sheet	1	
	L-Mesitran Hydro sheet	1	
	L-Mesitran Net sheet	1	
Insight Medical Products Ltd	Actibalm dressing	1	Manuka
Integra NeuroSciences Ltd	Medihoney Antibacterial Honey Apinate dressing	2	Manuka
	Medihoney Gel Sheet dressing	2	
	Medihoney HCS dressing	4	
	Medihoney HCS dressing with adhesive border	2	
	Medihoney HCS Surgical dressing with adhesive border	1	
	Medihoney Antibacterial Medical Honey dressing	2	
	Medihoney Antibacterial Wound Gel dressing	2	
	Medihoney Tulle dressing	2	
LMP (UK) Ltd	Manuka Fill dressing	2	Manuka
Manuka Medical Ltd	MANUKApli dressing	1	Manuka
Oswell Penda Pharmaceutical Ltd	Revamil Melginate dressing	2	Monofloral

Company	Technology	Sizes available	Sub-agent
	Revamil Balm sachet	1	
	Revamil Balm dressing	2	
	Revamil Wound Gel dressing	2	
	Revamil dressing	4	
	Revamil Collagen dressing	1	
SanoMed Manufacturing BV	Melladerm Plus dressing	2	Polyfloral
	Melloxy dressing	2	
	Melladerm Plus Tulle dressing	1	
Iodine dressings			
C D Medical Ltd	Povitulle dressing	2	Povidone iodine
Smith & Nephew Healthcare Ltd	Iodoflex paste dressing*	3	Cadexomer iodine
	Iodosorb ointment dressing*	2	Cadexomer iodine
	Iodosorb powder dressing sachets*	1	Cadexomer iodine
Systagenix Wound Management Ltd	Inadine dressing	2	Povidone iodine
Octenidine dressings			
Schulke & Mayr UK Ltd	Octenilin Wound Gel dressing	2	NA
PHMB dressings			
Advanced Medical Solutions Ltd	ActivHeal PHMB Foam Non-Adhesive dressing	6	PHMB in foam
	ActivHeal PHMB Foam Silicone Border dressing	6	PHMB in foam
B.Braun Medical Ltd	Prontosan Wound Gel dressing*	1	Unknown PHMB
	Prontosan Wound Gel X dressing*	2	Unknown PHMB
H & R Healthcare Ltd	Kendall AMD Antimicrobial foam dressing*	5	PHMB in foam

Company	Technology	Sizes available	Sub-agent
	Kendall AMD Antimicrobial foam dressing fenestrated*	1	PHMB in foam
	Kendall AMD Antimicrobial foam dressing fenestrated disc*	2	PHMB in foam
	Kendall AMD Antimicrobial Plus foam dressing*	1	PHMB in foam
	Kendall AMD Antimicrobial Plus foam dressing fenestrated*	1	PHMB in foam
	Kendall Telfa Clear dressing*	4	PHMB in foam
	Kerlix AMD Antimicrobial gauze dressing*	1	PHMB-coated gauze
	Kerlix AMD Antimicrobial Super Sponges*	1	Unknown PHMB
Lohmann & Rauscher	Suprasorb X + PHMB dressing	4	PHMB in hydrated biocellulose
Medicareplus International Ltd	CelluDress - PHMB dressing	1	PHMB in hydrated biocellulose
Silver dressings			
3M Health Care Ltd	KerraCel Ag dressing	4	Silver salts and compounds
	Tegaderm Alginate Ag dressing	2	
Advanced Medical Solutions Ltd	ActivHeal Aquafiber Ag dressing	3	Silver salts and compounds
Aspen Medical Europe Ltd	Sorbsan Silver Flat dressing	3	Silver salts and compounds
B.Braun Medical Ltd	Askina Calgitrol Thin dressing	1	Elemental silver
	Askina Calgitrol Paste dressing	2	Silver salts and compounds
Coloplast Ltd	Biatain Alginate Ag dressing	3	Silver salts and compounds
	Biatain Ag dressing	7	
	Biatain Silicone Ag dressing	7	
ConvaTec Ltd	Aquacel Ag+ Extra dressing	7	Silver with anti-biofilm mechanisms
	Aquacel Ag Foam dressing (adhesive)	6	Silver salts and compounds

Company	Technology	Sizes available	Sub-agent
	Aquacel Ag Foam dressing (non-adhesive)	5	
Crawford Healthcare Ltd	KerraContact Ag dressing	4	Silver salts and compounds
Gentell UK Ltd	Algicell Ag dressing	4	Silver salts and compounds
H & R Healthcare Ltd	PolyMem Silver dressing	4	Elemental silver
L&R Medical UK Ltd	Suprasorb Liquacel Ag dressing	3	Elemental silver
Lohmann & Rauscher	Suprasorb A + Ag dressing	3	Silver salts and compounds
Molnlycke Health Care Ltd	Exufiber Ag+ dressing	7	Silver salts and compounds
	Melgisorb Ag dressing	3	
	Mepilex Ag dressing	5	
	Mepilex Border Ag dressing	7	
Paul Hartmann Ltd	Atrauman Ag dressing	3	Silver salts and compounds
Regen Medical Ltd	Silverlon Flex dressing	4	Elemental silver
Smith & Nephew Healthcare Ltd	Algisite Ag dressing	3	Silver salts and compounds (Walker and Parsons 2014)
	Durafiber Ag dressing	8	
	Allevyn Ag Adhesive dressing	4	
	Allevyn Ag Non-Adhesive dressing	4	
	Allevyn Ag Gentle Border dressing	4	
	Allevyn Ag Gentle dressing	5	
	Acticoat 7 dressing	3	Elemental silver
	Acticoat dressing	4	
	Acticoat Flex 3 dressing	4	
	Acticoat Flex 7 dressing	3	

Company	Technology	Sizes available	Sub-agent
	Acticoat Moisture Control dressing	3	
Systagenix Wound Management Ltd	Silvercel Non-Adherent dressing	3	Elemental silver
	Silvercel dressing	4	
	Actisorb Silver 220 dressing	3	
	Promogran Prisma dressing	2	Silver salts and compounds
Urgo Ltd	Urgosorb Silver dressing	3	Silver salts and compounds
	UrgoClean Ag dressing	3	
	Urgotul Silver dressing	2	

Abbreviations: AMD – Antimicrobial dressing; DACC - Dialkylcarboamoyl chloride; NA – Not applicable; PHMB – Polyhexamethylene biguanide; UK – United Kingdom.

*These dressings were identified from the CPRD-informed list of dressings provided to the EAG by NICE. Further information (including company name and number of sizes available) was sourced from the Drug Tariff.

3 Clinical context

The National Wound Care Strategy Programme (NWCSP) defines a leg ulcer as an ulcer between the knee and ankle that has not healed within 2 weeks (National Wound Care Strategy Programme (NWCSP) 2023). Most leg ulcers are caused by venous insufficiency (Vowden and Vowden 2009, Moffatt et al. 2004, Mekkes et al. 2003, Pannier and Rabe 2013). In a 2017/18 study of 3000 adult patient records from The Health Improvement Network (THIN) database (a UK-based primary care database), 53.1% of patients with a leg ulcer had a venous ulcer (Guest et al. 2020). In 34.3% of patients with a leg ulcer the cause was not specified. 9.7% of patients with a leg ulcer had a mixed venous and arterial cause, and in 2.9% the cause was arterial (Guest et al. 2020). A study of the point prevalence of complex wounds across community, primary and secondary care Leeds in 2011 also found that the majority of leg ulcers were venous ulcers (point prevalence 0.29, 95% confidence interval 0.25 to 0.33, compared to a point prevalence of 0.05 (0.04 to 0.07) for arterial leg ulcers and 0.11 (0.08 to 0.13) for mixed arterial/venous leg ulcers) (Hall et al. 2014). Other causes of leg ulcers include peripheral vascular disease, reduced mobility, cardiac failure, diabetes or sickle cell disease (Vowden and Vowden 2009, Moffatt et al. 2004, Mekkes et al. 2003, National Wound Care Strategy Programme (NWCSP) 2023). Recommendations for the care of leg ulcers are detailed by the NWCSP (National Wound Care Strategy Programme (NWCSP) 2023). These include assessment, cleaning and dressing of the wound, as well as management of any contributing disease (section 1.2, NICE 2024b).

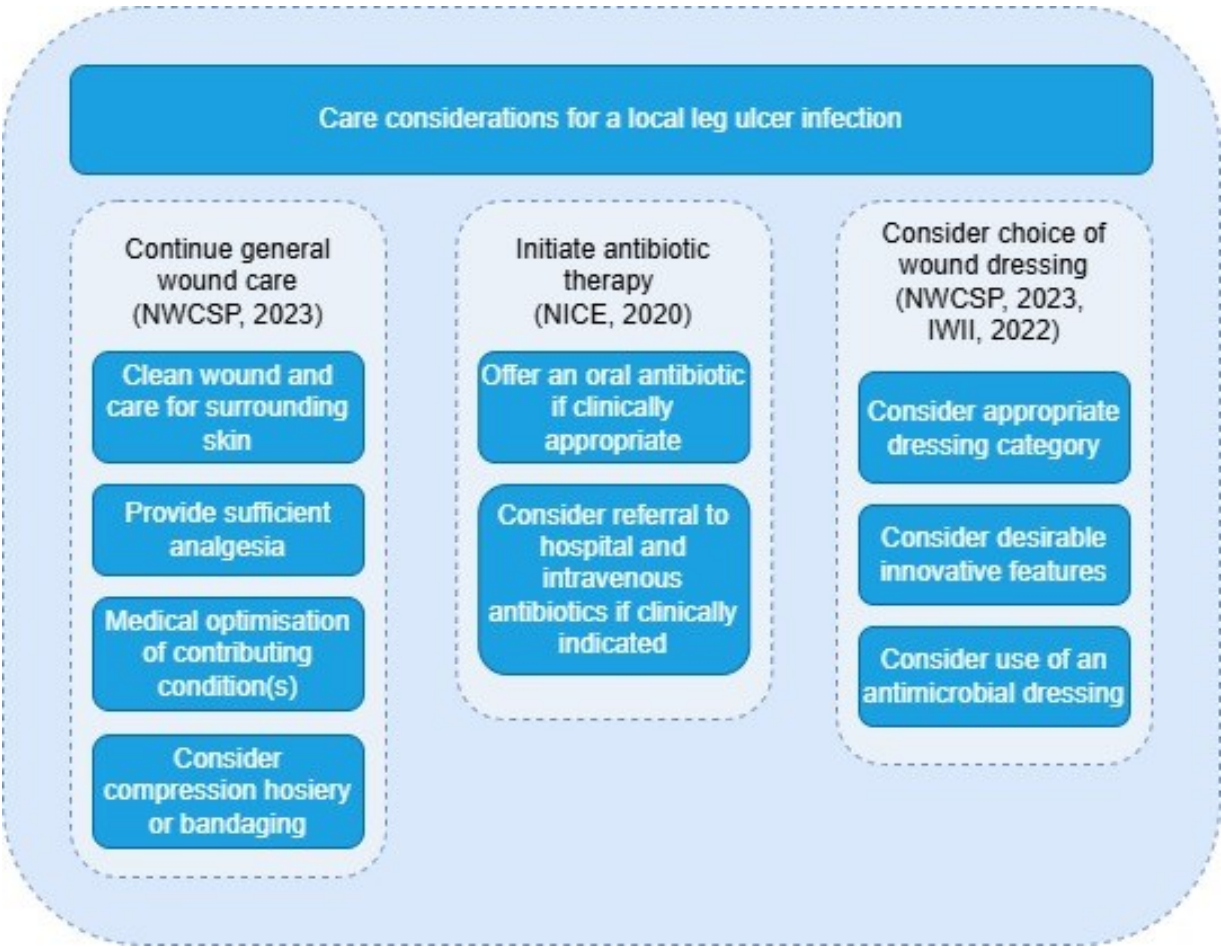
While most leg ulcers are colonised by bacteria, fewer are clinically infected (NICE 2020). Studies have found that 80% to 100% of leg ulcers may be colonized with bacteria (O'Meara et al. 2014, Moore et al. 2010, Halbert et al. 1992). The prevalence of infection is lower: 2 UK-based studies found infection rates of 18% (in leg ulcers of any cause) (Vowden and Vowden 2009) and 41% (in venous leg ulcers) (Guest et al. 2020). Local wound infection contributes to slower healing and increased resource use, including hospital admissions and antibiotic prescriptions (Guest et al. 2020, Mekkes et al. 2003, International Wound Infection Institute (IWII) 2022). Therefore, strategies to prevent infection and improve wound healing rates have been recommended (Guest et

al. 2020). The subset of leg ulcers with a local infection is the focus of this assessment (section 1.1, NICE 2024b).

Care of clinically infected leg ulcers includes additional considerations aimed at reducing the microbial burden of the wound (International Wound Infection Institute (IWII) 2022). These considerations include the use of systemic antimicrobial therapy (NICE 2020) and the choice of an appropriate AMD, when indicated. The choice of dressing is informed by the wound presentation and individual patient needs (section 1.2, NICE 2024b). As such, dressing choice often changes throughout the duration of a wound. A UK-based cohort study of 3000 patients with various wounds found that on average, patients were prescribed a mean of 8 different dressing types over the study period (1 March 2017 to 28 February 2018) (Guest et al. 2020). At the time of this assessment, there is a lack of national guidance on the use of topical AMDs to treat leg ulcer infections (NICE 2024b). This has led to development of local guidance by local formularies, and a wide variation in practice across the NHS.

A simplified care pathway for local leg ulcer infection in people aged 16 and over, informed by national guidelines, is illustrated in Figure 3.1 (National Wound Care Strategy Programme (NWCSP) 2023, NICE 2020, International Wound Infection Institute (IWII) 2022). Innovative features, while clinically relevant, are not considered in this assessment due to a paucity of data.

Figure 3.1: A diagram of the simplified care pathway for local leg ulcer infection in people aged 16 and over.



Wound biofilms are an additional clinical consideration relevant to chronic wounds such as leg ulcers. A biofilm is a structured community of microorganisms that produces unique infections, possesses significant tolerance to antimicrobials and is protected from host immunity (Haesler et al. 2019). It is recognised that biofilms influence chronic wound healing, although their influence is not yet fully understood (International Wound Infection Institute (IWII) 2022). Appropriate wound bed preparation, including debridement, is recommended to reduce biofilm presence (International Wound Infection Institute (IWII) 2022). The inclusion of biofilm in this assessment was discussed during the scoping period and it was decided that biofilms would not be included in this assessment, due to the difficulty in measuring performance of AMDs against it. Therefore, consideration of biofilm is outside the scope of this assessment.

3.1 *Equality issues*

Equality issues and considerations for this LSA are described in the equality impact assessment (NICE 2024a) published alongside the scope, and in the scope (section 3.1, NICE 2024b). No additional equality issues have been identified during the assessment.

4 Clinical and technological evidence selection

4.1 *Evidence search strategies and study selection*

Systematic database searches were conducted to identify studies of eligible dressings for infected leg ulcers. A single set of searches was conducted to identify both clinical and economic evidence. The search approach reflected that outlined in the [published protocol](#), apart from minor revisions to the MEDLINE strategy resulting from peer-review suggestions (to enhance potential sensitivity) and final line-checking. The database searches were conducted in a range of resources between 31 July 2024 and 03 August 2024. Full details of the search methods used are provided in Appendix 11.1.

The searches identified 3,840 records. Following deduplication, 3,206 records were assessed for relevance using the study eligibility criteria described in the [published protocol](#).

Where no evidence was found for an agent, or the evidence was limited (for example consisting of conference abstracts or studies with small sample sizes), the population criteria were broadened in stages until evidence for that agent was identified, as follows:

- No evidence in infected lower leg ulcers: studies of infected wounds of the foot were included (e.g. DFUs, pressure ulcers).

- No evidence in infected wounds of the lower limb: studies of infected wounds elsewhere on the body.
- No evidence in infected wounds elsewhere on the body: studies of non-infected (or not specified to be infected) lower-leg ulcers were included (excluding records with limited information such as conference abstracts).

As described in the published review protocol, only studies on lower leg ulcers (between knee and ankle) were eligible for the review, and the search methods were only designed to retrieve studies on this population. Any studies in a broader population were identified from these search results by systematically reviewing all records previously excluded for not meeting the NICE scope population criteria. No additional search to capture studies conducted in broader populations was conducted. As searches were not designed to identify evidence in populations beyond infected lower leg ulcers, there is an increased possibility that additional evidence on the use of AMDs in these broader populations is available but has not been included in the review. Any evidence included in this review, but conducted in populations that partly met the decision problem, should be viewed in the context of these limitations. Studies were considered to fully meet the scope where they reported that participants had infected leg ulcers, whether the criteria for infection were reported or not; the EAG notes that author reported definitions of “infection” may vary (particularly in older studies), and notes potential inconsistency in included populations as a further limitation.

Screening was conducted at an individual “agent” level, as set out in the final protocol. All studies that fully met the decision problem and assessed an eligible agent were included, regardless of the sub-agent assessed. Subsequent broadening of the population criteria was also conducted for each “agent”.

Information regarding which sub-agents were assessed by the included studies (where applicable) was identified later as part of the data extraction process, following a request from NICE after study selection had been completed. Included studies were categorised by sub-agent. No additional studies were included. This means that no evidence was included for some sub-agents (Nanoparticulate silver and Povidone

iodine) because sufficient evidence that fully met the decision problem had already been included for other sub-agents within that agent grouping. Further evidence from broader populations was not sought for missing sub-agents as this was not feasible within the scope and resource available to complete the LSA.

Consistent with the approach documented in the review protocol, laboratory studies were not included because in-human evidence was considered to be more useful in the context of this LSA. As well as assessing surrogate rather than clinical outcomes, laboratory studies also approximate the patient population and as such have poor generalisability to the scoped setting and population. While such studies might demonstrate proof of concept, they are unable to provide data on the clinical efficacy of individual AMDs.

Of the 3,206 unique records identified, 660 obviously irrelevant records (such as those reporting studies in animals, and ineligible intervention types including plasma therapy and irradiation) were excluded at first pass by a senior reviewer. The remaining 2,546 titles and abstracts were screened by 1 reviewer with the first 10% assessed by 2 reviewers independently. Of these, 2,098 records were excluded and a total of 448 full papers were retrieved and examined for eligibility by 1 reviewer, with a second reviewer independently assessing the first 10%.

In addition to the EAG searches, 17 companies (Advancis Medical, B Braun Medical, CD Medical, Coloplast, ConvaTec, Edge Medical, Essity, Flen Health, Integra Life Sciences, Lohmann & Rauscher, Manuka Med, Molnlycke Healthcare, Oswell Penda Pharmaceutical, Paul Hartmann, Schuelke, Smith and Nephew and Urgo Medical) submitted documents. These submissions totaled 259 files, of which 174 comprised administrative documents that were not considered relevant to the clinical or economic evidence review (e.g. declarations of conformity or product leaflets). 85 documents reporting potentially eligible studies were assessed. 82 were ineligible, including: RFI submission forms that provided no further data or study references for checking; ex vivo or ineligible population studies (where relevant in vivo or eligible population studies for the agent in question were available); and non-systematic review articles. 1 of these

provided unpublished sub-group data from a non-comparative study evaluating Aquacel Ag+ Extra/Ag Advantage dressings (Convatec) in an eligible population (infected leg ulcers). The EAG considered that this document did not provide sufficient information to allow an adequate assessment of the reliability of evidence, and was specifically lacking in details on the baseline data for this subgroup, descriptions of the study's design and outcome event numerators (key outcomes reported as proportions only). Therefore, this study was not included.

Thus 3 documents were added to the review library. The EAG also identified reference lists of potentially relevant studies in 16 documents (totaling 271 references) that were assessed, resulting in the addition of 11 records to the review library. Thus 14 records sourced from the company submission evidence were added to the review and assessed at full text retrieval stage and a total of 462 full text documents were screened.

405 records were initially excluded at the full text selection stage. Following this, 10 otherwise eligible studies evaluating dressings that did not appear in the [Part IX tariff](#) were re-reviewed with input from clinical experts. 5 studies evaluated dressings that were considered similar enough to products currently on the tariff and were therefore included (Physiotulle Ag wound contact layer (Jorgensen et al. 2008), 1% silver sulfadiazine cream (Degreef and Michiels 1984, Melotte et al. 1985), metallic and ionic silver Microlyte Ag (Manning et al. 2020) and PHMB PuraPly (Koullias et al. 2022)). 5 studies (in 7 reports) evaluated dressings that were considered dissimilar to any product on the tariff and were therefore excluded with reason “ineligible intervention” (2 studies evaluating irrigation solutions (Borges et al. 2018, Vanscheidt et al. 2012), 1 a topical povidone-iodine (Daroczy 2006), 1 a topical silver spray (Gazzabin et al. 2019), 1 a chitosan composite film (Abdollahimajd et al. 2022)).

In total, 412 records (including 24 papers identified from the EAG searches that could not be retrieved) were excluded as summarised in the PRISMA diagram (Appendix A, Figure 11.1) and the excluded studies list (Appendix B). Of the remaining 50 documents, 5 were economic studies that were included in the economic analysis but

did not provide relevant clinical data. Thus 45 documents were included in the clinical review.

4.2 *Included and excluded studies*

A total of 38 studies (in 45 documents) identified through the EAG searches and company submission evidence were included in the clinical review. Of these, 4 were ongoing studies (reported in 6 documents) and are summarised in Appendix E.

34 studies (in 39 documents) with results were extracted and synthesised, including 21 which fully met the decision problem and 13 which partly met the decision problem. Among the 21 studies that fully met the decision problem, the distribution of included studies evaluated the following agents:

- Silver: 14 studies that fully met the decision problem (4 RCTs comparing silver with no-agent, 7 single-arm trials, 3 prospective case series).
- Iodine: 1 RCT that fully met the decision problem comparing iodine and no agent.
- Octenidine: 1 non-randomised trial comparing octenillan gel with different secondary dressings that fully met the decision problem.
- Honey: 1 single-arm trial that fully met the decision problem was included though results are only available in a conference poster, thus evidence that partly met the decision problem was also sought.
- Comparing more than 1 eligible agent (4 studies):
 - 1 pilot RCT that fully met the decision problem was identified comparing DACC and silver dressings; as this was a pilot study this was not considered sufficient evidence for DACC, evidence that partly met the decision problem was also sought.
 - 1 prospective cohort study that fully met the decision problem comparing different silver dressings.
 - 1 RCT that fully met the decision problem comparing silver and iodine.

- 1 non-randomised comparative study that fully met the decision problem comparing silver and honey (conference abstract only).

Among the 13 studies that partly met the decision problem the distribution of included studies evaluated the following agents:

- DACC: 1 prospective case series in patients with infected wounds of other types (Bruce 2012).
- Honey: 1 single-arm trial (Moghazy et al. 2010) and 1 prospective case series (Biglari et al. 2013) in patients with infected wounds of other types were included.
- Enzyme Alginogel: 3 studies in patients with infected wounds of other types were included (Durante 2012, Jones and Oates 2018, King and Rolland 2023).
- Chitosan: 1 RCT (Mo et al. 2015) and 1 single-arm trial (Orig and Singleton 2016) study in patients with infected wounds of other types were included.
- PHMB: 1 RCT (Vallejo et al. 2022) and 1 prospective case series (Koullias et al. 2022) in patients with non-infected VLUs were included.
- Copper: 1 single-arm trial (Melamed et al. 2021) and 2 prospective case series (Dokic S et al. 2023, Treadwell T et al. 2022) in patients with non-infected lower-leg ulcers of various aetiologies were included.
- Chlorhexidine: No eligible studies, whether fully or partly meeting the decision problem, were identified that reported on chlorhexidine dressings.

The characteristics of the included studies are summarised in Table 4.1.

Table 4.1: Studies selected by the EAG as the clinical evidence base (34 studies in 39 documents)

Study name and details	Intervention(s) and comparator(s)	Participants and setting	Outcomes	EAG comments
Chitosan (number of included studies = 2)				
Mo 2015 (Mo et al. 2015) Design: RCT Follow-up: 4 weeks Location: China Analysis population: ITT	Intervention: Chitosan Comparator: No agent (Vaseline gauze)	Population: Patients (n=90, n=45 in each arm) over 18 with non-healing chronic leg wounds, 76.7% infected wounds. In patients with multiple wounds, 1 target wound was selected. AMBER Age (years, mean, SD): All population Chitosan: 61.22 (15.12) Comparator: 63.20 (18.65) Male gender n(%): All population Chitosan: 26 (57.8) Comparator: 23 (51.1) Subgroups: Lower limb vascular ulcer (n=25)	Decrease in wound area Pain following dressing removal Wound depth Level of exudate	11 patients lost to follow-up (3 in chitosan group, 8 in no agent group). There was no significant difference in withdrawal rate between groups (p=0.108). For efficacy analysis the last observation carried forward was used, thus ITT analysis Baseline characteristics differentiate between infected wounds (n=69) and wounds with infected/allergic skin (n=41). Outcome data is reported for the infected wound group

Study name and details	Intervention(s) and comparator(s)	Participants and setting	Outcomes	EAG comments
		Setting: 3 university hospital centres		
Orig et al 2016 (Orig and Singleton 2016) Design: Prospective single-arm trial Follow-up: Mean evaluation time 8.18 days Location: NR	Intervention: Chitosan (KytoCel dressing)	Population: 20 patients with infected wounds requiring tissue viability nurse assessment. Included 14 post-operative various locations, 5 chronic wounds (2 leg ulcers, 2 DFU, 1 pressure ulcer) and 1 traumatic wound. Overall 3 (15%) were on the shin or calf, 2 (10%) on the foot and 1 (5%) on the heel. Authors note that 14/20 (70%) participants had multiple underlying conditions including coronary heart disease, diabetes or anaemia which affect healing due to compromised circulation AMBER Age (years, mean SD): 66.7 Male gender n(%): 11/20 (55%)	Wound healing Wound improvement	Variation in wound types and locations and therefore in secondary dressings used, difficult to generalise. 40% of patients received adjunct oral or intravenous antifungals antibiotics, thus it is difficult to draw conclusion on the efficacy of the dressing in isolation.

Study name and details	Intervention(s) and comparator(s)	Participants and setting	Outcomes	EAG comments
		Subgroup: NR Setting: Acute hospital ward		
Copper (number of included studies = 3)				
Dokic 2023 (Dokic S et al. 2023) Design: Prospective case series Follow-up: 3 months Location: Slovenia	Intervention: Copper wound dressings (MedCu)	Population: Patients (n= 12) with chronic wounds AMBER Age (years, mean SD): NR Male gender n(%): NR Subgroup: NR Setting: Hospital	Wound healing Wound infection Pain	Very limited information about the participants and their wounds as baseline and also outcome level. Study of 12 people which may lead to issues with generalisability.
Melamed 2021 (Melamed et al. 2021) Design: Single-arm trial Follow-up: 4 weeks of treatment and 2 weeks of follow up using “standard of	Intervention: Cupric oxide dressing (MedCu)	Population: Diabetic patients with non-infected chronic wounds (n=13) Non-plantar foot wounds: 10 Plantar foot wounds: 3 AMBER	Wound area Wound infection signs Granulation Peri-wound redness	The study included a screening phase (7-14 days) in which patients were treated with “standard of care” dressings (details and whether they were antimicrobial NR). If

Study name and details	Intervention(s) and comparator(s)	Participants and setting	Outcomes	EAG comments
care" dressings (dressing type NR); results are reported for the 4 week treatment phase separately. Location: Israel		Age (years, mean SD): 58 (7.73) Male gender n(%): 8 (61*) Subgroup: NR Setting: Outpatient hospital clinic		wound size reduced by >35% they were excluded. The paper does not reported how many patients were excluded at this stage but 13 patients received the copper dressing and were included in the analysis. Wound surface area was quite varied at baseline, ranging from 1.35 to 23.6 cm ² .
Treadwell 2022 (Treadwell T et al. 2022) Design: Prospective case series Follow-up: NR Location: Alabama, USA	Intervention: Cupric oxide wound dressing (MedCu)	Population: 25 patients with acute and chronic hard to heal wounds (post-operative wounds, traumatic wounds, VLU, DFUs) AMBER Age (years, range): 68 (63 to 71) Male gender n(%): NR Subgroup: VLU (NR separately)	Wound healing	Conference poster with limited information about patients and their wounds at baseline Patients have different types of wounds and the number of patients with each type if wound is not reported. Outcomes are reported overall and not per wound type

Study name and details	Intervention(s) and comparator(s)	Participants and setting	Outcomes	EAG comments
		Setting: Medical centre		
DACC (number of included studies = 1)				
Bruce 2012 (Bruce 2012) Study design: Prospective case series Follow-up: 28 days (or until infection reduced) Location: UK and Ireland	Intervention: Cutimed Sorbact Hydroactive dressings (Cutimed)	Population: 13 patients with 14 chronic wounds (1 wound was not considered chronic as it had not remained unhealed for over 6 weeks) VLU (n=9) Traumatic wounds (n=4) Mixed arterial ulcers (n=1) AMBER Age (years, mean, range): 70 (52 to 87) Male gender n(%): 7 (54*) Subgroups: VLU (n=9) Setting: 4 community centres and 2 acute hospitals	Change in (%) infection Exudate Wound healing Dressing performance (ease of application and removal, pain during and between dressing changes)	Mixed wounds, thus there may be problems with generalisability of the results. No power calculation was reported to test the suitability of the sample size
Enzyme Alginogel (number of included studies = 3)				

Study name and details	Intervention(s) and comparator(s)	Participants and setting	Outcomes	EAG comments
Durante 2012 (Durante 2012) Design: Prospective case series Follow-up: 60 days Location: Italy	Intervention: Enzyme Alginogel (Flaminal)	Population: 23 patients with acute or chronic wounds of any duration and aetiology (9 pressure ulcer, 7 diabetic ulcer, 3 traumatic wounds, 1 arterial ulcer, 3 other). 16/63 (70%) of patients had chronic wounds with various underlying pathologies. 3 patients had infections at baseline (1 DFU, 2 pressure ulcers) AMBER Age (years, mean SD): 54 (23) Male gender n(%): 13 (57) Subgroup: NR Setting: Hospital, with continuation in home setting	Wound size Wound bed Infection Pain	3 wounds not included in wound assessment; 1 discontinued treatment due to allergic reaction and 2 closed surgically prior to final assessment as enzyme alginogel was used to prepared wound bed for skin graft

Study name and details	Intervention(s) and comparator(s)	Participants and setting	Outcomes	EAG comments
Jones et al 2018 (Jones and Oates 2018) Design: Prospective case series Follow-up: Unclear Location: UK	Intervention: Enzyme Alginogel (Flaminal)	Population: 356 patients with critically colonised or infected wounds (84 leg ulcer, 75 pressure ulcer, 11 DFU, 21 moisture lesion, 5 unspecified ulcer, 28 trauma/skin tear, 5 burn, other 101, 26 not specified) AMBER Age (years, mean SD): NR Male gender n(%): NR Subgroup: NR Setting: Primary care (forms completed by district nurses)	Wound bed condition Peri-wound skin condition Infection improvement Signs of infection (exudate) Partial wound healing (granulation) Pain	It is unclear whether or how many patients had infections at baseline
King et al 2023 (King and Rolland 2023) Design: Prospective case series	Intervention: Enzyme Alginogel (Flaminal).	Population: 1657 patients with critically colonised or infected wounds (various wound types including leg ulcers, pressure	Wound bed condition Peri-wound skin condition Infection improvement Pain	It is unclear whether or how many patients had infections at baseline. District nurses were asked to complete evaluation

Study name and details	Intervention(s) and comparator(s)	Participants and setting	Outcomes	EAG comments
Follow-up: Unclear Location: UK		ulcers, diabetic foot ulcers, moisture lesions and burns) AMBER Age (years, mean SD): NR Male gender n(%): NR Subgroup: NR Setting: Primary care (forms completed by district nurses)		forms for patients treated with Flaminal. A total of 1657 evaluations were completed over a 22 month period. Data analysed using a standard binomial test with 95% confidence intervals calculated using the Wilson method. All p values reported were one-tailed
Honey (number of included studies = 3)				
Biglari et al 2013 (Biglari et al. 2013) Design: Prospective case series Follow-up: 4.88 (SD 4.4) weeks Location: 9 sites in Germany and 1 in Austria	Intervention: Honey (various Medihoney™ dressing products) In 66% of all treatments, antibacterial honey (Medihoney™) was applied, in 22%, antibacterial wound gel (Medihoney™),	Population: 154 wounds in 121 adult and paediatric (almost 50% were <18 years old) patients with infected wounds of various aetiologies (26 post-operative, 20 decubitus, 8 soft tissue infections, 4 general wounds, 2 burns/scalds, 2 tumour/skin lesions, 9 unknown, 27 other, 32	Wound healing Pain Change in slough/necrosis Adverse events	17/121 patients (comprising 24 wounds) dropped out (10 discharged, or transferred, 6 non-compliant, 1 pain) are lost to follow-up. Authors state that data is reported for 104 patients, however for wound healing it appears that data is only

Study name and details	Intervention(s) and comparator(s)	Participants and setting	Outcomes	EAG comments
	in 6%, a combination of both, and in 6%, the product was not specified.	undergoing treatment for cancer). 29% of patients exhibited signs of systemic Infections AMBER Age (years, mean SD): 33.2 (27.5) Male gender n(%): 56% Subgroup: NR Setting: Hospital dermatology clinic		reported for 101 patients and for pain data is only reported for 102 patients 70% of wounds were treated with antiseptics (e.g. octenidine hydrochloride, polyhexanide or polyvidoneiodine); 37% of wounds were treated at least once with systemic antibiotics - because of these precautionary measures considered necessary by the participating physicians, conclusive analysis of the antibacterial effects due to honey alone could not be performed Adverse events are reported, though in 9.7% of assessments tolerance was not monitored
Yang et al 2015 (Yang K et al. 2015)	Intervention: Honey (manuka topical medical grade honey)	Population: Patients with chronically infected VLUs (n=20)	Wound size	Only available as conference abstract and poster, limited information.

Study name and details	Intervention(s) and comparator(s)	Participants and setting	Outcomes	EAG comments
Design: Prospective single-arm study Follow-up: 4 weeks Location: USA		GREEN Age (years, mean SD): NR Male gender n(%): 12/20 (60*%) Subgroup: NR Setting: Hospital		
Moghazy et al 2010 (Moghazy et al. 2010) Design: Prospective single-arm trial Follow-up: 3 months Location: Egypt	Intervention: Honey (monofloral, with medium-pored non-sterile gauze)	Population: 30 patients with infected DFUs. Only 6 patients (20%) had no vascular disease AMBER Age (years, mean SD): 52.3 Male gender n(%): 20/30 (66.6%)	Wound size Complete healing Partial healing Exudate Purulent discharge Inflammation	Patient selection was done by randomly allocating patients presenting to Surgery Department, either through outpatient or consultation from inpatient till reaching the sample size (30 patients) 2 patients underwent amputation within 1 month and 2 patients said to have

Study name and details	Intervention(s) and comparator(s)	Participants and setting	Outcomes	EAG comments
		Subgroup: NR Setting: Referred to outpatient care from hospital admission		partially healed received skin grafts
Iodine (number of included studies = 1)				
Skog 1983 (Skog et al. 1983) Design: RCT Follow-up: 6 weeks Location: Sweden	Intervention: Cadexomer iodine (Iodosorb) Comparator: No agent (Standard treatment - Paraffin-impregnated dressings were most commonly used, but saline dressings and bland ointments were also used occasionally. Additional agents (not specifically antimicrobials) employed included merbrominc, Salvstrumpa" and systemic antibiotics.)	Population: 93 patients with infected, chronic venous ulcers GREEN Age (years, mean SD): Standard treatment: 72.1 (3.54) Cadexomer iodine: 68.1 (1.99) Male gender n(%): Standard treatment: 8/36 Cadexomer iodine: 10/38 Subgroup: NR Setting: 10 centres. Mixed; at home (visiting nurse) or hospital clinic	Change in (%) ulcer size Pain Signs of infection	There are many different kinds of dressing classed as standard care. 21 patients were excluded from statistical analysis

Study name and details	Intervention(s) and comparator(s)	Participants and setting	Outcomes	EAG comments
Octenidine (number of included studies = 1)				
Hammerle and Strohal, 2016 (Hammerle and Strohal 2016) Study design: Non-randomised trial Follow-up: 42 days Location: Austria	Intervention: Octenidine (Octenilin gel, primary dressing with foam or alginate secondary dressing) Comparator: Octenidine (Octenilin gel, primary dressing with non-adhering wound contact layer and suction gauze secondary dressing) Comparator: Foam with or without silver, alginate with or without silver, or hydrogel (wound-phase adapted dressing selected by expert investigator). Plus secondary foam dressing.	Population: 16 infected wounds (out of a total population of 44 adults with 49 VLU with wound size up to 20 x 10m²) GREEN Foam/alginate with/without silver (6 infected wounds), octenidine with dressing (5 infected wounds), octenidine without dressing (5 infected wounds) Age (years, mean, SD): NR (full study population: 38 to 87, median age 66.2) Male gender n(%): NR (full study population: 31, 70.5%) Subgroup: NR Setting: Secondary care (single centre)	% granulation tissue in wound Secondary: Wound size (% change) Bioburden (% change in slough, eschar, debris and sero-crusts) Infection Patient sensory perception of wound AEs	Non-randomised study without rationale for allocation to treatment arm The foam with or without silver study arm comprised a mixed silver/no agent intervention with various dressing types that was considered ineligible; this study was therefore extracted and synthesised as a 2-arm study.
PHMB (number of included studies = 2)				

Study name and details	Intervention(s) and comparator(s)	Participants and setting	Outcomes	EAG comments
Vallejo et al 2022 (Vallejo et al. 2022) Associated records: Protocol: Vallejo et al 2021 (Vallejo 2021) Design: RCT Follow-up: 12 weeks Location: Australia Analysis population: ITT	Intervention: Various forms of PHMB dressing (AMD foam, or gel with PHMB, or Kerlix AMD gauze) Comparator: No agent	Population: 50 patients with hard-to-heal leg ulcers of >6 weeks duration with mixed aetiologies. Wounds were absent of clinical signs of infection at baseline. PHMB (n=25): venous 15 (60%), arterial 1 (4%), mixed 9 (36%). No agent (n=25): venous 17 (68%), arterial 2 (8%), mixed 6 (24%) AMBER Age (years, median IQR): 82 (13) PHMB: 85 (15) No agent: 81 (13) Male gender n(%): 24/50 (48%) PHMB: 14/25 (56%) No agent: 10/25 (40%) Subgroup:	Wound healing Wound deterioration Wound score (PUSH) Wound size Pain Adverse events Wound QoL score	Power calculation to detect 20% difference in healing rate required 23 participants in each group, sample size achieved ITT analysis conducted, LOCF used with baseline scores as a covariate Higher rate of discontinuations in the no agent arm (n=12) vs PHMB arm (n=5), mostly due to greater number of deterioration (11 vs 2 respectively, p=0.01). Thus the number of patients followed to week 12 was 20 (80%) in the PHMB arm and 13 (52%) in the no agent arm Authors note that some these participants took systemic antibiotics during the trial which may have influenced results. The number of patients is not reported

Study name and details	Intervention(s) and comparator(s)	Participants and setting	Outcomes	EAG comments
		Small (<10cm ²) and large (>10cm ²) wounds Setting: 1 community wound clinic		
Koullias 2022 (Koullias et al. 2022) Study design: Prospective case series Follow-up: 32 weeks Location: USA	Intervention: PuraPly AM Type 1 collagen matrix PHMB barrier	Population: 67 patients with VLUs (not reported to be infected). AMBER Age (years, mean, SD): 75.9 (12.29) Male gender n(%): 28 (41.8) Subgroups: NR Setting: Unclear (dressings applied by physicians in unclear settings)	Change (%) in wound area Wound closure	Infected wounds NR separately
Silver (number of included studies = 14)				

Study name and details	Intervention(s) and comparator(s)	Participants and setting	Outcomes	EAG comments
Dimakakos et al 2009 (Dimakakos et al. 2009) Study Design: RCT Follow up: 9 weeks Location: Greece Analysis population: ITT	Intervention: Ionic silver complex silver releasing dressing (Contreet Ag) Comparator: No agent (non-adhesive dressing (Biatain))	Population: Patients with infected VLU's (n=42; intervention n=21, control n=21) GREEN Mean age: Silver: 61.2 years No agent: 58.7 years Male gender n(%): Silver : 9 (43*) No agent: 7 (33*) Subgroup: Venous ulcers Setting: NR	Pain Ulcer healing Adverse events	12 patients in the intervention group and 14 in the comparator group had a history of delayed ulcer healing Initial ulcer diameter and depth differed between patients but this was not a significant difference No power calculation was carried out ITT population used for all analysis
Degreeef et al 1984 (Degreeef and Michiels 1984) Study Design: Prospective case series Follow up: 4 weeks Location: Belgium	Intervention: Silver, 1% silver sulfadiazine cream covered by a sterile bandage (Flammazine cream)	Population: 29 patients with infected leg ulcers (11 venous, 6 arteriosclerotic-venous ulcers and 8 arteriosclerotic-diabetic ulcers). 4 patients had ulcers with traumatic origin worsened by poor vascular status GREEN	Bacterial load Ulcer healing Adverse events	Limited information on recruitment reported, e.g. unclear if patients included consecutively. Number of patients excluded (criteria included sensitivity to treatment components, systemic antibiotics, pregnancy, etc.) not reported. Older study, thus may not be as

Study name and details	Intervention(s) and comparator(s)	Participants and setting	Outcomes	EAG comments
		Mean age: 73.51 Male gender n(%): 6 (20.7%) Subgroup: NR Setting: Hospital		generalisable to current wound care practice. Some lack of clarity in patient characteristics, e.g. all reported to have vascular or partly vascular aetiology but 4 had traumatic ulcer cause, of whom only 3 reported to be worsened by vascular status Authors note that 1% silver sulfadiazine cream causes an atonic ulcer by the formation of a pseudomembranous structure with long-term use. Authors note that this phenomenon was recognised at the beginning of the study, after which they limited treatment duration for patients taken up later in the study by ceasing intervention after 2 negative wound cultures. Treatment may have differed between patients

Study name and details	Intervention(s) and comparator(s)	Participants and setting	Outcomes	EAG comments
				over time due to this effect.
Forlee 2014 (Forlee et al. 2014) Study design: Single-arm trial Follow-up: 8 weeks (The wound was swabbed every 7 days) Location: South Africa Analysis population: ITT	Intervention: Gelling fibre dressing containing ionic silver (DURAFIBER™ Ag)	Population: 14 people with chronic exuding VLU's that showed clinical signs of infection GREEN Mean age: 70 Male gender n(%): 5 (35*) Subgroup: NR Setting: 3 secondary care centres	Health-related quality of life Change (%) in signs of local infection Changes to wound bed condition Change (%) in wound area Pain and discomfort levels Adverse events	All 14 patients included in analysis.
Humbert 2006 (Humbert et al. 2006) Study Design: RCT Follow up: 6 weeks Location: France Analysis population: ITT	Intervention: Silver (Biatain Ag) Comparator: No agent (calcium alginate fibre dressing)	Population: 80 patients with venous or mixed-aetiology leg ulcers exhibiting local signs of infection. Silver n=40 No agent n=40	Wound size/area Pain and discomfort Clinical signs of infection Wound bed condition Adverse events	21 patients discontinued the study (19 withdrew due to intercurrent event, 1 lost to follow-up, 1 withdrew consent). Among 19 withdrawals for intercurrent events 8/40 (20%) were in silver arm and 11/40 (27.5%) in no

Study name and details	Intervention(s) and comparator(s)	Participants and setting	Outcomes	EAG comments
		GREEN Age (years, mean SD): Silver: 72.9 (9.7) Calcium: 73.5 (12.5) Male gender n(%): Silver: 12 (30.0) Calcium: 17 (42.5) Subgroup: NR Setting: 17 sites that included dermatology, vascular, angiology, phlebology and dermatology practices; 85% of silver arm and 72.5% of no agent arm were outpatients		agent arm; a causal relationship with the dressing could not be ruled out in 3 and 7 patients respectively
Manning 2020 (Manning et al. 2020) Study Design: Single-arm trial Follow up: 12 weeks Associated Records: Conference abstract:	Intervention: Bioabsorbable polymeric matrix containing ionic and metallic silver (Microlyte Ag)	Population: 32 patients (comprising 35 wounds) with non-healing chronic wounds (including 19 VLU, 8 DFU, 3 post-operative wounds, 2 trauma wounds, 1 pressure ulcer, 1 pilonidal cyst, 1 burn) showing signs of clinical infection. Results are reported	Wound size/area Wound healing	It is not clearly reported how many wounds to patients there were in the VLU group, but context implies that multiple wounds were only present among the other (non-VLU or DFU) wound types. Thus appears 19 VLU patients were included.

Study name and details	Intervention(s) and comparator(s)	Participants and setting	Outcomes	EAG comments
Manning 2019 (Manning et al. 2019) Location: USA		separately for VLU wounds (n=19) GREEN Mean age: NR median age for VLU subgroup 66 (range 43 to 95) Male gender n (%): NR Subgroup: Venous aetiology Setting: Wound care clinic within a secondary care setting		3/19 VLU patients are lost to follow-up and not included in the results Wound size reduction is only reported for 11/16 of the VLU patients whose wounds improved
Meaume et al, 2005 (Meaume et al. 2005) Study design: RCT Follow-up: 4 weeks (daily assessment in first 14 days, weekly thereafter) Location: UK Analysis population: ITT (select outcomes PP)	Intervention: Silver-releasing hydroalginate dressing (Silvercel) (n=38) Comparator: No agent (pure calcium alginate dressing (Algosteril) (n=33)	Population: 99 people hospitalised with venous leg or pressure ulcers with at least 2 signs of local infection. Some results are reported for patients with leg ulcers (n=71). Silver: 51 (38 leg ulcers) No agent: 48 (33 leg ulcers) GREEN Age (years, mean, SD):	Modified ASEPSIS index Antibiotic use Wound healing (reduction in wound area) Rate of wound healing. Wound severity score Wound healing (full closure) Adverse events	ITT analysis conducted using last observation carried forward (LOCF) Power calculation required 50 participants in each arm to detect an 8 to 10 point between-group difference in modified ASEPSIS score.

Study name and details	Intervention(s) and comparator(s)	Participants and setting	Outcomes	EAG comments
		Silver: 74.9 (9.0) No agent: 77.6 (10.9) Male gender n(%): Silver: 41.2% No agent: 31.2% Subgroups: NR Setting: 13 hospital centres		Baseline characteristics compared statistically, no significant differences between groups apart from fewer patients >80 years (p=0.005) and more diabetic patients (p=0.018) in silver arm
Melotte 1985 (Melotte et al. 1985) Study design: Prospective case series Follow-up: 6 weeks Location: Belgium	Intervention: 1% silver sulfadiazine cream (Flammazine)	Population: 19 patients with leg ulcers (11 venous, 5 hypertensive, 2 arterial, 1 decubitus) with bacteriological infection GREEN Age (years, mean, range): 72.5 (47 – 89) Male gender n(%): 1 (5*) Subgroups: VLUs (n=11) Setting: NR	Infection resolution Pain	No information provided about the setting or reasons for the selection of these specific patients. Older study, thus may not be as generalisable to current wound-care practice, with limited outcome data. No statistical analysis was carried out

Study name and details	Intervention(s) and comparator(s)	Participants and setting	Outcomes	EAG comments
Molnlycke Health Care AB 2014 (NCT01036438) (NCT01036438 2009) Study design: RCT Follow-up: 8 weeks Location: Czech Republic, France, Germany and the Netherlands Analysis population: ITT	Intervention: Silver (absorbent foam silver dressing, Mepilex Ag, ITT n=100) Comparator: No agent (absorbent foam dressing, Mepilex without silver, ITT n=101)	Population: 201 patients with VLU or mixed leg ulcer with prior compression therapy, presenting with at least 3 signs of local infection. Silver (n=100), no agent (n=101) GREEN Age (years, mean, SD): Silver: 68.4 (13.4) No agent: 66.4 (14.9) Male gender n(%): Silver: 42 (42%) No agent: 47 (46.5%) Subgroups: NR Setting: Unclear, appears to be hospital	Change (%) in wound size Inflammation Adverse events	Results are only published with the NCT registry webpage, limited further information on study design or results available. 10 patients in silver arm (8 AEs, 1 death, 1 no treatment effect) and 10 patients in no agent arm (7 AEs, 3 no treatment effect) discontinued. Results are reported for all randomised patients (ITT), but no details on imputation are reported
Truchetet 2012 (Truchetet et al. 2012) Study design: Prospective case series	Intervention: Mepilex Ag	Population: Patients (n=794) with infected wounds including 534 with VLUs. GREEN	Wound and peri-wound skin assessment Infection Pain Satisfaction with dressing	Large sample size with concomitant diseases at baseline reported.

Study name and details	Intervention(s) and comparator(s)	Participants and setting	Outcomes	EAG comments
Follow up: Median 19 days (7 to 97) Location: France		Other wounds: pressure ulcers (n=32), diabetic foot ulcers (n=14), oncology (n=4) Acute wounds: traumatic (n=120), partial-thickness burns (n=60), surgical wounds (n=19), animal bites (n=212) Age (years, mean SD): 74 (10) Male gender n(%): 187* (35) Subgroups: VLUs Setting: Private outpatient	Performance of dressing	
Woolstencroft 2018 (Woolstencroft 2018) Study design: Single-arm trial Follow-up: 4 weeks Location: UK	Intervention: KerraContact Ag dressing with Ag Oxysalts	Population: Patients (n=31) with infected (apart from 4 patients at risk of infection) venous, arterial or mixed aetiology leg ulcers (diabetic n=2, rheumatoid arthritis n=2, VLUs n=26, unclear n=1). GREEN	Clinical signs of infection (exudate) Dressing changes Antibiotic use	Authors assumed that patients who were previously receiving additional compression therapy continue to do so during the study but this was not recorded 31 patients included in the study but demographic and outcome data is not

Study name and details	Intervention(s) and comparator(s)	Participants and setting	Outcomes	EAG comments
		Age (years, range (%): 30 (13.3) to 90 (13.3). Information only provided by 15/31 patients Male gender n(%): 9 (52.9). Information reported by 17/31 patients Subgroups: NR Setting: Secondary care (10 tissue viability clinics)		reported for all patients. Study reported the number of responses for each outcome instead Fifteen patients (48%) had been using a silver-containing dressing before entering the study, the most common being Aquacel Ag Extra (n=7, 46.6%). 2 patients (6.4%) had Flaminal and Silvercel applied. Wounds had been assessed at each dressing change and fully reassessed at 2 weeks of using silver, those wounds which had shown progression of healing but increase in infection continued to receive a silver regime
Harding 2016 (Harding et al. 2016) Study design: Prospective single-arm trial Follow-up: 8 weeks	Intervention: Aquacel Ag+ dressing Week 1-4, Aquacel wound dressings Week 5-8	Population: 42 VLU patients, including 10 patients with infections. GREEN	Wound healing Progression in wound condition (% change in ulcer area) AEs Antibiotic use	Many outcomes not reported separately for clinically infected subgroup.

Study name and details	Intervention(s) and comparator(s)	Participants and setting	Outcomes	EAG comments
Location: UK and Poland		Age (years, mean, SD): Clinically infected (n=10): 65.6 (13.3) Not clinically infected (n=32): 73.2 (11.9) Total (n=42): 71.4 (12.5) Male gender n(%): Clinically infected (n=10): 6 (60.0) Not clinically infected (n=32): 10 (31.3) Total (n=42): 16 (38.1) Subgroups: NR Setting: 6 study centres, unclear treatment setting		
Lantis 2011 (Lantis and Gendics 2011) Study design: Prospective single-arm trial Follow-up: 12 weeks Location: USA	Intervention: A non-adhesive silver sulphadiazine, polyurethane foam dressing (Allevyn Ag Non-Adhesive)	Population: 24 patients with infected VLU with a VLU bacterial count of >105 colony forming units (cfu/g) per gram of tissue GREEN Age (years, mean, SD):	Wound healing (% change in ulcer area, wound closure) Time to achieve closure Change (%) in clinical signs of infection Change in wound bed/peri-wound skin condition Wound recurrence	2 patients loss to follow-up (1 died, 1 withdrew) included in ITT analysis.

Study name and details	Intervention(s) and comparator(s)	Participants and setting	Outcomes	EAG comments
		59.8 (range: 37–82) Male gender n(%) : 15 (62.5%) Subgroups : NR Setting : Tertiary care wound practice	AEs Pain	
Vanscheidt 2003 (Vanscheidt et al. 2003) Study design : Prospective single-arm trial Follow-up : 28 days Location : France and Germany	Intervention : Aquacel Ag	Population : 18 subjects with chronic leg ulcers (majority venous or mixed aetiology) that had been present for a mean of 2.59 years (range 0.12–7.00) and were more than 2cm ² in size GREEN Age (years, mean, SD) : 78.2 (range 63.0–91.0) Male gender n(%) : 8 (44.4%)	AEs Dressing changes Resolution of infection Change (%) in wound area	The tables and figures for the article are unavailable, so much of the data could not be extracted. Very few outcomes are reported for infected ulcers separately

Study name and details	Intervention(s) and comparator(s)	Participants and setting	Outcomes	EAG comments
		Subgroups: Infected and non-infected. Infection, based purely on generally accepted clinical criteria, was present at baseline in 11 of 15 (73%) evaluable subjects. Setting: NR		
Jorgensen 2008 (Jorgensen et al. 2008) Study design: Prospective single-arm trial Follow-up: 31 days ($\pm$ 2 days) Location: Denmark and Canada	Intervention: Silver-releasing permeable wound contact layer (Physiotulle Ag) and a non-adhesive ibuprofen releasing foam (Biatain-Ibu Non-adhesive foam dressing)	Population: 24 patients with painful, exuding, locally infected, delayed healing, venous leg ulcers GREEN Age (years, mean, SD): 73.3(15.5) Male gender n(%): 17 (70.8%) Subgroups: NR Setting: Outpatient clinics at 4 centres	Pain Wound healing Clinical signs of infection AEs	Authors note that wound swabs were not taken, thus inter-centre reliability in identification of infection could not be verified.
Comparative studies of eligible agents (number of included studies = 4)				

Study name and details	Intervention(s) and comparator(s)	Participants and setting	Outcomes	EAG comments
Miller et al, 2010 (Miller et al. 2010) Associated records: Trial registration: (ACTRN12606000094572 2006) Paper reporting effect of adherence to compression bandaging: (Miller et al. 2011a) Paper reporting relationship of bacterial wound swab results and clinical observations (not reported by intervention arm): (Miller et al. 2011b) Study design: RCT Follow-up: 12 weeks (data collected at 2 week intervals up to 12 weeks or wound closure) Location: UK Analysis population: PP	Intervention: Ionic silver dressing (Acticoat (nanocrystalline silver) with compression bandaging (complete case analysis, n=133) Comparator: Cadexomer iodine dressing (Iodosorb (cadexomer iodine) with compression bandaging (complete case analysis, n=133)	Population: 281 people with lower leg ulcers (73.7% venous; remaining were of mixed aetiologies) at least 1 clinical sign of infection or critical colonization. GREEN Age (years, mean, SD): Silver: 79.35 (12.66) Iodine: 79.99 (10.90) Male gender n(%): Silver: 54.4*% Iodine: 38.3*% Subgroups: Wound age and wound size at recruitment Setting: 2 large community nursing services	Wound healing (% change in wound size) Rate of wound healing. Number of healed wounds (100% closure)	Non-ITT (complete case) analysis, though 94.6*% included and loss to follow-up similar in both arms Power calculation required sample size of 117 participants per group for reduction in wound size, which was achieved Some significant differences at baseline: Wounds in the silver arm significantly smaller than in iodine arm (p<0.05) Wounds in silver arm had significantly less granulation tissue (p value NR) To adjust for the differences in wound size, a baseline wound size was used as a covariate in all analyses where wound size was identified as having a significant

Study name and details	Intervention(s) and comparator(s)	Participants and setting	Outcomes	EAG comments
				relationship with the dependent variable Segmentation analysis reported for shorter vs longer duration wounds (wound duration at recruitment of less than or greater than 12 weeks) and small (<3.6 cm ²) vs large (> 3.6 cm ²) wounds
Molle 2023 (Molle et al. 2023) Design: Non-randomised clinical trial Follow-up: 30 Location: NR	Intervention: Honey (manuka honey-based dressings) Comparator: Silver (silver-based dressing)	Population: 50 people with infected venous ulcers. Manuka honey, n=25 Silver, n=25 GREEN Mean age: NR Male gender n(%): NR Subgroup: NR	Wound healing Clinical signs of infection	Conference abstract only, limited information reported

Study name and details	Intervention(s) and comparator(s)	Participants and setting	Outcomes	EAG comments
		Setting: NR		
Mosti et al, 2015 (Mosti et al. 2015) Study design: Pilot RCT Follow-up: 4 days Location: UK Analysis population: ITT	Intervention: Silver (Silver-containing hydrofiber, Aquacel Ag) Comparator: DACC (microorganism-binding, Cutimed Sorbact)	Population: 40 adults with critically colonised (multiplying bacteria causing delayed healing) or locally infected (multiplying bacteria with sign of local tissue damage) ulcers of vascular aetiology, duration ≥ 6 months and ankle brachial pressure index >0.6. Silver (n=20; venous 15, arterial 5), DACC (n=20; venous 15, arterial 5) GREEN Age (years, mean, SD): Silver: 69.7 (15.2) DACC: 69.4 (12.2) Male gender n(%): Silver: 7/20 (35%) DACC: 9/20 (45%) Subgroups: NR	Bacterial load Pain Pain medication Adverse events	Pilot study, no testing of statistical significance Short follow-up period, thus healing not reported Blinding of treatment not possible because both dressings can be distinguished by appearance

Study name and details	Intervention(s) and comparator(s)	Participants and setting	Outcomes	EAG comments
		Setting: Community nursing services		
Gago 2008 (Gago et al. 2008) Study design: Prospective cohort study Follow-up: 8 weeks Location: Spain	Intervention 1: Silver (Acticoat) Dressings were changed 3 times a week Intervention 2: Silver; Comfeel or Biatain Ag Intervention 3: Aquacel Ag	Population: Patients (n=75) with infected chronic leg ulcers GREEN Intervention 1: 14 leg ulcers, 5 pressure ulcers, 4 diabetic foot ulcers, 2 post-traumatic ulcers Intervention 2: 19 leg ulcers, 5 pressure ulcers, 0 diabetic foot ulcers) Intervention 3: 17 leg ulcers, 5 pressure ulcers, 2 diabetic foot ulcers, 1 post-traumatic ulcer Age (years, mean SD): Intervention 1: 68.56 (12.66) Intervention 2: 70.04 (10.69) Intervention 3: 64.48 (11.46) Male gender n(%): 30 (40)	Time to resolve all signs of local infections Time to total wound healing AEs	Power calculations were carried out and determined 24 patients were needed in each group to detect a minimum difference of 1.3 weeks in the time to resolve infection. From the description of the intervention groups it appears that patients were treated once with a silver dressing and then subsequently with a non-silver dressing. This may have an impact on the results in terms of determining causality between healing and silver

Study name and details	Intervention(s) and comparator(s)	Participants and setting	Outcomes	EAG comments
		Subgroups: NR Setting: Community health centre		

Key: AMD – Antimicrobial dressing; CEAP – Clinical, etiological, anatomical, and pathophysiological; DACC – Dialkylcarbamoyl chloride; DFU – Diabetic foot ulcer; EAG – External assessment group; IQR – Interquartile range; ITT – Intention-to-treat; LOCF – Last observation carried forward; NR – Not reported; OHP – Octenidine dihydrochloride/phenoxyethanol; PCMP – Polyhexamethylene biguanide antimicrobial; PHMB – Polyhexamethylene biguanide; PP – Per protocol; PUSH – Pressure ulcer scale for healing; RCT – Randomised controlled trial; SD – Standard deviation; SE – Standard error; UK – United Kingdom; USA – United States of America; VLU – Venous leg ulcer.

* - reviewer-calculated data

GREEN – study population fully met the decision problem

AMBER – study population partly met the decision problem

5 Clinical and technological evidence review

5.1 *Overview of methodology of included studies*

Study design

Studies that fully met the decision problem

21 studies that fully met the decision problem were identified. 10 were comparative, including 7 RCTs (Dimakakos et al. 2009, Humbert et al. 2006, Meaume et al. 2005, Miller et al. 2010, NCT01036438 2009, Mosti et al. 2015, Skog et al. 1983), 2 non-randomised controlled trials (Hammerle and Strohal 2016, Molle et al. 2023), and 1 prospective cohort study (Gago et al. 2008). 1 non-randomised controlled trial included 3 study arms, 1 of which comprised a mixed silver/no agent intervention with various dressing types that was considered ineligible; this study was therefore extracted and synthesised as a 2-arm study (Hammerle and Strohal 2016).

The other 11 studies were non-comparative, including 8 single-arm trials (Forlee et al. 2014, Harding et al. 2016, Jorgensen et al. 2008, Lantis and Gendics 2011, Manning et al. 2020, Vanscheidt et al. 2003, Yang K et al. 2015, Woolstencroft 2018) and 3 prospective case series (Degreef and Michiels 1984, Melotte et al. 1985, Truchetet et al. 2012).

Studies that partly met the decision problem

13 studies that partly met the decision problem were included that evaluated AMDs for which evidence was otherwise limited.

The review did not include evidence for all sub-agents, as screening and subsequent broadening of the population criteria were conducted at an “agent” rather than “sub-agent” level. No evidence that partly met the decision problem was included for silver, as sufficient evidence that fully met the decision problem had already been identified for studies of this AMD.

2 studies were comparative RCTs (Mo et al. 2015, Vallejo et al. 2022). The other 11 studies were non-comparative, including 3 single-arm trials (Melamed et al. 2021, Moghazy et al. 2010, Orig and Singleton 2016) and 8 prospective case series (Biglari et al. 2013, Bruce 2012, Dokic S et al. 2023, Durante 2012, Jones and Oates 2018, King and Rolland 2023, Koullias et al. 2022, Treadwell T et al. 2022).

Patients

The included studies categorised by antimicrobial agent and extent to which they met the review decision problem are summarised in Table 5.1.

Studies that fully met the decision problem

Of 7 RCTs 2 included patients with infected VLUs (Dimakakos et al. 2009, Skog et al. 1983), 3 included patients with lower leg ulcers of mixed aetiologies (most frequently venous and arterial) with signs of local infection (Humbert et al. 2006, Meaume et al. 2005, NCT01036438 2009) and 2 included patients with lower leg ulcers of mixed aetiology with signs of either infection or critical colonisation (Miller et al. 2010, Mosti et al. 2015).

Both non-randomised comparative studies included patients with infected VLUs (Molle et al. 2023), with 1 study assessing a mixed population of infected and non-infected ulcers for which results were reported separately (Hammerle and Strohal 2016). The prospective cohort study included patients with infected lower leg ulcers including VLUs, DFUs and traumatic wounds, of which >80% were infected VLUs (Gago et al. 2008).

Of the 8 single-arm trials, 4 included patients with infected VLUs (Forlee et al. 2014, Jorgensen et al. 2008, Lantis and Gendics 2011, Yang K et al. 2015) and 1 included patients with infected leg ulcers of mixed aetiology (venous, arterial or mixed) (Woolstencroft 2018). 2 single-arm trials included patients with infected and non-infected lower-leg ulcers (VLU and/or mixed aetiology), reporting results separately for the infected population (Harding et al. 2016, Vanscheidt et al. 2003), and 1

included patients with infected wounds of various types including a subgroup VLU patients for whom results were reported separately (Manning et al. 2020).

Of the 3 case series, 2 included patients with infected leg ulcers of mixed aetiology (generally venous, arterial or multiple-aetiology) (Degreef and Michiels 1984, Melotte et al. 1985) and 1 included patients with infected wounds of various types including a subgroup of those with VLUs for whom results were reported separately.

Studies that partly met the decision problem

13 studies that partly met the decision problem were included which evaluated AMDs for which evidence was otherwise limited.

9 studies assessed patients with infected wounds of other kinds:

- Honey: 2 studies including 1 single-arm trial in patients with infected DFUs (Moghazy et al. 2010) and 1 prospective case series in patients with infected wounds of various aetiologies and locations (Biglari et al. 2013).
- DACC: 1 prospective case series in patients with wounds mostly on the lower leg with mixed venous, arterial and traumatic aetiologies (Bruce 2012).
- Enzyme Alginogel: 3 prospective case series in patients with mixed wound types and mixed non-infected/infected wounds (with some results reported separately for those with infections) (Durante 2012, Jones and Oates 2018, King and Rolland 2023).
- Chitosan: 2 studies including 1 RCT (comparing to no agent) in patients with infected wounds of various kinds (Mo et al. 2015) and 1 single-arm trial in patients with infected wounds of various types (Orig and Singleton 2016).

6 studies were included in patients with lower-leg ulcers that were not infected or mixed infected/non-infected:

- PHMB: 2 studies including 1 RCT (comparing to no agent) in patients with non-infected venous and/or arterial leg ulcers (Vallejo et al. 2022) and 1 prospective case series in patients with non-infected VLUs (Koullias et al. 2022).

Copper: 3 studies including 1 single-arm trial in patients with non-infected DFUs (Melamed et al. 2021) and 2 prospective case series in patients with mixed infected/non-infected lower-leg and foot ulcers (Dokic S et al. 2023, Treadwell T et al. 2022).

Table 5.1: Alignment of the evidence base with the decision problem

Alignment with decision problem	Chitosan	Copper	DACC	Enzyme Alginogel	Honey	Iodine	Octenidine	PHMB	Silver
Infected lower leg ulcers (fully met the decision problem)	-	-	(Mosti et al. 2015) Green	-	(Molle et al. 2023, Yang K et al. 2015) Green	(Miller et al. 2010, Skog et al. 1983) Green	(Hammerle and Strohal 2016) Green	-	4 studies comparing 1 or more eligible interventions (Miller et al. 2010, Mosti et al. 2015, Molle et al. 2023, Gago et al. 2008) 14 additional studies (Dimakakos et al. 2009, Degreef and Michiels 1984, Forlee et al. 2014, Humbert et al. 2006, Manning et al. 2020, Meaume et al. 2005, Melotte et al. 1985, NCT01036438 2009, Truchetet et al. 2012, Woolstencroft 2018, Harding et al. 2016, Lantis and Gendics 2011, Vanscheidt et al. 2003, Jorgensen et al. 2008) Green

Alignment with decision problem	Chitosan	Copper	DACC	Enzyme Alginogel	Honey	Iodine	Octenidine	PHMB	Silver
Infected wounds on the lower limb (foot or mixed leg/foot)	-	-	-	-	(Moghazy et al. 2010) Yellow	-	-	-	-
Infected wounds elsewhere on body (including mixed lower limb/elsewhere)	(Orig and Singleton 2016, Mo et al. 2015) Yellow	-	(Bruce 2012) Yellow	(Jones and Oates 2018, King and Rolland 2023, Durante 2012) Yellow	(Biglari et al. 2013) Yellow	-	-	-	-
Non-infected / infection status unclear lower leg ulcers	-	-	-	-	-	-	-	(Vallejo et al. 2022, Koullias et al. 2022) Orange	-

Alignment with decision problem	Chitosan	Copper	DACC	Enzyme Alginogel	Honey	Iodine	Octenidine	PHMB	Silver
Non-infected (or unclear infection status) wounds on the foot or elsewhere (or mixed lower-leg with foot/elsewhere ulcers).	-	(Dokic S et al. 2023, Melamed et al. 2021, Treadwell T et al. 2022) Orange	-	-	-	-	-	-	-

Key: DACC – Dialkylcarbamoyl chloride; PHMB – Polyhexamethylene biguanide.

Green cells indicate studies that fully met the decision problem. **Yellow** and **Orange** cells indicate studies that partly met the decision problem but still included infected wounds, studies in orange cells partly met the decision problem but with queries over infection status

Interventions and comparators

Study dressings were categorised according to the sub-agent (where applicable) and dressing type, as listed in Table 2.1 and Table 2.2. Wound bed preparation protocols and secondary dressings (e.g. compression bandaging) varied across studies. A summary of the evidence for each sub-agent is presented in Table 5.2, with full intervention characteristics presented in Appendix C, Section 11.3.1. No studies evaluating chlorhexidine were identified. The EAG notes that a some of the included AMDs may no longer be available (such as Aquacel Ag).

Studies that fully met the decision problem

Of the 21 studies that fully met the decision problem, 10 were comparative. 4 compared different eligible AMDs including:

- 1 RCT that compared Acticoat/Acticoat 7 and Acticoat Absorbent ionic silver (polyethylene barrier dressing and alginate dressing type respectively, dressing category: mixed wound contact layer, gauze and alginate, gelling fibre, absorbent fibre) to cadexomer iodine Iodosorb (ointment or powder dressing, dressing category: ointments, gels, hydrogels), both with compression bandaging (wound bed preparation NR) (Miller et al. 2010).
- 1 pilot RCT that compared ionic silver Aquacel Ag (Hydrofiber, dressing category: alginate, gelling fibre, absorbent fibre) to DACC Cutimed Sorbact (dressing category wound contact layer, gauze) following sharp debridement and cleansing solution (secondary dressings NR) (Mosti et al. 2015).
- 1 non-randomised comparative study that compared manuka honey (unclear dressing category) silver (unclear sub-agent type and dressing category) dressings (wound bed preparation and secondary dressings NR) (Molle et al. 2023).
- 1 prospective cohort study that compared ionic silver Aquacel Ag (Hydrofiber, dressing category: “alginate, gelling fibre, absorbent fibre”) to Acticoat ionic

silver (polyethylene barrier dressing, dressing category: wound contact layer, gauze) with secondary foam dressing; wound bed preparation and other secondary dressings were not reported (Gago et al. 2008).

The other 6 RCTs compared AMD dressings to non-AMD dressings:

- 2 RCTs comparing ionic silver Biatain Ag foam dressing (dressing category: foam, absorbent pads) to:
 - Biatain non-adhesive foam (dressing category: foams, absorbent pads); both arms received cleansing with saline and 10% iodine solution, and compression (Dimakakos et al. 2009).
 - Algosteril calcium alginate fibre (dressing category: alginate, gelling fibre, absorbent fibre); both arms received saline cleansing, and compression was applied if indicated (Humbert et al. 2006).
- 1 RCT comparing metallic silver Silvercel hydro-alginate to Algosteril calcium alginate fibre (both dressing category: alginate, gelling fibre, absorbent fibre), both after removal of necrotic plaque by mechanical or surgical debridement and saline cleansing with secondary dressing pads (Meaume et al. 2005).
- 1 RCT comparing silver sulphate Mepilex Ag foam dressing to Mepilex foam dressing (both dressing category: foams, absorbent pads); both arms received sharp debridement where indicated and wound cleansing with Ringer's solution (details of secondary dressings NR) (NCT01036438 2009).
- 1 RCT comparing cadexomer iodine Iodosorb powder (dressing category: ointments, gels, hydrogels) to standard treatment including paraffin-impregnated dressings, saline dressings and bland ointments; wounds in both arms were cleansed with running water and received compression bandaging (Skog et al. 1983).
- 1 non-randomised trial compared two octenillín gel arms against a third arm including different forms of wound preparation and secondary dressing. The two octenillín gel arms (dressing category: ointments, gels, hydrogels) were

gel with secondary foam or alginate, and gel with suction gauze following cleansing with sodium chloride (or Octenisept irrigation if locally infected) (Hammerle and Strohal 2016). While the study does not provide comparative data for two different AMDs, both octenillan arms are extracted as eligible single arms.

The other 11 studies that fully met the decision problem were single-arm in design, including 10 studies evaluating silver dressings. 7 were single-arm trials, of which:

- 1 evaluated silver sulphadiazine (1 Physiotulle Ag, dressing category: wound contact layer (Jorgensen et al. 2008).
- 1 Allevyn Ag foam dressing, dressing category: foams, absorbent pads (Lantis and Gendics 2011)).
- 1 evaluated ionic silver with antibiofilm (1 Aquacel Ag+, dressing category: alginate, gelling fibre, absorbent fibre) (Harding et al. 2016, Vanscheidt et al. 2003))
- 1 evaluated ionic silver (DURAFIBRE Ag, dressing category: alginate, gelling fibre, absorbent fibre (Forlee et al. 2014)).
- 1 evaluated silver oxysalt (KerraContact Ag, dressing category: alginate, gelling fibre, absorbent fibre (Woolstencroft 2018)).
- 1 evaluated a silver AMD (metallic and ionic silver) of uncertain dressing category (Microlyte Ag matrix (Manning et al. 2020)).

Compression was applied for all patients in 3 single-arm trials (Jorgensen et al. 2008, Lantis and Gendics 2011, Harding et al. 2016) and only where required in 2 trials (Vanscheidt et al. 2003, Forlee et al. 2014); 1 trial used unspecified secondary dressings for all patients (Manning et al. 2020) and 1 did not report details of secondary dressings (Woolstencroft 2018). Debridement and/or saline cleansing were applied as required in 5 trials (Jorgensen et al. 2008, Manning et al. 2020,

Forlee et al. 2014, Woolstencroft 2018, Lantis and Gendics 2011); the other 2 trials did not report details of wound bed preparation (Harding et al. 2016, Vanscheidt et al. 2003).

3 further silver single-arm studies were prospective case series, of which 2 evaluated 1% silver sulphadiazine cream (dressing category: ointments, gels, hydrogels) with secondary sterile bandaging (wound bed preparation NR) (Degreef and Michiels 1984, Melotte et al. 1985) and 1 evaluated silver sulphate Mepilex Ag foam (dressing category: foams, absorbent pads; wound preparation and secondary dressings NR) (Truchetet et al. 2012).

The remaining single-arm study evaluated other AMDs:

- Honey: 1 single-arm trial evaluated a manuka topical medical honey (dressing type: ointments, gels, hydrogels) with compression wrap following wound debridement (Yang K et al. 2015).

Studies that partly met the decision problem

The 13 studies that partly met the decision problem population criteria evaluated various AMDs:

- PHMB: 2 studies including:
 - 1 RCT that compared a PHMB dressings of various types (including AMD foam, PHMB gel or Kerlix gauze) to various non-medicated dressings of a similar type (both arms dressing category: mixed). Both arms received ultrasonic debridement at first dressing application, after which the PHMB arm received a 15 minute application of PHMB-soaked gauze and the control arm received irrigation with clean water or saline solution. Secondary absorbent pads were applied if required (Vallejo et al. 2022).
 - 1 prospective case series evaluated a collagen matrix with PHMB barrier (considered as unclear dressing categorization). No details of wound bed preparation or secondary dressings were reported (Koullias et al. 2022).

- Chitosan: 2 studies evaluating KytoCel (dressing category: alginate, gelling fibre, absorbent fibre), including 1 RCT that compared KytoCel to non-AMD gauze after saline irrigation in both groups (dressing category: wound contact layer, gauze; details of secondary dressings were not reported) (Mo et al. 2015) and 1 prospective case series in which various secondary dressings including foams and absorbent or surgical pads were used (details of wound bed preparation were not reported) (Orig and Singleton 2016).
- Honey: 2 studies including:
 - 1 single-arm trial which evaluated honey-soaked gauze (reported as “clover honey” and therefore considered monofloral honey, dressing category: wound contact layer, gauze) after debridement and saline irrigation with secondary “fluffy” (as described by study authors) dressing and bandaging (Moghazy et al. 2010).
 - 1 prospective case series which evaluated topical MediHoney or MediHoney wound gel (manuka honey, dressing category: ointment, gels, hydrogels). Different centres conducted their own treatment protocol but were advised to irrigate wounds with saline solution and apply Cavilon cream. Secondary dressings varied across centres and included alginate, hydrofiber and gauze (Biglari et al. 2013).
- Enzyme Alginogel: 3 prospective case series evaluated Flaminal gel (dressing category: ointments, gels, hydrogels) (Durante 2012, Jones and Oates 2018, King and Rolland 2023). Details of wound preparation and secondary dressings were reported by 1 of these case series, in which wounds were cleansed with polyhexanide solution and secondary bandaging consisted of foam or gauze (Durante 2012).
- Copper: 3 studies including 1 single-arm trial which evaluated agent subtype cupric oxide (barrier dressing, dressing category: wound contact layer, gauze) (Melamed et al. 2021) and 2 prospective case series evaluating copper dressings of uncertain subtype and dressing categorization (Dokic S et al. 2023, Treadwell T et al. 2022). Of these studies 1 case series reported details of wound preparation and secondary dressings, in which wounds were

debrided and secondary dressings were used depending on diagnosis (Treadwell T et al. 2022).

- DACC: 1 prospective case series evaluated Cutimed Sorbact (dressing category: wound contact layer, gauze) followed by secondary dressing of clinician choosing, including retention, tubular and compression bandages. No details of wound preparation were reported (Bruce 2012).

No studies that partly met the decision problem that evaluated chlorhexidine dressings were identified.

Setting

The scope specified that patients in primary and community care settings in the UK were eligible, though in the absence of such evidence patients in broader settings were also eligible. Included studies were conducted across a range of countries and varied in setting.

Studies that fully met the decision problem

The 18 silver studies (including 4 studies comparing 2 or more eligible AMDs) varied in country and setting. 3 of the 6 silver RCTs were conducted in the UK, of which 2 were conducted in a community nursing service (Mosti et al. 2015, Miller et al. 2010) and 1 was conducted in a hospital setting (Meaume et al. 2005). In 1 French RCT, most patients (72.5% to 85%) were treated in an outpatient setting (Humbert et al. 2006). The remaining 2 RCTs were conducted in several European locations in unclear treatment settings (1 in Greece (Dimakakos et al. 2009), 1 in the Czech Republic, France, Germany and the Netherlands in unclear treatment settings (NCT01036438 2009)).

The prospective cohort study was conducted in a Spanish community health centre (Gago et al. 2008) and the non-randomised comparative study was conducted in an unclear location and setting (Molle et al. 2023).

Of 7 silver single-arm trials, 2 were conducted in the UK: 1 in secondary care settings (10 tissue viability centres) (Woolstencroft 2018) and 1 in unclear treatment settings partly in UK, with some study locations also in Poland (Harding et al. 2016). 4 were conducted in other locations:

- 1 conducted in Danish and Canadian outpatient clinics (Jorgensen et al. 2008).
- 3 conducted in secondary care settings (2 US (Manning et al. 2020, Lantis and Gendics 2011), 1 South Africa (Forlee et al. 2014)).
- 1 conducted in unclear settings in France and Germany (Vanscheidt et al. 2003).

The 3 prospective case series were conducted in non-UK settings, 2 in Belgium (1 in a hospital setting (Degreeef and Michiels 1984) and 1 in an unclear setting (Melotte et al. 1985)) and 1 in France (in an outpatient setting).

The studies that fully met the decision problem that evaluated other agents were conducted in non-UK, non-primary care settings:

- Iodine: 1 RCT conducted in Sweden in mixed home (visiting nurse) or hospital settings (Skog et al. 1983).
- Octenidine: 1 non-randomised trial in an Austrian secondary care centre (Hammerle and Strohal 2016).

Studies that partly met the decision problem

The 13 studies that partly met the decision problem also varied in location and setting of study:

- Chitosan: 2 studies conducted in hospital settings including 1 RCT in China (Mo et al. 2015)) and 1 single-arm trial in the UK (Orig and Singleton 2016).

- Honey: 1 single-arm trial conducted in an Egyptian outpatient care setting (following hospital admission) (Moghazy et al. 2010) and 1 case series in German and Austrian hospital settings (Biglari et al. 2013).
- PHMB: 1 RCT conducted in an Australian community wound clinic setting (Vallejo et al. 2022) and 1 prospective case series conducted in the USA in unclear treatment settings (Koullias et al. 2022).
- Copper: 1 single-arm trial conducted in an outpatient clinic setting in Israel (Melamed et al. 2021). 2 prospective case series, 1 conducted in a Slovenian hospital setting (Dokic S et al. 2023) and 1 in an unclear setting in the US (Treadwell T et al. 2022).
- DACC: 1 prospective case series conducted in a mixed setting of 4 community centres and 2 acute hospitals in the UK and Ireland (Bruce 2012).
- Enzyme Alginogel: Of 3 prospective case series 2 were conducted in UK community care settings (data were surveyed from district nurses) (Jones and Oates 2018, King and Rolland 2023) and 1 was conducted in Italy in a mixed treatment setting (hospital dressings were followed by at-home continuation) (Durante 2012).

Table 5.2: Available evidence for each sub-agent or agent

Agent/sub-agent	Comparative evidence	Single arm evidence
Silver		
Ionic silver with antibiofilm agents	None	1 single arm trial (4 weeks, followed by 4 weeks with non-antimicrobial dressing) (Harding et al. 2016)
Ionic silver	2 RCTs (Miller et al. 2010, Mosti et al. 2015), 1 prospective cohort study (Gago et al. 2008)	2 single arm trials (Vanscheidt et al. 2003, Forlee et al. 2014)
Ionic silver complex	2 RCTs (Dimakakos et al. 2009, Humbert et al. 2006) and 1 prospective cohort study (Gago et al. 2008)	None
Silver sulphate	1 RCT (NCT01036438 2009)	None
Silver sulphadiazine	None	2 single arm trials (Jorgensen et al. 2008, Lantis and Gendics 2011) and 2 prospective case series (Melotte et al. 1985) (Degreef and Michiels 1984)
Metallic/elemental silver	1 RCT (Meaume et al. 2005)	None
Silver oxysalts	None	1 single arm trial (Woolstencroft 2018)
Nanoparticulate silver	None	None
Insufficient information reported to determine silver type	1 non-randomised comparative trial (Molle et al. 2023)	1 single arm trial (metallic and ionic silver) (Manning et al. 2020)
Iodine		
Cadexomer iodine	2 RCTs (Skog et al. 1983, Miller et al. 2010)	None
Povidone iodine	None	None
Octenidine		
Octenidine	1 non-randomised comparative study (Hammerle and Strohal 2016)	None
Honey		
Manuka	1 non-randomised trial (Molle et al. 2023)	1 single arm trial (Yang K et al. 2015) and 1 prospective case series (Biglari et al. 2013)
Monofloral	None	1 single arm trial (Moghazy et al. 2010)
Polyfloral	None	None
Enzyme Alginogel		

Enzyme Alginogel	None	3 prospective case series (Durante 2012, Jones and Oates 2018, King and Rolland 2023)
Chitosan		
Chitosan	1 RCT (Mo et al. 2015)	1 single-arm trial(Orig and Singleton 2016)
Copper		
Cupric oxide	None	1 single-arm trial (Melamed et al. 2021) and 2 prospective case series (Dokic S et al. 2023, Treadwell T et al. 2022)
DACC		
DACC	1 RCT (Mosti et al. 2015)	1 prospective case series (Bruce 2012)
PHMB		
PHMB	1 RCT (Vallejo et al. 2022)	1 prospective case series (Koullias et al. 2022)

Key: AMD – Antimicrobial dressing; DACC - Dialkylcarbonyl chloride; NR – Not reported; PHMB - Polyhexamethylene biguanide; RCT – Randomised controlled trial.

5.2 *Risk of bias assessment of studies*

The following section summarises the formal risk of bias assessment for the 21 studies that fully met the decision problem. Full details of each risk of bias assessment are reported in Appendix C. For the 13 studies that partly met the decision problem, no formal risk of bias assessment was conducted.

No studies that fully met the decision problem were identified for chitosan, copper, enzyme alginogel, or PHMB. No studies either fully or partly aligned with the decision problem were identified for chlorhexidine.

All but 4 of the 21 studies that fully met the decision problem (1 RCT (Miller et al. 2010) and 3 single-arm studies (Harding et al. 2016, Lantis and Gendics 2011, Vanscheidt et al. 2003)) were judged to have a moderate or high risk of bias.

Of the 7 RCTs that fully met the decision problem, 1 (Miller et al. 2010) was judged to be at a low risk of bias. 3 RCTs had a moderate risk of bias, due to a lack of reporting of allocation generation and concealment (Dimakakos et al. 2009, Meaume et al. 2005, Humbert et al. 2006). 3 RCTs had a high risk of bias (Mosti et al. 2015, NCT01036438 2009, Skog et al. 1983), due to short follow up (Mosti et al. 2015), a heterogenous control arm (Skog et al. 1983), exclusion of patients from statistical analysis (Skog et al. 1983), and inadequate of reporting of methods and outcomes (NCT01036438 2009).

2 of the 3 non-randomised comparative studies were at a moderate risk of bias due to baseline imbalance between groups (Gago et al. 2008) and possibility of confounding factors which were not controlled for (Hammerle and Strohal 2016). The final non-randomised comparative study had a high risk of bias due to very limited reporting (Molle et al. 2023).

Of the 12 single-arm studies and case series that fully met the decision problem, 3 had a low risk of bias (Harding et al. 2016, Lantis and Gendics 2011, Vanscheidt et al. 2003). 6 had a moderate risk of bias, due to incomplete inclusion of participants and a lack of outcome reporting for the full population (Biglari et al. 2013, Jorgensen

et al. 2008, Manning et al. 2020, Forlee et al. 2014, Truchetet et al. 2012) and a lack of reporting of methods (Truchetet et al. 2012), including details of the statistical analysis methods used (Woolstencroft 2018). 2 prospective case series had a high risk of bias, largely due to poor or unclear reporting (Degreef and Michiels 1984, Melotte et al. 1985).

Only 2 studies, both RCTs (NCT01036438 2009, Vallejo et al. 2022), explicitly reported that outcome assessors were blinded to treatment / the AMD used. As wound healing is a subjective outcome, the lack of blinding employed by the majority of studies may have influenced the outcomes recorded.

5.3 *Generalisability of the evidence base*

The EAG had several concerns regarding the generalisability of the 34 included studies to the use of AMDs to treat infected leg ulcers in the UK NHS setting. These were:

- 13 studies evaluated patient populations or interventions that were broader in scope than the NICE decision problem (see Table 5.1). This was particularly with regards to the study populations, with many studies including infected wounds other than lower leg ulcers, wounds in locations other than the leg, and non-infected wounds. Treatment outcomes may therefore not be fully generalisable to a population with infected lower leg ulcers. This issue is particularly relevant to chitosan, copper, enzyme alginogel, and PHMB, for which agents no studies that fully met the decision problem were identified.
- 31 included studies were published between 2003 and 2023, with 3 studies published between 1983 and 1985 (Skog et al. 1983, Degreef and Michiels 1984, Melotte et al. 1985). The breadth of dates across which the studies were conducted may limit the applicability of their findings to current care, particularly for the 3 studies published in the 1980s (changes in care since this time include Doppler ultrasound diagnosis, development of modern

dressing materials and advances in compression bandaging)(Moffat et al. 2004).

- A minority of the included evidence was from the UK (8 of 34 studies were conducted at least in part in the UK (Bruce 2012, Jones and Oates 2018, King and Rolland 2023, Meaume et al. 2005, Miller et al. 2010, Mosti et al. 2015, Woolstencroft 2018) (Harding et al. 2016)). Most studies were conducted outside of the UK (23 studies), although 3 studies did not explicitly report where they were conducted (Orig and Singleton 2016, Skog et al. 1983, Molle et al. 2023). The nature of standard care and care settings may be less generalisable to the UK NHS; this is particularly true for studies located outside Europe and Canada.
- The evidence base included studies assessing care provided in inpatient, outpatient, home, and community care settings. Variation in study settings and wound types means that it was difficult to generalise outcomes to the scenario detailed in the scope.
- A lack of reporting meant that for some studies, it was difficult to ascertain their setting and the specific dressing(s) assessed.
- Wounds were not always reported to be clinically assessed as “infected”, with some studies instead describing the presence of a range of signs of infection. Where wounds were explicitly reported to be infected, the criteria used by assessors for making this judgement were often unreported.
- The reporting of concomitant care was poor and inconsistent, so the EAG cannot be certain that the care received by patients in the included studies is reflective of that offered as standard by the UK NHS.
- Wound bed preparation and secondary dressing treatment protocols varied across studies and were often not clearly reported, which introduces uncertainty when generalising to use in the NHS.

5.4 *Synthesis of evidence*

Of the 34 studies included in the review, 11 provided comparative evidence (Dimakakos et al. 2009, Gago et al. 2008, Humbert et al. 2006, Meaume et al. 2005, Miller et al. 2010, Mo et al. 2015, Molle et al. 2023, NCT01036438 2009, Mosti et al. 2015, Skog et al. 1983, Vallejo et al. 2022) while 23 provided single-arm evidence (Biglari et al. 2013, Bruce 2012, Degreeef and Michiels 1984, Dokic S et al. 2023, Durante 2012, Jones and Oates 2018, King and Rolland 2023, Forlee et al. 2014, Harding et al. 2016, Jorgensen et al. 2008, Koullias et al. 2022, Lantis and Gendics 2011, Manning et al. 2020, Melamed et al. 2021, Melotte et al. 1985, Moghazy et al. 2010, Orig and Singleton 2016, Treadwell T et al. 2022, Truchetet et al. 2012, Vanscheidt et al. 2003, Woolstencroft 2018, Yang K et al. 2015, Hammerle and Strohal 2016). 9 of the 11 comparative studies fully met the decision problem, and 2 partly met the decision problem due to including patients with a mix of infected and non-infected leg ulcers (Vallejo et al. 2022) or assessing infected wounds in various locations on the body (Mo et al. 2015). 12 of the 23 single-arm studies fully met the decision problem, while 11 partly met it.

5.4.1 *Wound healing, complete*

Detailed narrative summaries are provided in Section 11.6.3.2 (complete healing) and Section 11.6.3.3 (partial healing). Full outcome data are presented in Appendix A, Section 11.7.1.

5.4.1.1 Comparative studies

Table 5.3: Comparative studies: complete healing by sub-agent

	Non-antimicrobial dressing	Ionic silver	Cadexomer iodine	Manuka honey
Ionic silver complex	Favours ionic silver complex: Dimakakos, 2009 ^{StatSig}	Favours ionic silver: Gago, 2008 ^{StatSig}	-	-
Metallic / elemental silver	Favours metallic/elemental silver: Meaume, 2005	-	-	-
Ionic silver	-	-	No difference: Miller, 2010 ^{StatSig}	-
Silver (further details NR)	-	-	-	Favours silver: Molle, 2023
Chitosan (further details NR)	Favours chitosan: Mo, 2015	-	-	-
PHMB (further details NR)	No difference: Vallejo, 2022	-	-	-

Key: PHMB – Polyhexamethylene biguanide; NR – Not reported.

Underlined studies fully met the decision problem

Studies with no underline partly met the decision problem.

StatSig indicates that the study reported this finding to be statistically significant

7 comparative studies reported complete healing outcomes, of which 5 fully met the decision problem (Dimakakos et al. 2009, Miller et al. 2010, Meaume et al. 2005, Molle et al. 2023, Gago et al. 2008) and 2 partly met the decision problem (Mo et al. 2015, Vallejo et al. 2022). A summary of effect direction and significance is provided in Table 5.3. Outcomes were reported at timepoints between 4 and 12 weeks.

4 studies compared silver (Dimakakos et al. 2009, Meaume et al. 2005), chitosan (Mo et al. 2015) or PHMB (Vallejo et al. 2022) to non-antimicrobial dressings. Of the silver studies, 1 reported a statistically significantly higher complete healing rate for ionic silver complex compared to non-antimicrobial dressings (n=42 (Dimakakos et al. 2009)) and 1 reported no difference between metallic/elemental silver and non-antimicrobial dressings (n=99 (Meaume et al. 2005)). Studies evaluating chitosan

(n=69) and PHMB (n=50) partly met the decision problem and reported improved healing and similar healing respectively; statistical significance was not reported for either study.

2 studies compared silver to other agents, 1 to iodine (n=266) (Miller et al. 2010) and 1 to honey (n=50) (Molle et al. 2023). Silver was not statistically significantly different to iodine in extent of healing, and appeared numerically superior to honey, though the difference against honey was not tested for statistical significance.

1 study compared 2 arms with ionic silver dressings (Acticoat and Aquacel Ag) and 1 arm with mixed ionic silver complex dressings (Comfeel hydrocolloid/Biatain Ag foam) (n=25 in each arm) (Gago et al. 2008), finding statistically faster complete healing with Acticoat ionic silver compared to ionic silver Aquacel Ag and ionic silver complex Comfeel/Biatain Ag.

5.4.1.2 *Single-arm studies*

7 silver studies that fully met the decision problem reported the proportion of ulcers completely healed at disparate timepoints and using disparate measurement methods. Table 5.4 summarises their findings by sub-agent.

Studies evaluated few patients (≥ 30) with the exception of the silver sulphate study that reported at a single timepoint. Findings varied widely between studies, including between the 3 studies evaluating the same sub-agent (silver sulphadiazine). At 4 weeks, the highest proportion of patients healed was reported in the silver sulphadiazine study and the lowest proportion in the silver oxysalts and ionic silver studies. At 8 weeks, these results appeared reversed with the highest proportion reported for ionic silver, and lower rates for silver sulphadiazine. Ionic silver plus antibiofilm for 4 weeks followed by non-antimicrobial dressing for 4 weeks reported the lowest rate at this timepoint.

Table 5.4: Single arm studies: complete healing, silver AMDs by sub-agent

	Ionic silver ^a	4 week with ionic silver +antibiofilm, then 4 weeks with non-antimicrobial ^b	Silver sulphadiazine ^{c,d,e}	Silver oxysalts ^f	Silver sulphate ^g
1-2 weeks	0 (0/14)	-	3.4% (1/29) ^c 0 (0/24) ^d	-	-
3-4 weeks	Week 3: 7.1% (1/14) Week 4: 21.4% (3/14)		Week 3: 4.2% (1/24) ^d Week 4: 57.9% (11/19) ^e	6.7%* (2/30)	9.8% (52/534*)
5-6 weeks	28.6% (4/14)	-	-	-	-
7-8 weeks	Week 7: 35.7% (5/14) Week 8: 50.0% (7/14)	10% (1/10)	29.2% (7/24) ^d	-	-
9-10 weeks	-	-	-	-	-
11-12 weeks	-	-	45.8% (11/24) ^d	-	-
> 12 weeks	-	-	-	-	-

Table 5.4: PHMB - Polyhexamethylene biguanide.

^a (Forlee et al. 2014); ^b (Harding et al. 2016); ^c (Degreef and Michiels 1984); ^d (Lantis and Gendics 2011); ^e (Melotte et al. 1985); ^f (Woolstencroft 2018); ^g (Truchetet et al. 2012)

* reviewer calculated

Table 5.5 summarises complete wound healing by agent or sub-agent (where applicable) for the 7 studies partially meeting the decision problem. Findings were reported at disparate timepoints, using disparate measurement methods and varied widely, with ranges for each timepoint overlapping considerably. Studies were generally small, and 6 studies did not assess the statistical significance of changes from baseline.

At 4 weeks, the most complete healing was reported by the enzyme alginogel study and the lowest by chitosan. At 8 weeks this finding was maintained (no further

timepoints reported for enzyme alginogel). At 12 weeks 100% healing was achieved for copper (the smallest study with only 12 patients), with lowest healing reported by the monofloral honey study. Statistical significance of findings was reported by 1 study, finding that significantly more patients receiving PHMB had healed wounds at 4 weeks (9%), 16 weeks (45.4%) and 32 weeks (72.4%) when compared to baseline (Koullias et al. 2022).

Table 5.5: Single-arm studies: complete healing, non-silver AMDs by agent/sub-agent

	Enzyme alginogel	PHMB ^b	Chitosan	Monofloral honey ^d	Manuka honey ^e	Cupric oxide ^{f,g}
1-2 weeks	4.3% (1/23)	-	20.0% (4/20)	-	-	32% (8/25) ^f
3-4 weeks	30.4% (7/23)	9% (6/67) ^{StatSig}	4.2% (1/24)	13.3% (4/30)	-	-
5-6 weeks	-	-	-	13.3% (4/30)	31.4% (32/101)	-
7-8 weeks	52.2% (12/23)	33.1% (33/67)*	29.2% (7/24)	-	-	-
9-10 weeks	-	-	-	-	-	-
11-12 weeks	-	41.8% (28/67)	45.8% (11/24)	16.7% (5/30)	-	100% (12/12) ^g
> 12 weeks	-	16 weeks: 45.4% (30/67) ^{StatSig} 24 weeks: 53.1% (36/67) 32 weeks: 72.4% (49/67) ^{StatSig}	-	-	-	-

Key: PHMB – Polyhexamethylene biguanide.

^a (Durante 2012); ^b (Koullias et al. 2022); ^c (Orig and Singleton 2016); ^d (Moghazy et al. 2010); ^e (Biglari et al. 2013); ^f (Treadwell T et al. 2022); ^g (Dokic S et al. 2023)

^{StatSig} indicates that the study reported a statistically significant difference from baseline

*reviewer-calculated

5.4.2 Wound healing, partial

5.4.2.1 Comparative studies

3 studies reported partial healing of which 1 fully met the decision problem (metallic silver (Meaume et al. 2005)) and 2 partly met the decision problem (chitosan (Mo et al. 2015)); PHMB (Vallejo et al. 2022)). All compared antimicrobial dressings with non-antimicrobial dressings. A summary of effect direction and significance is provided in Table 5.6. Outcomes were reported at timepoints between 4 and 12 weeks. 1 study reported greater partial healing in the chitosan arm, though did not test for statistical significance (n=69 (Mo et al. 2015)). The studies evaluating metallic silver (n=99 (Meaume et al. 2005)) and PHMB (n=50 (Vallejo et al. 2022)) tested statistical significance and reported no difference between their respective interventions and non-antimicrobial dressings.

Table 5.6: Comparative studies: partial healing by agent and sub-agent

	Non-antimicrobial dressing
Metallic / elemental silver	No difference: Meaume, 2005
Chitosan (further details NR)	Favours chitosan: Mo, 2015
PHMB (further details NR)	No difference: Vallejo, 2022

Key: NR – Not reported; PHMB – Polyhexamethylene biguanide.

Underlined studies fully met the decision problem

Studies with no underline partly met the decision problem

5.4.2.2 Single arm studies

4 silver studies that fully met the decision problem reported partial healing or wound improvement, including an ionic silver with antibiofilm agent for 4 weeks followed by 4 weeks non-antimicrobial dressing (Harding et al. 2016), silver oxysalt dressing (Woolstencroft 2018), silver sulphate dressing (Truchetet et al. 2012) and a metallic and ionic silver dressing (Manning et al. 2020). 3 studies reported the number of patients with partial healing at 4 weeks, which ranged from 68.75% (Manning et al. 2020) to 90% (Woolstencroft 2018).

Table 5.7: Single arm studies: partial healing, silver AMDs by sub-agent

% partially healed	Metallic and ionic silver (Microlyte Ag) ^a	4 weeks ionic silver +antibiofilm, then 4 week non-antimicrobial ^b	Silver oxysalts ^c	Silver sulphate ^d
1-2 weeks	-	-	-	-
3-4 weeks	11/16 (68.75%*)	-	Significant improvement: 18/30* (60%) Improvement: 9/30* (30%)	411/534* (77%)
5-6 weeks	-	-	-	-
7-8 weeks	-	Marked improvement: 8/10 (80%) Mild improvement: 1/10 (10%)	-	-
9-10 weeks	-	-	-	-
11-12 weeks	-	-	-	-
> 12 weeks	-	-	-	-

^a (Manning et al. 2020); ^b (Harding et al. 2016); ^c (Woolstencroft 2018); ^d (Truchetet et al. 2012)

* reviewer calculated

Five single arm studies that partly met the decision problem reported partial healing, including studies evaluating enzyme alginogel (Durante 2012), chitosan (Orig and Singleton 2016), monofloral honey (Moghazy et al. 2010), manuka honey (Biglari et al. 2013) and DACC (Bruce 2012). The measures of wound healing and timepoints reported varied across studies.

Table 5.8: Single arm studies: partial healing, non-silver AMDs by agent/sub-agent

	Enzyme alginogel ^a	Kytocel chitosan ^b	Monofloral honey ^c	Manuka honey ^d	DACC ^e
1-2 weeks	-	11/20 (55%)	-	-	
3-4 weeks	-	-	-	-	Number of wounds with granulation tissue: Baseline: 10 (71%) Week 4: 11 (79%) Number of wounds with epithelialisation: Baseline: 3 (21%) Week 4: 8 (57%) These are reported to be signs of progression towards healing
5-6 weeks	-	-	-	Patients with improved wounds (wound area reducing): 53.3%	-
7-8 weeks	Patients with significant decrease in wound area and volume: 60 days: 20/20 (100%)	-	-	-	-
9-10 weeks	-	-	-	-	-
11-12 weeks	-	-	-	-	-
> 12 weeks	-	-	1 month: 0/30 (0) 2 months: 0/30 (0) 3 months: 13/30 (43.3)	-	-

^a (Durante 2012); ^b (Orig and Singleton 2016); ^c (Moghazy et al. 2010); ^d (Biglari et al. 2013); ^e (Bruce 2012)

5.4.3 Infection

5.4.3.1 Comparative studies

Table 5.9: Comparative studies: infection outcomes by sub-agent

	Non-antimicrobial dressing	Ionic silver	Manuka honey
Ionic silver complex	-	Favours ionic silver: Gago, 2008 ^{StatSig}	-
Silver (further details NR)	-	-	Favours honey: Molle, 2023
Metallic / elemental silver	No difference: Meaume, 2005 ^{StatSig}	-	-

Key: NR – Not reported.

Underlined studies fully met the decision problem

Studies with no underline partly met the decision problem

^{StatSig} indicates that the study reported this finding to be statistically significant

3 comparative studies reported infection outcomes, all of which fully met the decision problem (Gago et al. 2008, Molle et al. 2023, Meaume et al. 2005). A summary of effect direction and significance is provided in Table 5.9. Outcome definitions varied and were reported at 4 weeks or 8 weeks.

1 study (n=50) (Molle et al. 2023) favoured honey over silver in the number of ulcers with negative bacterial swab tests at day 15, although statistical significance was not reported.

1 study (n=99) (Meaume et al. 2005) found no statistically significant difference between silver and non-antimicrobial dressings in ASEPSIS score.

1 study (n=75) (Gago et al. 2008) reported that infections resolved statistically significantly faster in the ionic silver arm than the ionic silver complex arm.

5.4.3.2 Single arm studies

6 silver studies that fully met the decision problem reported local infection outcomes, evaluating ionic silver (Forlee et al. 2014, Vanscheidt et al. 2003), silver

sulphadiazine (Degreef and Michiels 1984, Melotte et al. 1985, Lantis and Gendics 2011) and silver sulphate dressings (Truchetet et al. 2012). All studies reported results at 3 to 4 weeks, but each reported a different measure of infection. 2 studies reported the number of infected wounds at 4 and 8 weeks, which ranged from 0% (Forlee et al. 2014) to 78.3% (Lantis and Gendics 2011) at 4 weeks and 7.1% (Forlee et al. 2014) to 60.9% (Lantis and Gendics 2011) at 8 weeks. The change in proportion of patients or wounds with signs of infection compared to baseline was statistically significant in both studies at all timepoints. 1 study reported a statistically significant change in the mean number of infection signs in the included wounds (silver sulphate, -2.2 SD 1.5) (Truchetet et al. 2012).

Table 5.10: Single arm studies: infection outcomes, silver AMDs by sub-agent

	Ionic silver ^{a, b}	Silver sulphadiazine ^{c, d, e}	Silver sulphate ^f
1-2 weeks	-	Patients with negative ulcer swab cultures^c: 14 (48.2%) Time to negative swab cultures in days (mean, range)^d 14 (7 to 33) Number of infected wounds^e: 22 (91.7%) Number of clinical signs of infection, mean (median; range)^e: 3.5 (4; 0 to 6)^{StatSig}	-
3-4 weeks	Median time to complete resolution of clinical signs of infection^a: 29.5 days (95% CI 14 to 49 days) Number of infected wounds^a: 0 (0%)^{StatSig} Resolution of infection^b 28 days: 2/11 (18%*)	Patients with negative ulcer swab cultures^c: 19 (65.5%) Number of infected wounds^e: 18 (78.3%) Number of clinical signs of infection, mean (median; range)^e: 2.6 (3; 0 to 6)^{StatSig}	Change in number of signs of infection in venous leg ulcer wounds (mean, SD): -2.2 (1.5)^{StatSig}
5-6 weeks	-	-	-
7-8 weeks	Number of infected wounds ^a : 1 (7.1%) ^{StatSig}	Number of infected wounds ^e : 14 (60.9%) ^{StatSig}	-

	Ionic silver ^{a, b}	Silver sulphadiazine ^{c, d, e}	Silver sulphate ^f
		Number of clinical signs of infection, mean (median; range) ^e : 1.6 (1; 0 to 6) ^{StatSig}	
9-10 weeks	-	-	-
11-12 weeks	-	-	-
> 12 weeks	-	-	-

Key: CI – Confidence interval; SD – Standard deviation.

^a (Forlee et al. 2014); ^b (Vanscheidt et al. 2003); ^c (Degreef and Michiels 1984); ^d (Melotte et al. 1985); ^e (Lantis and Gendics 2011); ^f (Truchetet et al. 2012)

^{StatSig} indicates that the study reported a statistically significant difference from baseline

* reviewer-calculated

4 single arm studies that partly met the decision problem reported infection resolution including 3 studies evaluating Enzyme alginogel (Durante 2012, Jones and Oates 2018, King and Rolland 2023), and 1 each evaluating DACC (Bruce 2012), Octenillan gel (Hammerle and Strohal 2016) and cupric oxide (Dokic S et al. 2023). 3 studies reported the number of patients with resolved or improved infections at 3 to 4 weeks, which ranged from 14% (Bruce 2012) to 100% (Durante 2012).

Table 5.11: Single arm studies: infection outcomes, non-silver AMDs by agent/sub-agent

	Enzyme alginogel ^{a,b,c}	DACC ^d	Octenidine ^e	Cupric oxide ^f
1-2 weeks	2/3 (66.66%*)	-	<u>Octenidine with foam or alginate</u> Patients with no sign of infection: 3 days: 0/5 (0%) 5 days: 0/5 (0%) 12 days: 0/5 (0%) <u>Octenidine gel with wound contact layer</u> Patients with no sign of infection: 3 days: 0/5 (0%) 5 days: 0/5 (0%) 12 days: 2/5 (40%*)	-
3-4 weeks	3/3 (100%)	Wounds with reduced signs of infection: 2 (14%)	<u>Octenidine gel with foam or alginate</u> Patients with no sign of infection: 26 days: 1/5 (20%*) <u>Octenidine gel with wound contact layer</u> Patients with no sign of infection: 26 days: 3/5 (60%*)	-
5-6 weeks	-	-	<u>Octenidine gel with foam or alginate</u> Patients with no sign of infection: 42 days: 1/4 (25%*) <u>Octenidine gel with wound contact layer</u> Patients with no sign of infection: 42 days: 4/4 (100%*)	-
7-8 weeks	-	-	-	-

	Enzyme alginogel ^{a,b,c}	DACC ^d	Octenidine ^e	Cupric oxide ^f
9-10 weeks	-	-	-	-
11-12 weeks	-	-	-	12/12 (100%)
> 12 weeks	-	-	-	-
Unclear	Clinician reported improvement in signs of infection/critical colonisation^b: Improvement: 253/340 (74.41%) StatSig* No change or worsening: 87 (25.59%) Clinician reported improvement in signs of infection/critical colonisation^c: Improvement: 1114/1528 (72.9%) StatSig* No change or worsening: 414/1528 (27.1)			

^a (Durante 2012); ^b (Jones and Oates 2018); ^c (King and Rolland 2023); ^d(Bruce 2012); ^e (Hammerle and Strohal 2016); ^f (Dokic S et al. 2023)

* reviewer-calculated

StatSig* indicates that the study reported a statistically significant difference between the observed value and the expected value of 50%

5.4.4 Clinical signs of infection

5.4.4.1 Comparative studies

2 comparative studies reported outcomes relating to clinical signs of infection, both of which fully met the decision problem (Skog et al. 1983, Humbert et al. 2006). Outcomes were reported at 6 weeks in both studies.

1 study (n=74) (Skog et al. 1983) reported that cadexomer iodine performed statistically significantly better than non-antimicrobial dressings for resolving / preventing local erythema, although no difference between arms was found for resolving discharge (statistical significance not reported for this latter outcome). The second study (n=80) (Humbert et al. 2006) found that ionic silver performed around 25% better than non-antimicrobial dressings for resolving wound malodor, but statistical significance was not reported.

5.4.4.2 Single arm studies – covert signs of infection

2 silver studies, both fully meeting the decision problem, reported covert signs of infection, 1 evaluating ionic silver (Forlee et al. 2014) and 1 evaluating silver sulphadiazine (Lantis and Gendics 2011). Both reported the number of patients with friable granulation at 7 to 8 weeks which ranged from 0% (Forlee et al. 2014) to 17.4% (Lantis and Gendics 2011).

Table 5.12: Single arm studies: covert signs of infection, silver AMDs by sub-agent

	Ionic silver ^a	Silver sulphadiazine ^b
1-2 weeks	-	Patients with friable granulation: 4 (16.7%)
3-4 weeks	-	Patients with friable granulation: 5 (21.7%)
5-6 weeks	-	-
7-8 weeks	Patients with friable granulation: 0 (0%)	Patients with friable granulation: 4 (17.4%)
9-10 weeks	-	-
11-12 weeks	-	-
> 12 weeks	-	-

^a (Forlee et al. 2014); ^b (Lantis and Gendics 2011)

5.4.4.3 Single-arm studies – overt signs of infection

6 silver studies, all fully meeting the decision problem, reported overt signs of infection as numbers of patients or wounds, using varying criteria and at different timepoints. Table 5.13 summarises their findings by sub-agent.

Table 5.13: Single arm studies: overt signs of infection, silver AMDs by sub-agent

	Ionic silver ^{a,b}	Silver sulphadiazine ^{c, d}	Silver oxysalts ^e	Silver sulphate ^f
1-2 weeks	-	Local peri-ulcer erythema ^c : 16 (66.7%) Increased temperature around ulcer ^c : 1 (4.2%) Purulent exudate ^c : 6 (25%) Malodour ^c : 9 (37.5%) Patients with wound malodour ^d : 8%	-	-
3-4 weeks	Patients with redness and inflammation ^b : 3/11 (27%)	Local peri-ulcer erythema ^c : 10 (43.5%) Increased temperature around ulcer ^c : 0 (0%) Purulent exudate ^c : 4 (17.4%) Malodour ^c : 8 (34.8%)	Reduction in wound odour: 77% of wounds Significant reduction in wound odour (definition NR): 64.4%	Erythematous peri-wound skin: 52% at follow up Wounds with malodour: 1% at follow up
5-6 weeks		Patients with wound malodour ^d : 4%		
7-8 weeks	Patients with wound increased peri-wound temperature ^a : 0 (0%) Patients with wound purulent discharge ^a : 0 (0%) Patients with wound malodour ^a : 0 (0)	Local peri-ulcer erythema ^c : 8 (34.8) Increased temperature around ulcer ^c : 0 (0%) Purulent exudate ^c : 2 (8.7%) Malodour ^c : 8 (34.8)	-	-
9-10 weeks	-	-	-	-

	Ionic silver ^{a,b}	Silver sulphadiazine ^{c, d}	Silver oxysalts ^e	Silver sulphate ^f
11-12 weeks	-	-	-	-
> 12 weeks	-	-	-	-

Key: NR – Not reported.

^a (Forlee et al. 2014); ^b (Vanscheidt et al. 2003); ^c (Lantis and Gendics 2011); ^d (Jorgensen et al. 2008); ^e (Woolstencroft 2018); ^f (Truchetet et al. 2012)

5.4.5 Change in wound size / area

5.4.5.1 Comparative studies

Table 5.14: Comparative studies: change in wound size / area by sub-agent

	Non-antimicrobial dressing	Ionic silver
Cadexomer iodine	Favours iodine: Skog, 1983 ^{StatSig}	No difference: Miller, 2010 ^{StatSig}
Ionic silver complex	Favours ionic silver complex: Humbert, 2006 ^{StatSig}	-
Silver sulphate:	No difference: NCT01036438, 2009	-
Metallic / elemental silver	No difference: Meaume, 2005 ^{StatSig}	-
Chitosan (further details NR)	Favours chitosan: Mo, 2015 ^{StatSig}	-
PHMB (further details NR)	Favours PHMB: Vallejo, 2022 ^{StatSig}	-

Key: NR – Not reported, PHMB – Polyhexamethylene biguanide.

Underlined studies fully met the decision problem

Studies with no underline partly met the decision problem

^{StatSig} indicates that the study reported this finding to be statistically significant

7 comparative studies reported the change in wound size and / or area. 5 studies fully met the decision problem while 2 partly met the decision problem as they assessed either a mix of infected and non-infected leg ulcers (Vallejo et al. 2022), or mixed infected wounds on various locations across the body (Mo et al. 2015). A summary of effect direction and significance is provided in Table 5.14. Outcomes were reported at time points between 4 weeks and 12 weeks.

4 studies assessed silver dressings. 1 study found ionic silver complex to be statistically significantly better than non-antimicrobial dressings for reducing wound

area (n=80) (Humbert et al. 2006). 2 studies found no difference between silver and non-antimicrobial dressings for reducing wound area (silver sulphate, n=201 (NCT01036438 2009); metallic silver n=99 (Meaume et al. 2005)), although only 1 study reported the lack of statistical significance of this finding (Meaume et al. 2005). The fourth study found no statistically significant difference in the rate of change of wound size between ionic silver and cadexomer iodine dressings (n=266) (Miller et al. 2010).

3 studies found chitosan (n=90) (Mo et al. 2015), iodine (n=74) (Skog et al. 1983) and PHMB dressings (n=70) (Vallejo 2021) to be statistically significantly better than non-antimicrobial dressings for reducing wound or ulcer area.

5.4.5.2 *Single arm studies*

6 silver studies that fully met the decision problem reported the change in wound size or area, including 2 studies evaluating ionic silver (Forlee et al. 2014, Vanscheidt et al. 2003), 2 evaluating silver sulphadiazine (Lantis and Gendics 2011, Jorgensen et al. 2008) and 1 each evaluating ionic silver with antibiofilm agent (for 4 weeks followed by non-antimicrobial dressing for 4 weeks) (Harding et al. 2016) and metallic and ionic silver (Manning et al. 2020). Various measures and timepoints were reported, of which the most frequently reported was mean percentage change in wound area at 3 to 4 weeks which in 3 studies ranged from -32.5% (Vanscheidt et al. 2003) to -60% (Manning et al. 2020).

1 single arm study evaluating silver sulphadiazine reported the rate of change in wound size (data not tabulated) and reported a linear healing rate (reduction in area divided by mean of wound circumference) of 0.32 at 4 weeks (Jorgensen et al. 2008).

Table 5.15: Single-arm studies: change in wound size / area, silver AMDs by sub-agent

	Metallic and ionic silver (Microlyte Ag)^a	Ionic silver^{b, c}	4 weeks ionic silver +antibiofilm, then 4 weeks non-antimicrobial^d	Silver sulphadiazine^{e, f}
1-2 weeks	-	Median percentage change in wound area ^b : Week 1 (n=13): 4.7% Week 2 (n=13): -28.0%	-	Median percentage change ^e : 2 weeks (n=24): -28.1
3-4 weeks	Mean percentage change in wound area (n=11 patients with improved ulcers): Week 3: -60%	Median percentage change in wound area ^b : Week 3 (n=13): -38.9% Week 4 (n=13): -43.5% Mean percentage change in wound area ^c : -32.5%	-	Median percentage change ^e : 4 weeks (n=23): -56.4 Mean % relative wound area change (n=24)f: -42%
5-6 weeks	-	Median percentage change in wound area ^b : Week 5 (n=14): -56.9% Week 6 (n=14): -73.8%	-	-
7-8 weeks	-	Median percentage change in wound area ^b : Week 7 (n=14): -91.1% Week 8 (n=14): -98.2% (mean 78.3, range 30.2 to 100)	Mean wound area reduction in patients with clinically infected ulcers (%): 8 weeks: 70.2 (SD 24.7%, range 13.6 to 100%)	Median percentage change ^e : 8 weeks (n=23): -93.4 Patients achieving at least a 75% reduction in ulcer area from baseline, n (%) ^e : 8 weeks: 19/24 (79.2)
9-10 weeks	-	-	-	-

	Metallic and ionic silver (Microlyte Ag)^a	Ionic silver^{b, c}	4 weeks ionic silver +antibiofilm, then 4 weeks non-antimicrobial^d	Silver sulphadiazine^{e, f}
11-12 weeks	Average percentage change in wound area from baseline at 12 weeks (n=16): Reduction >75%	-	-	Median percentage change ^e : 12 weeks (n=24): -96.9StatSig
> 12 weeks	-	-	-	-

^a (Manning et al. 2020); ^b (Forlee et al. 2014); ^c (Vanscheidt et al. 2003); ^d (Harding et al. 2016); ^e (Lantis and Gendics 2011); ^f (Jorgensen et al. 2008)

StatSig indicates that the study reported a statistically significant difference from baseline

7 single arm studies that partly met the decision problem reported the change in wound size or area, including 2 evaluating manuka honey (Biglari et al. 2013, Yang K et al. 2015) and 1 each evaluating cupric oxide (Melamed et al. 2021), enzyme alginogel (Durante 2012), DACC (Bruce 2012), monofloral honey (Moghazy et al. 2010), Octenidine gel (Hammerle and Strohal 2016) and PHMB (Koullias et al. 2022). The measures and timepoints reported varied across studies and are summarised below.

Table 5.16: Single-arm studies: change in wound size / area, non-silver AMDs by agent/sub-agent

	Cupric oxide ^a	Enzyme alginogel ^b	DACC^c	Manuka honey^{d, e}	Monofloral honey^f	Octenidine ^g	PHMB^h
1-2 weeks	-	Wound surface area (cm ² , mean SD): Baseline (n=23): 2.6 (3.8) Day 14 (n=22): 1.9 (2.6)	-	-	-	-	-

	Cupric oxide^a	Enzyme alginogel^b	DACC^c	Manuka honey^{d, e}	Monofloral honey^f	Octenidine^g	PHMB^h
3-4 weeks	Mean change in wound size: - 53.2% ^{StatSig}	Wound surface area (cm ² , mean SD): Day 30 (n=21): 0.6 (0.8)	Wounds reduced in size (n %) 11/14 (79) Wounds reduced >75% in size (n %) 6/14 (43)	Wound area (cm ² , mean SD) ^d : Baseline: 29.66 (57.57) Mean 4.8, SD 4.4 weeks: 11.32 (33.3) ^{StatSig} Overall change in wound area (%) from baseline ^e : -21 ^{StatSig}	Proportion of patients by range of wound size (cm ²) 0 4/30 (13.3) 1 to 5: 9/30 (30) 6 to 10: 8/30 (26.8) 11 to 15: 2/30 (6.7) 16 to 20: 1/30 (3.3) 21 to 105: 4/30 (13.3)	-	-
5-6 weeks	-	-	-	-	-	Percentage wound area change from baseline to day 42: Octenidine with alginate/gel dressing: - 64.1%, Octenidine with wound contact layer dressing:- 96.2	-
7-8 weeks	-	Wound surface area (cm ² , mean SD): Day 60 (n=13): 0.4 (0.8) ^{StatSig}	-	-	Proportion of patients by range of wound size (cm ²) 0: 8/30 (includes 4 resurfaced ulcers, 26.8)	-	-

	Cupric oxide ^a	Enzyme alginogel ^b	DACC ^c	Manuka honey ^{d, e}	Monofloral honey ^f	Octenidine ^g	PHMB ^h
					1 to 5: 10/30 (33.3) 6 to 10: 4 (13.3) 11 to 15: 1/30 (3.3) 16 to 20: 1/30 (3.3) 21 to 75: 3/30 (10) Chi-squared test: <0.0001 ^{StatSig}		
9-10 weeks	Mean change in wound (after 4 weeks with copper dressing and 6 weeks with standard care): -65 ^{StatSig}	-	-	-	-	-	-
11-12 weeks	-	-	-	-	Proportion of patients by range of wound size (cm ²) <u>3 months:</u> 0: 13/30 (includes 8 resurfaced ulcers, 43.3) 1 to 5: 10/30 (33.3) 6 to 10: 0/30 (0) 11 to 15: 1/30 (3.3) 16 to 20: 1/30 (3.3) 21 to 24: 1/30 (3.3)	-	-

	Cupric oxide ^a	Enzyme alginogel ^b	DACC ^c	Manuka honey ^{d, e}	Monofloral honey ^f	Octenidine ^g	PHMB ^h
					Chi-squared test: <0.0001 ^{StatSig}		
> 12 weeks	-	-	-	-	-	-	Incidence of reduction from baseline ulcer area, depth and volume (%) <u>32 weeks</u> >60% reduction in area: 77.61 >60% reduction in depth: 70.15 >75% reduction in volume: 86.57

Key: SD – Standard deviation, PHMB – Polyhexamethylene biguanide.

^a (Melamed et al. 2021); ^b (Durante 2012); ^c (Bruce 2012); ^d (Biglari et al. 2013); ^e (Yang K et al. 2015); ^f (Moghazy et al. 2010); ^g (Hammerle and Strohal 2016); ^h (Koullias et al. 2022)

StatSig indicates that the study reported a statistically significant difference from baseline

5.4.6 Wound bed/ peri-wound skin condition

5.4.6.1 Comparative studies

3 comparative studies reported changes in the wound bed / peri-wound bed. 2 studies fully met the decision problem (Skog et al. 1983, Humbert et al. 2006) while a third study assessed mixed infected wounds on various locations across the body (Mo et al. 2015). Outcomes were reported at 4 or 6 weeks.

The 3 studies found chitosan (n=90 (Mo et al. 2015); further details NR), cadexomer iodine (n=74, (Skog et al. 1983)), and ionic silver complex (n=80, (Humbert et al. 2006)) to be statistically significantly better than non-antimicrobial dressings for reducing exudate.

5.4.6.2 Single arm studies – change in slough

2 studies that fully met the decision problem reported change in wound slough, both evaluating silver sulphadiazine (Jorgensen et al. 2008, Lantis and Gendics 2011). 1 reported that the mean percentage of wound bed covered by slough fell from 11% at baseline to 5% at day 31 (n=24) (Jorgensen et al. 2008) and 1 reported that the mean percentage of yellow slough or black necrotic wound tissue fell from 21.9% to 5.4% at 12 weeks (n=24) (Lantis and Gendics 2011).

5 single arm studies that partly met the decision problem reported change in wound slough, including 2 evaluating enzyme alginogel (Jones and Oates 2018, King and Rolland 2023) and 1 each evaluating Manuka honey (Biglari et al. 2013) and DACC (Bruce 2012). The measures and timepoints reported varied across studies and are summarised below.

Table 5.17: Single arm studies: change in slough, non-silver AMDs by agent/sub-agent

	DACC ^a	Enzyme alginogel ^{b,c}	Manuka honey ^d
1-2 weeks	-	-	-
3-4 weeks	Wounds with slough (n=14): Baseline: 6 End of treatment: 4	-	Mean slough/necrosis score (average of scores from grade 0 (presence of slough/necrosis) to grade 1 (no slough/necrosis): Baseline: 0.16 (0.37) End of study (mean 4.88 weeks, SD 4.4): 0.74 (0.44) ^{StatSig}

5-6 weeks	-	-	-
7-8 weeks	-	-	-
9-10 weeks	-	-	-
11-12 weeks	-	-	-
> 12 weeks	-	-	-
Unclear follow-up	-	Change in wound bed (debridement of slough/necrotic tissue) per clinician assessment (n=331 respondents)^b: Improved: 278/331 (84)^{StatSig*} No change or worsening: 53/331 (16) Change in wound bed (debridement of slough/necrotic tissue) per clinician assessment (n=1503 respondents)^c: Improved: 1211/1503 (81)^{StatSig*} No change or worsening: 292/1503 (19)	-

Key: SD – Standard deviation.

^a (Bruce 2012); ^b (Jones and Oates 2018); ^c (King and Rolland 2023); ^d (Biglari et al. 2013)

StatSig indicates that the study reported a statistically significant difference from baseline

StatSig* statistically significant difference between observed value and the expected value of 50%

5.4.6.3 Single arm studies – change in exudate

6 silver studies, all fully meeting the decision problem, reported overt signs of infection including 1 each evaluating ionic silver (Forlee et al. 2014), silver sulphadiazine (Lantis and Gendics 2011), silver oxysalts (Woolstencroft 2018) and silver sulphate (Truchetet et al. 2012). 2 studies reported the number of wounds or patients with high exudate at 3 to 4 weeks, which ranged from 4.5% (n=794) (Truchetet et al. 2012) to 13% (n=23) (Lantis and Gendics 2011), and 2 studies reported this at 8 weeks (0% in both studies (Forlee et al. 2014, Lantis and Gendics 2011)).

Table 5.18: Single arm studies: change in exudate, silver AMDs by sub-agent

	Ionic silver ^a	Silver sulphadiazine ^b	Silver sulphate ^c	Silver oxysalts ^d
1-2 weeks	Patients with increased exudate/secretion levels: Baseline 9 (64.3)	Patients with increased exudate: Baseline (Week 0): 19 (79.2) Week 2: 9 (37.5)	Wounds highly exudative: Baseline: 55%	-
3-4 weeks	-	Patients with increased exudate: Week 4 (n=23): 3 (13%)	Wounds highly exudative: Follow-up (median 19 days, n=794): 4.5%	Patients with reduced exudate: 83%
5-6 weeks	-	-	-	-
7-8 weeks	Patients with increased exudate/secretion levels: Week 8: 0 (0)	Patients with increased exudate: Week 8 (n=23): 0	-	-
9-10 weeks	-	-	-	-
11-12 weeks	-	Patients with increased exudate: Week 12: 3 (12.5%)StatSig	-	-
> 12 weeks	-	-	-	-

^a (Forlee et al. 2014); ^b (Lantis and Gendics 2011); ^c (Truchetet et al. 2012); ^d (Woolstencroft 2018)
StatSig indicates that the study reported a statistically significant difference from baseline

4 single arm studies that partly met the decision problem reported wound exudate, including 2 evaluating enzyme alginogel (Jones and Oates 2018, King and Rolland 2023) and 1 each evaluating DACC (Bruce 2012) and manuka honey (Moghazy et al. 2010). The measures and timepoints varied across studies and are summarised below.

Table 5.19: Single arm studies: change in exudate, non-silver AMDs by agent/sub-agent

	DACC^a	Enzyme alginogel^{b,c}	Manuka honey^d
1-2 weeks	-	-	Patients with healthy (scanty, serous) exudate: Baseline: 0
3-4 weeks	Wounds with exudate: Baseline:14 End of treatment: 10	-	Patients with healthy (scanty, serous) exudate: 1 month: 0
5-6 weeks	-	-	-
7-8 weeks	-	-	Patients with healthy (scanty, serous) exudate: 2 month: 11/30 (36.7%)
9-10 weeks	-	-	-
11-12 weeks	-	-	Patients with healthy (scanty, serous) exudate: 3 month: 12/30 (40%)
> 12 weeks	-	-	-
Unclear follow-up	-	Change in moisture balance per clinician assessment (n=352 respondents) ^b : Improved: 294/352 (83.52) ^{StatSig*} No change/worsening: 58/352 (16.48) Management of moisture balance per clinician assessment (n=1599 respondents) ^c : Well-managed: 1321/1599 (82.6) ^{StatSig*} No change/not managed: 278/1599 (17.4)	-

^a (Bruce 2012); ^b (Jones and Oates 2018); ^c (King and Rolland 2023); ^d (Moghazy et al. 2010)
StatSig* statistically significant difference between observed value and the expected value of 50%

5.4.6.4 Single arm studies – change in granulation

3 silver studies, all of which fully met the decision problem, reported granulation including 1 evaluating ionic silver (Forlee et al. 2014) and 2 evaluating silver sulphadiazine (Lantis and Gendics 2011, Jorgensen et al. 2008). Various measures and timepoints were reported; 2 studies reported the number of patients with discoloured granulation tissue at 8 weeks which ranged from 0% (n=14) (Forlee et al. 2014) to 13% (n=23) (Lantis and Gendics 2011).

Table 5.20: Single arm studies: change in granulation, silver AMDs by sub-agent

	Ionic silver ^a	Silver sulphadiazine ^{b, c}
1-2 weeks	Patients with discolouration of granulation tissue: Baseline: 2 (14.3)	Patients with discolouration of granulation tissue ^c : Baseline (Week 0): 6 (25) Week 2: 2 (8.3) Wound bed covered by healthy granulation tissue%, mean (SD) ^b : Baseline: 32 (30)
3-4 weeks	-	Patients with discolouration of granulation tissue ^c : Week 4 (n=23): 1 (4.3) Wound bed covered by healthy granulation tissue%, mean (SD) ^b : Day 31: 59 (31)
5-6 weeks	-	-
7-8 weeks	Patients with discolouration of granulation tissue: Week 8 (n=14): 0 (0)	Patients with discolouration of granulation tissue ^c : Week 8 (n=23): 3 (13.0)
9-10 weeks	-	-
11-12 weeks	-	Patients with discolouration of granulation tissue ^c : Week 12 (n=23): 1 (4.2)
> 12 weeks	-	-

Key: SD – Standard deviation.

^a (Forlee et al. 2014); ^b (Jorgensen et al. 2008); ^c (Lantis and Gendics 2011)

6 single arm studies that partly met the decision problem reported granulation, including 3 evaluating enzyme alginogel (Durante 2012, Jones and Oates 2018, King and Rolland 2023) and 1 each evaluating cupric oxide (Melamed et al. 2021), monofloral honey (Moghazy et al. 2010) and octenidine (Hammerle and Strohal 2016). Various measures and timepoints were reported across studies, which are summarised below.

Table 5.21: Single arm studies: change in granulation, non-silver AMDs by agent/sub-agent

	Cupric oxide ^a	Enzyme alginogel ^{b, c, d}	Monofloral honey ^e	Octenidine ^f
1-2 weeks	Mean percentage change in granulation tissue after treatment: Week 1 (n=13): 28.5% ^{StatSig}	Percentage of wound area covered by granulation (% mean, SD) ^b : Baseline (n=23): 32 (29) Day 14 (n=22): 53 (29)	-	Patients with granulation tissue present (%) Octenidine with alginate/foam dressing: Baseline: 62 Day 3: 65 Day 5: 70 Day 12: 78 Octenidine with wound contact layer: Baseline: 52 Day 3: 63 Day 5: 74 Day 12: 80
3-4 weeks	-	Percentage of wound area covered by granulation (% mean, SD) ^b : Day 30 (n=21): 30 (31)	-	Patients with granulation tissue present (%) Octenidine with alginate/foam dressing: Day 12: 78 Day 26: 77

				Day 42: 79 Octenidine with wound contact layer: Baseline: 52 Day 26: 86 Day 42: 97
5-6 weeks	Mean percentage change in granulation tissue after treatment: Week 6 (latter 2 weeks with non-antimicrobial dressing, n=13): 43.37%	-	-	Patients with granulation tissue present (%) Octenidine with alginate/foam dressing: Day 42: 79 Octenidine with wound contact layer: Day 42: 97
7-8 weeks	-	Percentage of wound area covered by granulation (% mean, SD) ^b : Day 60 (n=13): 28 (37) ^{StatSig}	-	-
9-10 weeks	-	-	-	-
11-12 weeks	-	-	Wounds showing healthy granulation: 3 months: 13/30 (43.3%)	-
> 12 weeks	-	-	-	-
	-	Improvement in quality of granulation tissue (n=352 respondents) ^c : Improved: 276/352 (78.41) ^{StatSig*} No change or worsening: 76/352 (21.59) Improvement in quality of	-	-

		granulation tissue (n=1587 respondents respondents) ^d : Improved: 1230/1587 (77.5) ^{StatSig*} No change or worsening: 357/1587 (22.5)		

Key: SD – Standard deviation.

^a (Melamed et al. 2021); ^b (Durante 2012); ^c (Jones and Oates 2018); ^d (King and Rolland 2023); ^e (Moghazy et al. 2010); ^f (Hammerle and Strohal 2016)

StatSig indicates that the study reported a statistically significant difference from baseline

StatSig* statistically significant difference between observed value and the expected value of 50%

5.4.6.5 Single arm studies – change in oedema

2 silver studies, both fully meeting the decision problem, reported overt signs of infection including 1 evaluating ionic silver (Forlee et al. 2014) and 1 evaluating silver sulphadiazine (Lantis and Gendics 2011). Both reported the number of patients with oedema at 8 weeks, which ranged from 0% (n=14) (Forlee et al. 2014) to 21.7% (n=23) (Lantis and Gendics 2011).

Table 5.22: Single arm studies: change in oedema, silver AMDs by sub-agent

	Ionic silver ^a	Silver sulphadiazine ^b
1-2 weeks	Patients with oedema: Baseline 3 (21.4)	Patients with oedema: Baseline (Week 0): 22 (91.7) Week 2: 16 (66.7)
3-4 weeks	-	Patients with oedema: Week 4 (n=23): 13 (56.5)
5-6 weeks	-	-
7-8 weeks	Patients with oedema: Week 8: 0 (0)	Patients with oedema: Week 8 (n=23): 5 (21.7)
9-10 weeks	-	-
11-12 weeks	-	Patients with oedema: Week 12: 5 (20.8)
> 12 weeks	-	-

^a (Forlee et al. 2014); ^b (Lantis and Gendics 2011)

1 study single arm study (DACC) that partly met the decision problem reported the number of wounds with oedema, which fell from 8/14 at baseline to 1/14 at day 28 (Bruce 2012).

5.4.6.6 Single arm studies – change in peri-wound skin

5 single arm studies that partly met the decision problem reported granulation, including 3 evaluating enzyme alginogel (Durante 2012, Jones and Oates 2018, King and Rolland 2023) and 1 each evaluating cupric oxide (Melamed et al. 2021), and DACC (Bruce 2012). Various measures of peri-wound skin condition and timepoints were reported across studies, which are summarised below.

Table 5.23: Single arm studies: change in peri-wound skin condition, non-silver AMDs by agent/sub-agent

	Cupric oxide ^a	DACC ^b	Enzyme alginogel ^{c, d, e}
1-2 weeks	-	Wounds with healthy peri-wound skin: Baseline: 2/14	-
3-4 weeks	No peri-wound redness observed	Wounds with healthy peri-wound skin: End of treatment: 7/14	-
5-6 weeks	-	-	-
7-8 weeks	-	-	Surrounding skin evolution as assessed by care team (n=20) ^c : Excellent: 9 (45%) Good: 10 (50%) Poor: 1 (5%)
9-10 weeks	-	-	-
11-12 weeks	-	-	-
> 12 weeks	-	-	-
Unclear follow-up	-	-	Change in condition of peri-wound skin per clinician assessment (n= full response, 356 respondents) ^d : Improved: 255/356 (71.63) ^{StatSig*} No change or worsening: 101/356 (28.37) Change in condition of peri-wound skin per clinician assessment (n= full response, 1624 respondents) ^e : Improved: 1124/1624 (69.2) ^{StatSig*} No change or worsening: 500/1624 (30.8)

^a (Melamed et al. 2021); ^b (Bruce 2012); ^c (Durante 2012); ^d (Jones and Oates 2018); ^e (King and Rolland 2023)
StatSig* statistically significant difference between observed value and the expected value of 50%

5.4.7 Frequency of dressing changes and antibiotic use

5.4.7.1 Comparative studies

1 study (n=90 (Meaume et al. 2005)) that fully met the decision problem assessed the use of systemic antibiotics following the use of a metallic / elemental silver dressing or a non-antimicrobial dressing. No statistically significant difference was found between arms at 4 weeks.

1 study (n=75 (Gago et al. 2008)) that fully met the decision problem assessed the number of dressing changes required following the use of an ionic silver complex dressing or an ionic silver dressing. At 8 weeks' follow up, more dressings changes were recorded in the ionic silver complex dressing arm, but statistical significance was not reported and it was unclear what factors might be driving the difference.

5.4.7.2 Single arm studies

1 single arm study that fully met the decision problem reported the prescription of antibiotics. This study evaluated ionic silver and reported that at 8 weeks 10/14 (83.3%) patients had been prescribed antibiotics (Forlee et al. 2014).

2 single arm studies that fully met the decision problem reported the frequency of dressing changes or mean dressing wear time including 1 evaluating ionic silver which reported a mean wear time at 4 weeks of 6.4 days (Forlee et al. 2014) and 1 evaluating silver oxysalts which reported a mean wear time at 8 weeks of 19 days (Woolstencroft 2018).

5.4.8 Recurrence of wound or infection

5.4.8.1 Comparative studies

1 study (n=99 (Meaume et al. 2005)) that fully met the decision problem assessed the recurrence of infection following the use of a metallic / elemental silver dressing or a non-antimicrobial dressing. Although silver dressings appeared to perform better than non-antimicrobial dressings after 4 weeks' follow up, the difference was not statistically significant.

5.4.8.2 Single arm studies

1 single arm study that fully met the decision problem reported wound recurrence, which evaluated silver sulphadiazine. This study reported that at 12 weeks 5/11 (45.45%) patients whose wounds had healed earlier in the study experienced wound re-opening (Lantis and Gendics 2011).

1 single arm study that partly met the decision problem reported wound recurrence. This monofloral honey study reported that the number of patients who experienced closure, re-opening and re-closure of wounds during the study was 4/30 (13.3%*) at 2 months and 8/30 (26.6%*) at 3 months (Moghazy et al. 2010).

5.4.9 Pain and discomfort

5.4.9.1 Comparative studies

Table 5.24: Comparative studies: change in pain / discomfort by agent/sub-agent

	Standard of care	DACC
Cadexomer iodine	No difference: Skog, 1983	-
Ionic silver complex	Favours ionic silver complex: Humbert, 2006 ^{StatSig} , Dimikakos, 2009 ^{StatSig}	No difference: Mosti 2015 ^{StatSig}
Chitosan (further details NR)	Favours chitosan: Mo, 2015 ^{StatSig}	-
PHMB (mixed PHMB dressings)	Favours PHMB: Vallejo, 2022 ^{StatSig} (at 6 weeks, but no significant difference at other timepoints)	-

Key: DACC – Dialkylcarbamoyl chloride; NR – Not reported; PHMB –Polyhexamethylene biguanide.

Underlined studies fully met the decision problem

Studies with no underline partly met the decision problem

^{StatSig} indicates that the study reported this finding to be statistically significant

6 comparative studies reported change in pain or discomfort following the use of a dressing. 4 studies fully met the decision problem while 2 partly met the decision problem as they assessed either a mix of infected and non-infected leg ulcers (Vallejo et al. 2022), or mixed infected wounds on various locations across the body

(Mo et al. 2015). A summary of effect direction and significance is provided in Comparative studies

Table 5.24. Outcomes were reported at time points between 4 days and 12 weeks.

2 studies, both fully meeting the decision problem (n=42, (Dimakakos et al. 2009), n=80 (Humbert et al. 2006)), assessed ionic silver complex dressings against non-antimicrobial dressings. Both studies found that pain was statistically significantly less in the silver than the non-antimicrobial dressing arm, and 1 of the studies (Humbert et al. 2006) found that comfort was also statistically significantly better in the silver arm.

A third study of silver, also fully meeting the decision problem (n=40 (Mosti et al. 2015)), assessed silver against DACC dressings, and found no statistically significant difference between arms for reduction in pain from baseline.

1 study each assessed chitosan, iodine, and PHMB dressings against non-antimicrobial dressings. 1 study that partly met the decision problem (n=90 (Mo et al. 2015)) found that chitosan dressings resulted in statistically significantly less pain than non-antimicrobial dressings on dressing removal. 1 study that fully met the decision problem (n=74 (Skog et al. 1983)) found no apparent difference between iodine and non-antimicrobial dressings for reducing patients' pain, although statistical significance was not reported. The third study, which partly met the decision problem (n=50 (Vallejo et al. 2022)), found that statistically significantly lower pain scores were observed in the PHMB group than the non-antimicrobial dressings group at 6 weeks, but there was no statistically significant difference in pain levels at any other time point.

5.4.9.2 Single arm studies – pain scores

3 single arm studies that fully met the decision problem reported patient-reported pain scores including 1 each evaluating silver sulphate (Truchetet et al. 2012), ionic silver with anti-biofilm agent for 4 weeks followed by non-antimicrobial dressing (Harding et al. 2016) and silver sulphadiazine (Jorgensen et al. 2008). Pain scores

were either measures for general wound pain or pain at dressing change and timepoints reported varied across studies.

Table 5.25: Single arm studies: change in pain / discomfort, silver AMDs by sub-agent

	Silver sulphate ^a	4 week ionic silver with antibiofilm agent, then 4 week non-antimicrobial dressing ^b	Silver sulphadiazine ^c
1-2 weeks	All wound pain intensity (VAS 0 to 100), mean (SD): Baseline: 50 (24) Mean 19 days: 24.6 (20.9)	VAS pain score (0 to 10, mean): Baseline (n=32, 10 with infections):4.46	Persistent wound pain (11-point NBS), mean (SD): Baseline: 6.3 (2.2) 12 hours after the first dressing application: 3.0 (1.7) Pain after dressing removal (11-point NBS), mean (SD): Day 3: 2.4 (2.2)
3-4 weeks	-	VAS pain score (0 to 10, mean): Week 4 (n=32, 10 with infections): 2.98	Pain after dressing removal (11-point NBS), mean (SD): Day 31: 1.1 (2.1)
5-6 weeks	-	-	-
7-8 weeks	-	VAS pain score (0 to 10, mean): Week 8 (n=32, 10 with infections): 1.94	-
9-10 weeks	-	-	-
11-12 weeks	-	-	-
> 12 weeks	-	-	-

Key: NBS – Numerical box scale; SD – Standard deviation; VAS – Visual analogue scale.

^a (Truchetet et al. 2012); ^b (Harding et al. 2016); ^c (Jorgensen et al. 2008)

2 single arm studies that partly met the decision problem reported patient-reported pain scores including 1 each evaluating enzyme alginogel (Durante 2012) and manuka honey (Biglari et al. 2013). 1 reported pain score at dressing and 1 reported overall wound pain score.

Table 5.26: Single arm studies: change in pain / discomfort, non-silver AMDs by agent/sub-agent

	Enzyme alginogel ^a	Manuka honey ^b
1-2 weeks	VAS pain score (0 to 10; scores taken during dressing application at each timepoint), mean (SD): Baseline (n=23): 1.0 (1.9) Day 14 (n=22): 0.9 (1.7)	Pain score (adults graded 0 (no pain) to 10 (excruciating pain, paediatric patients used VAS 0 to 10), mean (SD): Baseline: 1.71 (1.89) Study end (mean 4.88, SD 4.4 weeks): 0.55 (1.22) ^{StatSig}
3-4 weeks	VAS pain score (0 to 10; scores taken during dressing application at each timepoint), mean (SD): Day 30 (n=21): 0.6 (1.02)	Pain score (adults graded 0 (no pain) to 10 (excruciating pain, paediatric patients used VAS 0 to 10), mean (SD): Study end (mean 4.88, SD 4.4 weeks): 0.55 (1.22) ^{StatSig}
5-6 weeks	-	-
7-8 weeks	VAS pain score (0 to 10; scores taken during dressing application at each timepoint), mean (SD): Day 60 (n=13): 0.2 (0.6)	-
9-10 weeks	-	-
11-12 weeks	-	-
> 12 weeks	-	-

Key: SD – Standard deviation, VAS – Visual analogue scale.

^a (Durante 2012); ^b (Biglari et al. 2013)

^{StatSig} indicates that the study reported a statistically significant difference from baseline

5.4.9.3 Single arm studies – number of patients reporting pain

3 single arm studies that fully met the decision problem reported the number of patients who reported pain, including 1 each evaluating ionic silver (Forlee et al. 2014), ionic silver with anti-biofilm agent (Harding et al. 2016) and silver sulphadiazine (Lantis and Gendics 2011). 2 studies reported the number of patients reporting wound pain at 8 weeks, which ranged from 0% (n=14) (Forlee et al. 2014) to 22.5% (n=40, after 4 weeks with ionic silver with antibiofilm and 4 weeks with non-antimicrobial dressing) (Harding et al. 2016).

Table 5.27: Single arm studies: patients reporting pain, silver AMDs by sub-agent

	Ionic silver ^a	4 weeks ionic silver with antibiofilm, then 4 weeks non-antimicrobial ^b	Silver sulphadiazine ^c
1-2 weeks	Patients reporting increased wound pain: Baseline (n=14): 5 (35.7)	Patients reporting moderate or severe pain between dressing changes: Baseline (n=42, 10 with infections): 27 (64.3%)	Patients reporting moderate pain from the ulcer during the preceding week <u>Baseline</u> No pain: NR Mild pain: NR Moderate pain: 14 (58.3)
3-4 weeks	-	Patients reporting moderate or severe pain between dressing changes: Week 4 (n=41, 10 with infections): 15 (36.6%)	-
5-6 weeks	-	-	-
7-8 weeks	Patients reporting increased wound pain: Week 8 (n=14): 0 (0)	Patients reporting moderate or severe pain between dressing changes: Week 8 (n=40, 10 with infections): 9 (22.5%)	-
9-10 weeks	-	-	-
11-12 weeks	-	-	Patients reporting moderate pain from the ulcer during the preceding week <u>12 weeks</u> No pain: 8 (33.3) Minimal pain: 4 (16.7) Moderate pain: 2 (8.3)
> 12 weeks	-	-	-

Key: NR – Not reported.

a (Forlee et al. 2014); b (Harding et al. 2016); c (Lantis and Gendics 2011)

6 single arm studies that partly met the decision problem reported the number of patients who reported pain, including 2 evaluating cupric oxide (Dokic S et al. 2023, Melamed et al. 2021), 2 evaluating enzyme alginogel (Jones and Oates 2018, King and Rolland 2023) and 1 each evaluating DACC (Bruce 2012) and manuka honey

(Biglari et al. 2013). 2 studies reported the number of patients reporting pain at 4 weeks, which ranged from 0% (among all patients, n=13) (Melamed et al. 2021) to 18% (among a subgroup of patients who reported pain at baseline) (Bruce 2012).

Table 5.28: Single arm studies: patients reporting pain, non-silver AMDs by agent/sub-agent

	Cupric oxide ^{a, b}	DACC ^c	Enzyme alginogel ^{d, e}	Manuka honey ^f
1-2 weeks	-	Patients reporting pain: Baseline: 11/13 (85*)	-	-
3-4 weeks	No patients reported pain (n=13) ^b	Patients reporting pain: Day 28 (among patients with pain at baseline): 2/11 (18)	-	Patients reporting pain compared to baseline at study end (mean 4.88 weeks, SD 4.4, n %): Improved (decrease in initial pain levels): 54/102 (55) No change in pain: 6/102 (5.8*) No wound pain at start of study: 42/102 (43)
5-6 weeks	-	-	-	-
7-8 weeks	-	-	-	-
9-10 weeks	-	-	-	-
11-12 weeks	No patients reported pain during dressing changes(n=12) ^a	-	-	-
> 12 weeks	-	-	-	-
	-	-	Patient-reported change in pain (n=344 respondents) ^d : Improvement: 170/344 (49.42%) No change or worsening: 174/344 (50.58%)	-

			Patient-reported change in pain (n=1571 respondents) ^e : Improvement: 830/1571 (52.8) No change or worsening: 741/1571 (47.2)	

Key: NR – Not reported.

a (Dokic S et al. 2023); b (Melamed et al. 2021); c (Bruce 2012); d (Jones and Oates 2018); e (King and Rolland 2023); f (Biglari et al. 2013)

5.4.9.4 Single arm studies - discomfort

1 single arm study that fully met the decision problem reported discomfort. This study reported that 17/30 (56%) patients reported greater comfort with silver oxysalt KerraContact Ag compared to their previous dressings (Woolstencroft 2018).

2 single arm studies that partly met the decision problem reported discomfort at 4 weeks. 1 study evaluated cupric oxide and reported that no patients experienced discomfort (n=13) (Melamed et al. 2021). The other study evaluated DACC reported a mean VAS 1 to 10 comfort score (10 being most satisfied with comfort) of 9 (n=13).

5.4.10 HRQoL

5.4.10.1 Comparative studies

1 study (n=50 (Vallejo et al. 2022)), that partly met the decision problem and assessed a mix of infected and non-infected leg ulcers found no statistically significant difference between PHMB and non-antimicrobial dressing arms for improving patients' HRQoL at 12 weeks' follow up.

5.4.11 Overall treatment-related adverse events (TRAEs)

5.4.11.1 Comparative studies

Table 5.29: Comparative studies: TRAEs by agent/sub-agent

	Non-antimicrobial dressing	Ionic silver	DACC
Ionic silver complex	No difference: <u>Humbert, 2006</u>	No difference: <u>Gago, 2008</u>	No difference: <u>Mosti, 2015</u>
Metallic / elemental silver	No difference: <u>Meaume, 2005</u>	-	-
Silver sulphate	No difference: <u>NCT01036438, 2009</u>	-	-
Cadexomer iodine	Favours non-antimicrobial dressings: <u>Skog, 1983</u>	-	-
Chitosan (further details NR)	No difference: Mo, 2015	-	-

Key: DACC – Dialkylcarbamoyl chloride; NR – Not reported.

Underlined studies fully met the decision problem

Studies with no underline partly met the decision problem

StatSig indicates that the study reported this finding to be statistically significant

7 comparative studies reported change in pain or discomfort following the use of a dressing (Humbert et al. 2006, Gago et al. 2008, Mosti et al. 2015, Meaume et al. 2005, NCT01036438 2009, Skog et al. 1983, Mo et al. 2015). All but 1 study fully met the decision problem; this study (Mo et al. 2015) assessed mixed infected wounds on various locations across the body. Timepoints of reporting ranged from 4 days to 8 weeks. A summary of effect direction is provided in Comparative studies

Table 5.29, but in general the number of TRAEs was very low. Statistical significance was not reported, but TRAEs were very similar across arms in 5 studies. The sixth study (n=90 (Mo et al. 2015)) reported no TRAEs at all in either arm. The final study (n=74, (Skog et al. 1983)) was the only one to report a difference between arms; more patients in the iodine than non-antimicrobial dressing arm had brief pain on dressing application, but statistical significance was not reported.

5.4.11.2 Single arm studies

3 single arm studies fully meeting the decision problem reported overall treatment-related adverse events, all evaluating silver sulphadiazine b (Lantis and Gendics 2011, Jorgensen et al. 2008, Degreef and Michiels 1984). The measures reported varied, including the number of patients experience TRAEs, the total number TRAEs overall, and the total number of specific TRAEs, and are summarised below.

Table 5.30: Single arm studies: TRAEs, silver AMDs by agent/sub-agent

	Silver sulphadiazine ^{a, b, c}
1-2 weeks	-
3-4 weeks	Patients experiencing treatment-related adverse events^a: 1/33 (3%*) Total treatment-related adverse events ^b: 4 (2 dermatitis, 2 local irritation/maceration) Total treatment-related adverse events ^c: 10/29 (34.5*) (all TRAEs reported were pseudomembrane in ulcer bed)
5-6 weeks	-
7-8 weeks	-
9-10 weeks	-
11-12 weeks	-
> 12 weeks	-

Key: TRAE – Treatment-related adverse events.

^a (Lantis and Gendics 2011); ^b (Jorgensen et al. 2008); ^c (Degreef and Michiels 1984)

* reviewer-calculated

4 single arm studies that partly met the decision problem reported overall TRAEs including 1 each evaluating cupric oxide (Melamed et al. 2021), enzyme alginogel (Durante 2012), manuka honey (Biglari et al. 2013) and octenidine (Hammerle and Strohal 2016). 3 studies reported the number of overall TRAEs at 8 weeks, which ranged from 1.3% (n=104) (Biglari et al. 2013) to 8.6%* (n=23) (Durante 2012).

Table 5.31: Single arm studies: TRAEs, non-silver AMDs by agent/sub-agent

	Cupric oxide ^a	Enzyme alginogel ^b	Manuka honey ^c	Octenidine ^d
1-2 weeks	-	-	-	-
3-4 weeks	No AEs reported by any patients	-	-	-
5-6 weeks	-	-	-	No AEs occurred
7-8 weeks	-	Overall TRAEs: 2/23 (8.6*); 1 allergic reaction and 1 transient maceration	Patients who experienced poor tolerance to dressing including skin reaction and pain (%; n=104): 1.3%	-
9-10 weeks	-	-	-	-
11-12 weeks	-	-	-	-
> 12 weeks	-	-	-	-

Key: AE – Adverse event; TRAE – Treatment-related adverse events.

^a (Melamed et al. 2021); ^b (Durante 2012); ^c (Biglari et al. 2013); ^d (Hammerle and Strohal 2016)

5.4.11.3 Single arm studies – overall serious treatment related adverse events

4 single arm studies that fully met the decision problem reported that no serious TRAEs occurred by final follow-up, including 2 evaluating silver sulphadiazine (n=24, 4 weeks (Jorgensen et al. 2008); n=24, 8 weeks (Lantis and Gendics 2011) and 1 each evaluating ionic silver (n=11, 4 weeks (Vanscheidt et al. 2003)) and ionic silver with anti-biofilm agent (n=10, 4 weeks followed by 4 weeks with non-antimicrobial dressing (Harding et al. 2016)).

2 single arm studies that partly met the decision problem reported that no serious TRAEs occurred by final follow-up, including 1 evaluating cupric oxide (n=13, 4 weeks (Melamed et al. 2021)) and 1 evaluating octenidine gel (n=29, 42 days (Hammerle and Strohal 2016)).

5.4.12 Specific AEs

5.4.12.1 Comparative studies

2 studies, both fully meeting the decision problem, reported the incidence of specific AEs following the use of silver dressings. 1 study (n=80 (Humbert et al. 2006)) reported statistically significantly less pain during dressing removal in the ionic silver complex than the non-antimicrobial dressing arm. The second study (n=75 (Gago et al. 2008)) assessed ionic silver complex against ionic silver dressings, and no pain related adverse events were reported by patients in either arm.

5.4.12.2 Single arm studies

The following specific AEs were reported across the single-arm studies:

- Skin discolouration
 - One study that fully met the decision problem (evaluating ionic silver) reported skin discolouration, reporting that 3/11 (27%) patients experienced redness and inflammation around the wound (Vanscheidt et al. 2003).
- Allergic reactions
 - Two studies that fully met the decision problem reported allergic reactions to dressings at 4 weeks, both evaluating silver sulphadiazine. 1 reported that 3/29 (10.3%*) patients experienced contact eczema related to ointment vehicle and not the silver agent (Degreef and Michiels 1984), and the other reported that no allergic reactions occurred (Melotte et al. 1985).
 - One study that partly met the decision problem reported that 1/23 (4/3%*) patients experienced an allergic reaction to enzyme alginogel at 60 days (Durante 2012).
- Increased pain due to dressing
 - Two studies that fully met the decision problem reported dressing pain including 1 evaluating ionic silver and 1 evaluating silver sulphadiazine. 1 reported that mild (2/96 2.1%) or moderate (2/96 2.1%) pain was reported at 2/96 (2.1%) and 2/96 (2.1%) dressing applications respectively, and that mild, moderate and severe pain was reported at 6/96 (6.3%), 3/95 (4.2%) and 1/95 (1.1%) dressing removals respectively over 8 weeks (Forlee et al. 2014). The other reported that

after 6 weeks 1/33 (3%*) patients had reported severe pain on dressing removal.

- One study that partly met the decision problem reported that 2/13 (15%) patients had reported “bearable” pain during DACC dressing removal after 4 weeks (Bruce 2012).

5.5 Summary of clinical evidence

Findings across studies are discussed narratively. The EAG explored the feasibility of conducting meta-analysis, concluding that no statistical pooling or quantitative analysis was appropriate due to the heterogeneity in study designs, populations, interventions and outcomes. The full rationale for this decision was supported by clinical input and is reported in Appendix D. A summary of ongoing studies can be found in Appendix E, while detailed results of all the included studies summarised in Appendix F and presented in tables in Appendix G.

The clinical review included 34 studies representing a heterogenous evidence base evaluating 9 different agents (chitosan, copper, DACC, enzyme alginogel, honey, iodine, octenidine, PHMB, and silver) and 11 different sub-agents for silver, iodine and honey AMDs (some studies did not report the sub-agents used). No appropriate evidence for chlorhexidine was identified by the EAG.

5.5.1 Clinical outcomes across studies

5.5.1.1 Complete healing

Comparative evidence generally appears to favour silver agents for achieving complete healing. However, comparisons between silver sub-agents are inconsistent and this observation may be due to the higher number of studies assessing silver than other agents.

All single-arm studies of silver sub-agents showed that the number of healed wounds increased with time. Of the silver sub-agents with data at more than one timepoint, complete healing with ionic silver showed most improvement with time in a linear fashion, while data for silver sulphadiazine also showed linear (but slower) improvement except for a peak at 4 weeks. This 4-week data point was informed by

one small study only. Data for chitosan showed a similar pattern but with a dip rather than a peak at 4 weeks. Data for PHMB showed consistent increases in complete healing over time, as did studies of enzyme alginogel and cupric oxide. Complete healing with monofloral honey was slower than for other non-silver sub-agents.

5.5.1.2 *Partial healing*

No comparative studies reporting partial healing assessed one AMD against another. Four studies of silver sub-agents (unclear, ionic + antibiofilm, oxysalts, and sulphate) reported partial healing of between 69% and 90% between 3 to 8 weeks. Data for the non-silver agents/sub-agents were less clustered, although all agents/sub-agents (enzyme alginogel, chitosan, monofloral and Manuka honeys, and DACC) reported an improvement in partial healing from baseline. None of the non-silver sub-agents reported at the same timepoint.

5.5.1.3 *Time to healing*

One comparative study reported no statistically significant difference in time to healing between ionic silver and cadexomer iodine dressings, but did not report the number of days to healing for either arm. 2 single arm studies, assessing silver sulphadiazine and monofloral honey, also reported time to healing. Time to healing for patients with fully closed wounds was median 13 weeks with silver sulphadiazine and mean 2.3 (SD 0.94) weeks with monfloral honey.

5.5.1.4 *Infection*

For achieving improvement in infection, 2 comparative studies favoured ionic silver over ionic silver complex, and Manuka honey over an unspecified silver AMD. Outcome definitions used by the individual studies varied widely. Single-arm data reported that at 3 to 4 weeks and 7 to 8 weeks, the percentage of infected wounds with ionic silver was 0% and 7%, while for silver sulphadiazine it was 78% and 61%. These differences in trends and in absolute percentages may indicate differences in the patient populations measured. One study of silver sulphate also reported a reduction in signs of infection. For non-silver agents/sub-agents, Octenidine gel with

a wound contact layer showed a faster and greater improvement than Octenidine gel with foam or alginate.

5.5.1.5 Signs of infection

No comparative studies assessed the performance of more than one AMD in reducing covert or overt signs of infection. Single-arm studies reported that friable granulation (a covert sign of infection) with the use of a silver sulphadiazine dressing rose from 17% at 1-2 weeks to 22% at 3-4 weeks, then dropped again to 17% at 7-8 weeks, while with an ionic silver dressing friable granulation was 0% at 7-8 weeks.

With the use of a silver sulphadiazine dressing, overt signs of infection reduced with time, with the exception of malodour, which remained at 35-38% between 1 and 8 weeks. Studies of ionic silver and silver sulphate both reported a lower proportion of patients with malodour (0% and 1% at between 3 and 8 weeks), while a study of silver oxysalts reported that 64% of patients experienced a significant reduction in wound odour at 3-4 weeks.

5.5.1.6 Change in wound size / area

Only one comparative study assessed multiple AMDs for changing wound size and found no difference between Cadexomer iodine and ionic silver.

Two single arm studies of ionic silver reported a consistent reduction in wound size up to -98% at week 8, with 2 further studies reporting a very similar trend for silver sulphadiazine. One study of enzyme alginogel also showed a consistent reduction over time, while a lack of comparable data points across time mean that it is hard to observe trends for cupric oxide, DACC, Manuka or monofloral honeys, Octenidine gel or PHMB.

5.5.1.7 Skin condition

No comparative studies assessed the performance of more than one AMD in changing wound bed / peri-wound bed condition. Two single-arm studies of silver sulphadiazine found that slough and necrotic tissue reduced over time, while

improvements were also observed by studies of Manuka honey, DACC, and enzyme alginogel. However, no studies reported data at more than one follow up timepoint so it is hard to compare the relative performance of agents/sub-agents.

5.5.1.8 *Frequency of dressing changes and antibiotic use*

One comparative study recorded more dressings changes in the ionic silver complex than the ionic silver dressing arm, but statistical significance was not reported, and it was unclear what factors might be driving the difference. Single-arm studies of this outcome reported at 1 timepoint per study, so direct comparisons between AMDs could not be made. Such comparisons may also not be appropriate due to the variety of dressing types assessed.

Antibiotic prescribing was reported by 1 single-arm study of ionic silver, so no comparisons could be made.

5.5.1.9 *Recurrence of wound or infection*

No comparative studies reporting wound recurrence assessed one AMD against another. 1 single-arm study reported that with a silver sulphadiazine dressing 45% of patients with healed wounds experienced wound re-opening.

5.5.1.10 *Pain and discomfort*

One comparative study reported no significant difference between DACC and ionic silver complex for reducing pain and discomfort. Single-arm studies of silver sulphadiazine and ionic silver with antibiofilm (the latter involving 4 weeks treatment with the ionic silver with antibiofilm dressing followed by 4 weeks with a non-antimicrobial dressing) reported that pain reduced consistently with time up to 4-8 weeks. A study of silver sulphate found that by 3 weeks, pain had halved from baseline, while studies of enzyme alginogel and Manuka honey also found a reduction in pain from baseline with time reported.

5.5.1.11 HRQoL

Only 1 comparative study and no single-arm studies reported HRQoL, but this study did not assess AMDs against each other.

5.5.1.12 Overall TRAEs

Neither of the 2 comparative studies comparing AMDs (ionic silver vs. ionic silver complex, and DACC vs. ionic silver complex) reported any difference between arms in TRAEs experienced. Both the comparative studies and 7 single-arm studies assessing silver sulphadiazine, cupric oxide, enzyme alginogel, Manuka honey and Octenidine gel reported the number of overall TRAEs to be very low. 6 single-arm studies reported no serious TRAEs.

Based on the available data, all the assessed AMDs appear to be safe. However, the EAG notes that patient numbers for many of the studies were relatively small, and the studies were unlikely to have been designed to identify the occurrence of rare and / or serious adverse events. Clinicians should remain aware of the potential for allergic reactions to all AMDs. Further, the EAG notes that in June 2024 a Medical Device Review led the British National Formulary (BNF) to update caution notices for povidone iodine fabric dressings (Inadine) to contraindications for patients with various conditions including kidney and thyroid diseases ([NICE 2024c](#)).

5.5.2 Limitations of the evidence

The review identified few comparative studies directly addressing the decision problem: 12 comparative studies were included, of which 4 directly compared different AMDs. 21 of the 34 studies fully met the decision problem, while the other 13 partly met the decision problem due to assessing infected leg wounds other than lower leg ulcers (n=2), infected wounds elsewhere on the body (n=6), non-infected lower leg ulcers (n=2), or populations with other types of wounds not fully meeting the decision problem (n=3). These were included due to a paucity of evidence fully meeting the decision problem for those agents. No studies fully meeting the decision problem were identified for 4 of the 9 agents (chitosan, copper, enzyme alginogel,

and PHMB). During screening, studies were considered to report data on infected wounds where the authors reported that participants had infected wounds. Author reports of infection were not always clearly defined, and the EAG notes that these may vary, potentially creating additional variability in the populations included in this review. This limitation of the evidence base is particularly likely to affect the older studies.

Generalisability of the evidence base for using AMDs to treat infected leg ulcers in a UK NHS setting was considered to be generally poor, as only 7 of the 34 studies were conducted in the UK. 4 of these fully met the decision problem (Meaume et al. 2005, Miller et al. 2010, Mosti et al. 2015, Woolstencroft 2018). UK evidence was available for 4 antimicrobial agents: DACC (Bruce 2012, Mosti et al. 2015), enzyme alginogel (Jones and Oates 2018, King and Rolland 2023), iodine (Miller et al. 2010) and silver (Meaume et al. 2005, Miller et al. 2010, Mosti et al. 2015, Woolstencroft 2018).

The 13 included studies that partly met the decision problem evaluated wound types and populations that may not be generalisable to a population with infected lower leg ulcers. Studies were also conducted in a broad range of settings, including inpatient, outpatient, home, and community care settings. Concomitant care, wound bed preparation, and the use of secondary dressings was variable and often poorly reported, introducing further uncertainty in the generalisability of the evidence base.

Formal risk of bias assessment of the studies that partly met the decision problem was not conducted. Of the 21 studies that fully met the decision problem, all but 4 were found to be at a moderate or high risk of bias following completion of an appropriate risk of bias tool. Key issues limiting the reliability of studies included the possibility of uncontrolled confounders, small sample sizes, and very limited reporting of methods. Outcome definitions and methods of measurement also differed across studies, were reported at varying timepoints and often did not assess the statistical significance of findings. This makes comparisons across the evidence base highly uncertain. In addition, some studies reported outcomes at timepoints that

may be too short to assess clinical efficacy, such as 4 days (Mosti et al. 2015) and 8 days (Orig and Singleton 2016).

Outcomes with the most available evidence were complete and partial healing, outcomes relating to wound infection status, and change in size or area of the wound / ulcer. Minimal data were found relating to patients' quality of life following the use of any particular dressing.

The disparate and heterogeneous nature of the evidence base across all AMDs (and therefore sub-agents) makes it challenging to identify trends across outcomes. Single-arm studies often reported at only 1 timepoint, meaning that conclusions across studies could not be drawn. Most outcomes were not well reported or were measured using different tools, making it difficult to draw conclusions across the data. Results for all outcomes were mixed and inconsistent when comparing AMDs to either non-antimicrobial dressings or to each other. Potential causes of this disparity in outcomes include differences in patient populations and settings, differences in approaches to outcome measurement and / or timepoints, differences in population size or other aspects of study design, or true differences in efficacy between the antimicrobials assessed. Due to the variation in study methods and reporting, it is not possible to isolate the reasons for these differences in outcome.

Based on the available evidence, adverse events across the different antimicrobial agents and dressing types were minimal. The most common adverse events included pain on application or removal of the dressing, itching, and rash. It is hard to determine whether these events were related to the ulcer, the specific antimicrobial agent or dressing type used, or to the general use of a dressing, although no serious adverse events were deemed to be dressing-related, and there was no evidence to suggest that any of the AMDs or dressing types assessed were unsafe. Clinicians should be aware of the possibility of allergic reactions, as many of the studies included in the evidence base were relatively small and were not designed to capture rare events.

For the reasons discussed above, the evidence base identified is not sufficient to determine whether there are clinically meaningful differences in efficacy between the AMDs of interest to this LSA.

6 Economic evidence searches and selection

6.1 *Evidence search strategy and study selection*

A single set of searches was conducted to identify both clinical and economic evidence (see Section 4.1). Full details of the search methods used are provided in Appendix A.

Studies were screened using the methods and eligibility criteria described in the [published protocol](#).

6.2 *Included and excluded studies*

The EAG identified 6 economic evaluations of AMD agents in order to help guide the development of the de novo model. These comprised 4 peer-reviewed papers (Hammerle and Strohal 2016, Jemec et al. 2014, Gueltzow et al. 2018, Nherera et al. 2016), one of which also contributed to the clinical review (Hammerle and Strohal 2016) and 2 conference abstracts (Walter et al. 2017, Mensor et al. 2017). None of the companies submitted their own economic evidence.

The 6 studies are summarised in Table 6.1 in Section 6.2.

- 6 of the 10 scoped agents of interest were evaluated by the selected studies as either the intervention or comparator: honey, iodine, silver, DACC, Octenidine and PHMB.
- The time horizon across the selected studies ranged from 4 weeks to 1 year.
- 3 economic evaluations used a Markov model structure (refs), 2 studies used a decision tree (refs) and 1 study used a cost-calculator.

One study was conducted in the UK. No studies focused exclusively on patients with infected leg ulcers. Two studies considered patients with a broader range of ulcers, including diabetic foot ulcers, either regardless of infection status (Mensor) or not reporting infection status (Walter). While the remaining 4 studies focused on patients with VLU, all included a mix of patients with and without infection. The generalisability of this evidence to the treatment of patients with infected leg ulcers within a UK health-care setting should therefore be considered.

Jemec 2014 was the only study from a UK setting (Jemec et al. 2014). The study compared silver dressings to non-silver dressings (non-AMDs) in a cost-comparison analysis. Efficacy data for the dressings was taken from a meta-analysis, comparators in the meta-analysis were foam dressing, calcium alginate and local best practice. The results suggest that silver dressing is cost saving compared to non-silver dressings, £141.57 per person. The study results also stated that time-to-healed wound for silver dressing was lower (13.8 weeks) compared with non-silver treatment (16.7 weeks). The results should be interpreted with caution due to a short 4 week time horizon and use of a decision tree structure resulting in limited tracking of patients between health states for the duration of having an ulcer. Infection was neither a key model outcome nor a health state.

Nherera 2016 was identified as a key study as it was the only study to incorporate utility data in the economic analysis (Nherera et al. 2016). Iodine dressing was compared to the standard care of dressings without iodine. Iodine dressing was found to be a dominant treatment with a QALY gain of 0.03 and cost savings of \$643 per patient over 52 weeks. The utility data was taken from a cost-utility study comparing bio-electric stimulation therapy compared to standard care in people with chronic non-healing wounds. The reliability of results may be limited as utility data was not specific to leg ulcers.

Hammerle 2014 was the only study to perform a cost evaluation of Octenidine (Hammerle and Strohal 2016). Octenidine gel was compared to wound-phase adapted dressing. Trial data collected by the authors on the number of dressing

changes over the 42 day time horizon was the only cost input. The study concluded that Octenidine-based wound gel alone had the lowest cost per patient (€244.12), followed by Octenidine-based wound gel with wound-phase adapted dressing (€330.35) and the highest costs per patient in wound-phase adapted dressing only (€336.27). The study was conducted in Austria and only used data collected from their trial to inform the economic evaluation, therefore the frequency of dressing changes may not align with clinical practice in the UK.

Gueltzow 2018 conducted a budget impact analysis which included DACC, silver and PHMB dressings (Gueltzow et al. 2018). 3 market shares of Cutimed Sorbact coated with DACC were modelled, the base case scenario 19.87%, Scenario A 50%, Scenario B 0%. The study suggested that increased use of DACC dressing over other dressings reduced the average treatment cost of VLU. Scenario A was cost saving compared to the base case (decrease of 21%) and Scenario B was cost incurring compared to the base case. Recurrence of the ulcer was included in their Markov model but assumed that the choice of dressing did not have an impact on ulcer recurrence. Secondary care costs or long-term complications were not included in the economic analysis.

Two conference abstracts were included, Walter 2017 and Mensor 2017 abstracts (Walter et al. 2017, Mensor et al. 2017). Conference abstracts are limited in detail regarding the methodology and data inputs however they can be helpful in observing the direction of results. Walter 2017 reported the cost of PluroGel (1% silver sulphadiazine) per person amounts to €3,771, silver dressings €4,644, hydrogel-dressings €4,538, medical-honey €4,676, impregnated dressings €4,324 and good wound care €6,764. Mensor 2017 reported results of a cost saving of approximately 40 thousand Brazilian Reais per patient with silver alginate dressing compared to calcium alginate dressing. Any limitations in the study methods are difficult to establish due to the limited word count of the abstracts.

Table 6.1: Included economic evaluations

Study author, design and location	Intervention(s) and comparator(s)	Population and key data sources	Model structure	Relevant outcomes	EAG comments
Author: Gueltzow, 2018 (Gueltzow et al. 2018) Design: Budget impact Location: Germany	Intervention: Cutimed Sorbact which is coated with DACC Comparator: Silver dressing and PHMB wound dressing. Scenarios: Market share of Cutimed Sorbact: Base case scenario 19.87%. Scenario A 50%. Scenario B 0%.	Population: Patients above the age of 60 with a VLU. 84% with an infection and 16% without. Data sources: The costs for pharmaceuticals and wound dressing were taken from the Lauer Taxe German reimbursement rate. No other costs were included.	Model structure: Markov model. 4 health states: wound infection, no wound infection, healed and death. Time horizon: 12 months Cycle length: 1 month	Primary outcome: Increased use of Cutimed Sorbact over other dressings reduced the average treatment cost of VLUs. Scenario A was cost saving compared to the base case, decrease of 21%. Scenario B was cost incurring compared to the base case. Secondary outcome: In the base-case scenario, the annual resource use per patient is 21 antimicrobial dressings and 39 moist dressings. In Scenario A the amount of antimicrobial dressings was reduced by 30%.	Recurrence of ulcer was included but assumed that the choice of dressing does not have an impact on ulcer recurrence. Limitation: Secondary care costs or long term complications were not modeled.

Study author, design and location	Intervention(s) and comparator(s)	Population and key data sources	Model structure	Relevant outcomes	EAG comments
Author: Hammerle, 2016 (Hammerle and Strohal 2016) Design: Cost-comparison Location: Austria	Intervention: Octenidine wound gel. Octenidine-based wound gel + wound-phase adapted dressing. Comparator: Wound-phase adapted dressing.	Population: Patients with infected (n=16) and non-infected (n=28) VLUs and a wound size up to 20 × 10 cm². Data sources: The number of dressings and costs were taken from the 42 day clinical trial conducted by the authors.	Model structure: Cost calculator. Time horizon: 42 days Cycle length: NA	Primary outcome: The highest costs per patient were observed in wound-phase adapted dressing only. €336.27 Octenidine-based wound gel + wound-phase adapted dressing was €330.35 per patient. Octenidine-based wound gel alone had the lowest cost per patient. €244.12 Outcomes driven by early healing as a result of Octenidine and reduction in the need for wound-phase adapted dressings.	Trial data was used to determine the number of dressing changes for each arm, rather than using assumptions. Limitation: Short time horizon which does not reflect the entire patient pathway.

Study author, design and location	Intervention(s) and comparator(s)	Population and key data sources	Model structure	Relevant outcomes	EAG comments
Author: Jemec, 2014 (Jemec et al. 2014) Design: Cost-comparison Location: United Kingdom	Intervention: Active ionic silver complex dressing (Biatain Ag) Comparator: Non-silver dressing	Population: People with hard-to-heal VLUs (infection and non-infected). Data sources: Unit costs: dressings from the Drug tariff and secondary care costs from NHS reference costs.	Model structure: Decision tree. 3 possible outcomes; healed, healing and no improvement. Those with no improvement then referred to specialist care. Time horizon: 4 weeks Cycle length: NA	Primary outcome: Sliver dressing was cost saving, £141.57 per person. The treatment cost with silver treatment (£1,326.57) compared with non-silver treatment (£1,468.14). Secondary outcome: Silver dressing time-to-healed wound was lower (13.8 weeks) compared with non-silver treatment (16.7 weeks).	VLU with no improvement resulted in referral to secondary care services. Secondary care included an initial assessment, follow up, Ankle Brachial Pressure Index assessment and duplex scan. Ulcer infection was not included as a health state. Limitation: Only a 4 week time horizon was used.

Study author, design and location	Intervention(s) and comparator(s)	Population and key data sources	Model structure	Relevant outcomes	EAG comments
Author: Mensor, 2017 (Mensor et al. 2017) Design: Cost- comparison Location: Brazil	Intervention: Silver alginate dressing Comparator: Calcium alginate dressing	Population: Infected (n NR) or critically colonised hard-to-heal wounds (n NR) (diabetic foot ulcers, leg venous ulcers and pressure ulcers) Data sources: Unknown	Model structure: Decision tree Time horizon: Unknown Cycle length: NA	Primary outcome: Cost savings of approximately 40 thousand Brazilian Reais per patient with silver alginate dressing. Treatment costs 35 to 40% less for the silver group. Secondary outcome: Positive bacteriological status and infection signs avoided 22% and 30% respectively with silver alginate dressing.	Limitation: Due to being a conference abstract there was limited detail on the sources of data used or methodology.

Study author, design and location	Intervention(s) and comparator(s)	Population and key data sources	Model structure	Relevant outcomes	EAG comments
Author: Nherera, 2016 (Nherera et al. 2016) Design: Cost-utility Location: United States	Intervention: Cadexomer iodine (CI; IODOSORB™) dressing plus standard care Comparator: Standard care (SOC) alone (dressing without iodine)	Population: Chronic VLU (>6 months' duration, infected and non-infected) Data sources: Utility data taken from a cost-utility study comparing bio-electric stimulation therapy compared to SOC with chronic, nonhealing wounds. US costs from Medicare. Costs include once weekly dressing change and debridement.	Model structure: Markov model with 4 health states; stalled/non-healing, healed, infected or dead. Time horizon: 52 weeks Cycle length: 1 week	Primary outcome: CI+SOC was found to be a dominant treatment. QALY gain of 0.03 and cost savings of \$643 per patient over 52 weeks. Secondary outcomes: 61% of wounds are expected to heal with CI+SOC compared to 54% treated with SOC alone over the 52-week period.	Infection was included as a health state but clearance of infection not a key outcome. Cost of additional adjunctive therapies such as negative pressure or low-dose ultrasound were not included; assumed to be used at the same rate between the treatment groups. Limitation: The utility data was taken from a UK study on chronic non-healing wounds, not infected leg ulcer specific.

Study author, design and location	Intervention(s) and comparator(s)	Population and key data sources	Model structure	Relevant outcomes	EAG comments
Author: Walter, 2017 (Walter et al. 2017) Design: Cost- comparison Location: Austria	Intervention: PluroGel micelle-matrix-based dressing with 1% silver sulphadiazine (Medline Industries, Inc) Comparator: Silver-dressing, Hydrogel-dressing, Medical-honey, Impregnated-dressing and Good-wound-care (GWC).	Population: People with complex wounds (ulcers): venous, diabetic, arterial, mixed. Data sources: Healing rates derived from a systematic literature review. Direct medical costs for Austria.	Model structure: Markov. 3 health states included unhealed, healed and death. Time horizon: 1 year Cycle length: Unknown	Primary outcome: In venous wounds PluroGel costs amount to €3,771 (silver dressing: €4,644 ; hydrogel-dressing: €4,538 ; medical-honey: €4,676 ; impregnated dressing: €4,324 ; GWC: €6,764). Secondary outcome: With PluroGel, patients reach the median healing-rate after 17 weeks. All comparators need prolonged healing-time (silver-dressing: 21 weeks; hydrogel-dressing: 21 weeks; medical-honey: 19 weeks; impregnated-dressing: 21 weeks; GWC: 22 weeks). Ulcer-free-weeks of PluroGel were 31 weeks. All treatment alternatives show significantly fewer ulcer-free weeks (24.5 to 27.5 weeks).	The model considered treatment changes and relapse. Limitation: Due to being a conference abstract there was limited detail on the sources of data used or methodology. The location of the complex wound was not detailed in the abstract.

Abbreviations: CI – Cadexomer iodine; cm – Centimetres; DACC – Dialkylcarbonyl chloride; NA – Not applicable; NHS – National Health Service; NR – Not recorded; PHMB – Polyhexamethylene biguanide; SOC – Standard of care; UK – United Kingdom; US – United States; VLU – Venous leg ulcer.

7 Economic evaluation

7.1 *Economic model*

A pragmatic literature search of published peer-reviewed model structures was conducted to help inform the economic model for this assessment. This was a high-level search of the NICE website and PubMed with no structured search strategy. All models identified were cohort models, with a Markovian structure being the most common (Chalkidou et al. 2018, NICE 2022, Ashby et al. 2014, Walzer et al. 2018, Scanlon et al. 2005, Graves et al. 2014, Guest et al. 2022). 1 decision tree model was identified (Jemec et al. 2014). Health states included in the Markov models usually were 'healed' and 'unhealed' or 'ulcer' or 'open' (Chalkidou et al. 2018, Ashby et al. 2014, Walzer et al. 2018, Scanlon et al. 2005, Graves et al. 2014, Guest et al. 2022). Some studies included states for 'infection' or 'complicated' or 'not infected' (Chalkidou et al. 2018, Walzer et al. 2018, Guest et al. 2022), or states to indicate wound progression (for example, 'deteriorating' or 'improved') (Walzer et al. 2018, Guest et al. 2022). 'Death' was included as a health state in 3 models (Chalkidou et al. 2018, Ashby et al. 2014, Graves et al. 2014).

The population in the decision problem for this assessment, as described in the scope (NICE 2024b), focused on leg ulcers with local infections. The EAG leveraged existing model structures and adapted them to include 4 health states: 'infected, unhealed'; 'non-infected, unhealed'; 'healed', and 'death' to align with the decision problem.

Additional components of the decision problem, in relation the economic analysis, including which sub-groups were not assessed are outlined in Table 7.1 (YHEC 2024). The interventions included in the model are AMDs available for prescription in the NHS listed on Part IX of the Drug Tariff. These have been grouped by agent and sub-agent as described in Section 2.2. The model user can select which analysis they would like to view, from the following options:

1. Principal analysis.
2. Silver sub-agent analysis.

- 3. Iodine sub-agent analysis.
- 4. Honey sub-agent analysis.

The principal analysis compares all agents. The model runs a fully incremental analysis and a pairwise analysis between agents. Additionally, sub-agent analyses can be run to compare the relevant sub-agents. The results of the principal and sub-agent analyses will present the total and incremental health effects and costs, as well as the incremental cost-effectiveness ratio (ICER) and incremental net monetary benefit (NMB).

A time horizon of 1 year has been used in the model to reflect the duration of key studies used to inform the model inputs (see sections below). The methods used to inform the model parameters are discussed in the following sections.

Table 7.1: Finalised key decision elements

Subgroups	No population subgroups were considered in the model, due to a paucity of evidence.
Time horizon	1 year.
Health effects	Quality adjusted life years (QALYs) and life years (LYs).
Model outcomes	Probabilistic and deterministic discounted, patient costs; QALYs, and LYs. Probabilistic and deterministic ICER; NMB. Probabilistic and deterministic fully incremental analysis.

Abbreviations: QALYs – Quality adjusted life years; LYs – Life years; ICER – Incremental cost effectiveness ratio; NMB – Net monetary benefit.

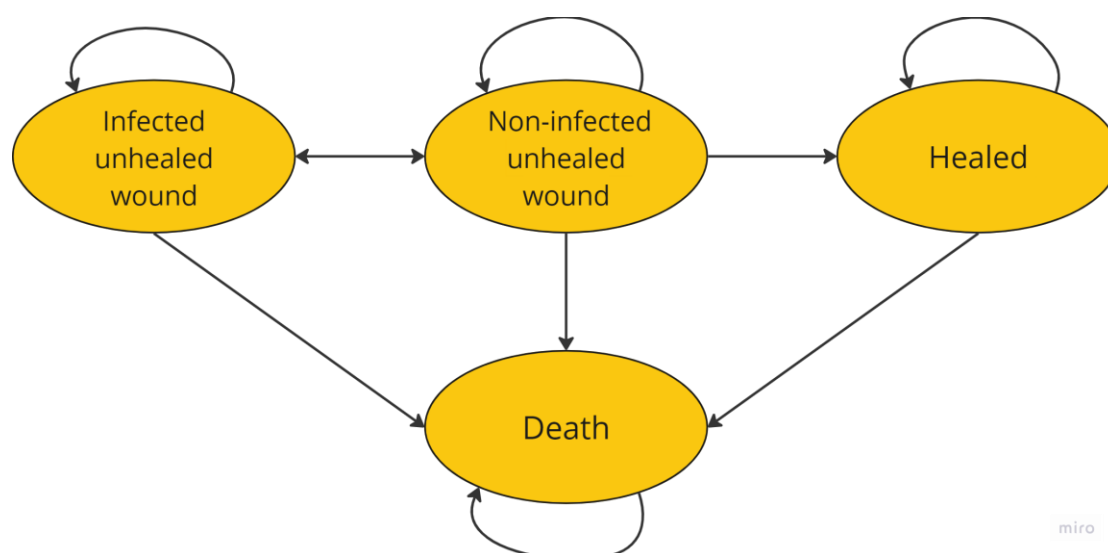
7.2 *Model structure*

As described in Section 7.1, the EAG developed a Markov model for this analysis. This model includes the following health states; ‘infected, unhealed’, ‘non-infected, unhealed’, ‘healed’, and ‘death’ (see Figure 7.1). The arrows represent direction of movement between health states. The cohort will begin in the ‘infected, unhealed’ health state and then either remain in this health state or transition to the ‘non-infected, unhealed’ health state. The cohort in the ‘non-infected, unhealed’ health state can

either return to the 'infected, unhealed' state or heal completely. It was assumed that, once healed, a leg ulcer could not reoccur within the time horizon (please see Section 7.2.1 for more detail about this assumption). Therefore, once the cohort has moved into the 'healed' health state, they remain in this health state until death or the end of the time horizon. The cohort can move to the death state from all health states.

The model has a 1-year time horizon, with weekly cycles, to capture the short-term impacts of infected leg ulcers (for example, adverse events and complications of infections). The EAG considered a 1-year time horizon to be the most appropriate to capture all relevant costs and consequences associated with treating infected leg ulcers. This approach aligns with previously published, peer reviewed economic models which, therefore, adds validation to this approach (Walzer et al. 2018, Guest et al. 2022). The EAG chose to focus on short-term impacts because the primary benefit of AMDs is infection resolution, which is the point at which the wound becomes uninfected (BMJ Publishing Group Ltd and the Royal Pharmaceutical Society of Great Britain 2024). The model captures the resource use and associated costs with treating an infected leg ulcer, as well as measuring HRQoL.

Figure 7.1: Model structure



7.2.1 *Model assumptions*

Table 7.2: Model assumptions

Assumption	Justification
Once healed, the cohort remain in the healed state or die. It was assumed that a wound (and/or infection of that wound) cannot reoccur, once the wound is healed, during the time horizon of the model.	The outcomes from the clinical SLR did not report the recurrence of a leg-ulcer. Furthermore, there is a paucity of data to inform whether time to local infection resolution and the initial choice of AMD would impact whether the leg ulcer would reoccur. Despite this lack of evidence, clinicians report that recurrences do occur, however, there is no rationale that AMDs change the relative risk of recurrence, according to clinical feedback.
The cohort remains on AMDs in the non-infected, unhealed wound health state.	The clinical data informing the model used the 'percentage with complete healing' end point and time to infection resolution was not reported in many studies. The participants in the clinical evidence informing the model did not discontinue the dressing following infection resolution. This is sometimes observed in clinical practice, however, the EAG acknowledge that this is not best practice. Best practice is to discontinue AMDs once infection has resolved. To avoid introducing additional uncertainty and underestimating the potential efficacy of AMDs, this assumption was required. Scenarios are explored around this assumption.
Once a percentage of the cohort transitions to the 'healed' health state, they automatically discontinue their AMD and transition to the second line treatment.	The EAG would not expect a healed ulcer to require an AMD, because AMDs are intended for wounds with infection based on AMD best practice.
The per-week rate of infection resolution was assumed to be proportional to the per-week healing rate at 4 weeks.	Clinical expert review of these assumptions suggested that the assumption that rate to healing was proportional to the rate to infection resolution was too simplistic. One clinical expert stated that there may be a link between infection resolution and healing but noted that this will be impacted by many components. Indeed, clinical experts highlighted that there were a range of other prognostic factors influencing the rate of infection resolution and healing, including, but not limited to ulcer size, wound duration and other treatments (for example, compression bandaging). However, these assumptions have been applied to the model due to the lack of evidence available to inform an alternative approach and rate of infection resolution was not included as an outcome in the studies informing

Assumption	Justification
	efficacy. The alternative option was to assume clinical equivalency.
When a proportion of the cohort discontinues an AMD, they move onto a weighted basket containing all types of AMD.	At the user preference workshop, clinical experts stated that cycling of different dressings could occur. In the absence of data to inform specific treatment pathways, or efficacy data for different lines, it was deemed appropriate to use a weighted basket.
When the cohort transitioned to second line, movement from the 'non-infected, unhealed' to the 'healed' health state adopted the trajectory of the curve reported in Guest et al (Equation 7.1.) (Guest et al. 2018).	The healing rate of leg ulcers over a year is not linear, as observed in Figure 1 of Guest et al (2018) (Guest et al. 2018). Therefore, applying a per-week, fixed transition probability would overestimate or underestimate the healing time. This was confirmed by clinical experts, who highlighted that applying a 12-week rate of healing to leg ulcers overestimated the percentage healed.
AMD-related adverse events and complications of leg ulcers were not modelled explicitly. Instead, the percentage of people hospitalised was used as a proxy.	The EAG identified a number of adverse events of interest including (NICE 2020): • Infection, including osteomyelitis and septicaemia • Allergic contact dermatitis • Malignancy • Chronic pain • Impaired mobility • Sinus formation and fistula Opinions from clinical experts differed regarding which complications were important to model. There was also a lack of robust data available to inform incidence rates and utility decrements. All clinical experts agreed that, in the absence of robust data to inform the model, it was appropriate to use hospitalisation rates as a proxy.

Assumption	Justification
Presence of a leg ulcer has no impact on mortality.	While there are some serious complications of leg ulcers that are fatal (for example sepsis), there is a lack of evidence to inform (i) rates of these complications and (ii) the mortality probability. Hospitalisation was used as a proxy for complications and, there was a paucity of evidence to show the percentage of people who die because of a leg ulcer hospitalisation. General population mortality was applied.
Where there was no data to inform the number of dressings per health state, a ratio of 2:1 was applied to the number of dressings in the 'non-infected, unhealed' health state to derive the number of dressings in the 'infected, unhealed' health state. This ratio was derived from Meaume et al (2005) who reported the number of elemental silver dressings used in the first 2 weeks and the following weeks (Meaume et al. 2005).	In best practice, AMDs are discontinued following resolution of infection, however, clinical experts highlighted that not all trusts will adhere to the best practice guidelines. Several studies observe a reduction in the number of dressings following infection resolution including case studies in Melamed et al, (2021) and Meaume et al (2005) (Melamed et al. 2021, Meaume et al. 2005). This was modelled as the base case.
Health state costs informed by resource use data from 2019 (Guest and Fuller 2023).	Most recent year that is not affected by the COVID-19 pandemic. Other scenarios can be done (e.g. 2021). Limitation because COVID-19 pandemic has affected primary and community care.
Health state cost is assumed equivalent for both unhealed wound states (that is, regardless of whether the wound was infected or not).	Guest et al (2023) did not disaggregate leg ulcer resource use by infection or healing status (Guest and Fuller 2023). Therefore, it was assumed that the resource use data was a combined cohort of people with unhealed infected and unhealed non-infected leg ulcers. It was noted by clinical experts that those with infected wounds would incur more resources and therefore higher costs. This was assessed in scenario analysis.
The utility associated with a locally-infected leg ulcer is assumed to be equal to the utility associated with a non-infected leg ulcer.	There was a paucity of data to inform utility values specific to locally-infected leg ulcers. A scenario was run as this may not reflect actual patient experiences.

Assumption	Justification
There is an ongoing cost associated with the 'healed' health state assumed to be 4.5 times less than the 'non-infected, unhealed' health state.	Guest et al (2023) did not disaggregate leg ulcer resource use by infection or healing status (Guest and Fuller 2023). However, it was highlighted in Guest et al (2018) that there was an associated cost. Indeed, over a year, Guest et al observed that the cost of managing a healed venous leg ulcer was 4.5 times less than that of managing an unhealed venous leg ulcer over a year (Guest et al. 2018). Given the properties of a markov model, it was not possible to track people to remove the healed cost after a certain period. Furthermore, a pragmatic search of literature could not identify how long a person would receive costs in the healed health state. However, given the time horizon of the model (1 year) aligns with the resource use data, the EAG find it appropriate to apply this cost for the total model time horizon.

Abbreviations: SLR – Systematic literature review; AMD – Antimicrobial dressing; EAG – External assessment group; NICE – National Institute for Health and Care Excellence; COVID – Coronavirus disease

7.2.2 *Model population*

The model population is informed by a retrospective cohort study of venous leg ulcer management in the NHS (Guest et al. 2018). This study was judged to be relevant to the decision problem because it considered a large population of adults with venous leg ulcers (n=505) living in the UK and being treated by the NHS. Based on this study, the model cohort was defined using an average starting age of 73 years with 39% of people being assigned male at birth.

7.2.3 *Clinical parameters*

The key clinical parameters used in the model were informed by published literature, where available. Clinical parameters used for the model were:

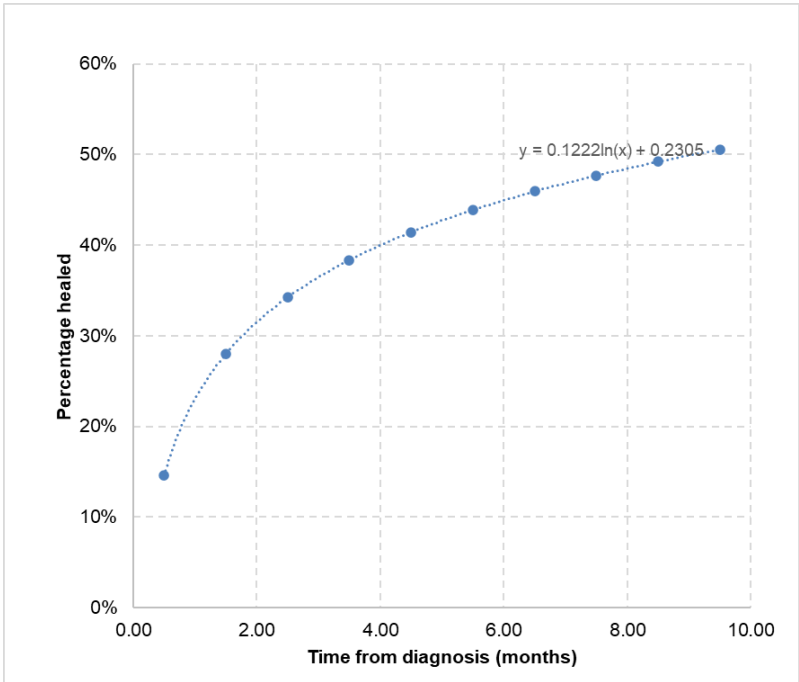
- Healing rate (See Section 7.2.3.1).
- Time to infection resolution (See Section 7.2.3.2).
- Recurrence of infection (See Section 7.2.3.3).
- Discontinuation (See Section 7.2.3.4).

7.2.3.1 Healing rate

The clinical review (Section 5) extracted several clinical endpoints from studies. The percentage of the population whose leg ulcers completely healed, at either 4 or 12 weeks, was reported in 22 studies across 6 agents. The studies determined by the EAG to be appropriate for each agent and sub-agent, and therefore used to inform the model, are presented in Table 7.3.

Real world evidence from the UK, of 505 people from the THIN database (Guest et al. 2018), showed that the percentage of leg ulcers completely healed in a population over time was non-linear. Therefore, studies reporting the percentage of the population completely healed at 4 weeks, if extrapolated linearly, were not comparable to the studies reporting the percentage of the population completely healed at 12 weeks. To allow for comparison, a non-linear equation (Equation 7.1) was fitted to data digitised from a plot presenting the percentage of venous leg ulcers healed over time (Figure 7.2 (Guest et al. 2018)). This was digitised using WebPlotDigitizer v4.8, a web-based tool to extract numerical data from plots and graph images (Rohatgi 2024). The results of the digitised plot were used to identify Equation 7.1.

Figure 7.2: Wound healing over time



Equation 7.1: Equation to derive the percentage of venous leg ulcers healed at any month

$$Y = 0.1222 * \ln(X) + 0.2305$$

It was assumed that the proportion of the population healed, regardless of the agent or sub-agent, would be a transformation of Equation 7.1. Therefore, Equation 7.1 was used to inform the percentage of leg ulcers healed at 4- and 12-weeks with standard of care. A ratio of these percentages allowed for the percentage of the population healed at 12 weeks to be estimated from the population healed at 4 weeks and vice versa.

Please note that Equation 7.1 was also used to inform percentage of the cohort moving from the 'non-infected unhealed wound' to the 'healed wound' health state, at a particular time point, for the cohort who discontinued to the second line basket.

The EAG base case used percentage healed to estimate a per-week rate of healing for each agent and sub-agent. Depending on the maximum number of weeks a particular agent was prescribed, as determined by clinical guidelines and evidence, the estimated per-week healing rate was used to inform the transition from the 'non-infected, unhealed' to the 'healed' health states. For example, agents that are prescribed for 12 weeks, such as honey, had a 12-week rate of healing applied. Agents that are prescribed for 4 weeks, such as silver, had a 4-week rate of healing applied. The details of the selected studies and their appropriateness is outlined in Table 7.3 and the per-week healing rate and the corresponding weeks to complete healing is presented in Table 7.4.

This per-week rate informed the model until discontinuation to the second line mixed basket. When the cohort transitioned to second line, movement from the 'non-infected, unhealed' to the 'healed' health state adopted the trajectory of Equation 7.1.

Once a percentage of the cohort transitions to the "healed" health state, they automatically discontinue their AMD and progress to the second line basket.

7.2.3.2 Time to infection resolution

Of the studies identified in the clinical review that informed the clinical evidence of this assessment, 11 reported outcomes related to infection resolution. However, there was a paucity of evidence to inform the average time to infection resolution (Section 5). Gago et al (2008) reported the weeks to infection resolution as 2.52, 3.80 and 3.88 for 3 types of silver dressings (Gago et al. 2008). An average was taken to estimate a mean time to infection resolution of 3.4 weeks (approximately 24 days) which falls within the range outlined by Melotte (1985) of 7 to 33 days and Forlee et al (2014) of 14 to 49 days (Melotte et al. 1985, Forlee et al. 2014). To allow for rate of infection resolution to differ by agent, it was necessary to assume the rate of infection resolution was proportional to the rate of healing, because of the lack of evidence. An alternative option, considered by the EAG, was to assume clinical equivalence between the agents. This option was deemed less appropriate as it was not supported by literature, would not provide an answer to the objectives of this assessment. However, the EAG conducted a scenario analysis in which clinical equivalence across all efficacy measures was assumed (i.e. a simple cost comparison).

Gago et al (2008) reported that 36% of the population had completely healed at 8 weeks (Gago et al. 2008). Using a conversion ratio (derived as per the methods in Section 7.2.3.1), the EAG estimated that 26% of the population had completely healed at 4 weeks. This estimate was used to derive a per-week healing rate from 0 to 4 weeks.

The ratio of the per-week infection resolution and per-week healing rates from 0 to 4 weeks was subsequently calculated as 3.85 using the aforementioned estimates from Gago et al (2008) (Gago et al. 2008). The ratio was applied to the per-week healing rate for each agent from week 0 to 4, to derive the time to infection resolution for each agent and sub-agent in the model. This data is presented in Table 7.4.

Table 7.3: Studies selected to inform the time to per-week healing rate

Agent	Study selected	Population	EAG comment on suitability
Silver	Forlee et al (2014) (Forlee et al. 2014)	See silver salts and compounds'	Assumed equivalent the sub-agent with the smallest percentage healed (conservative assumption)
Silver salts and compounds	Forlee et al (2014) (Forlee et al. 2014)	14 people with moderate to highly exuding venous leg ulcers with 1 or more clinical signs of infection	This population consisted of a small number of South African participants. The percentage healed at 4 weeks appeared comparable to findings from Miller et al. The indication aligns with the decision problem; however, the rate of infection resolution was not included as an endpoint.
Elemental silver	Miller et al (2010) (Miller et al. 2010)	133 people with at least one of the signs of infection or critical colonization in a lower leg ulcer.	Miller reported the healing rate at 4 and 12 weeks in a large, UK RCT. It is expected that the healing rate at 12 weeks is smaller than 4 weeks. This trend was not observed in Miller et al (with an increased healing rate at 12 weeks). Therefore, the 4 week input was used in the model. The indication aligns with the decision problem; however, the rate of infection resolution was not included as an endpoint.
Silver with anti-biofilm mechanisms	N/A	N/A	N/A
Iodine	Miller et al (2010) (Miller et al. 2010)	See 'elemental silver'	Assumed equivalent the sub-agent with the smallest percentage healed (conservative assumption)
Cadexomer iodine	Miller et al (2010) (Miller et al. 2010)	See 'elemental silver'	See 'elemental silver'
Povidone iodine	N/A	N/A	N/A
Honey	Moghazy et al (2010) (Moghazy et al. 2010)	See 'monofloral honey'	Assumed equivalent the sub-agent with the smallest percentage healed (conservative assumption)

Agent	Study selected	Population	EAG comment on suitability
Manuka honey	Molle et al (2023) (Molle et al. 2023)	25 people with infected leg ulcers	The indication aligned with the decision problem. However, the percentage healed at 4 weeks is not numerically superior compared with other AMDs (in general), which clinical experts found to be surprising. However, out of the 4 studies to inform honey, this study was the only study that reported the percentage of people with complete healing for manuka honey at 4 weeks. Biglari et al (2013) also reported the percentage of people with manuka honey dressings achieving complete healing, however, there was a large uncertainty estimate associated with the follow-up time (4.46 (3.83)). Therefore, the EAG questioned the appropriateness of this study. Molle et al (2023) reported that at day 15, 84% of infections had resolved, however, this could not be used for the model with its current structure. Caution is advised when drawing comparisons with the other agents. The EAG acknowledges the potential for varied impact of different Manuka honey based on the presence of specific components, such as methylglyoxal.
Monofloral honey	Moghazy et al (2010) (Moghazy et al. 2010)	30 people with infected diabetic foot ulcers.	This was the only population reporting monofloral honey, however, the indication (people with diabetic foot ulcers) differs from the decision problem. Caution is advised when drawing comparisons with the other agents.
Polyfloral honey	N/A	N/A	N/A
Chlorhexidine	N/A	N/A	N/A
Copper	Treadwell (2022) (Treadwell T et al. 2022)	25 people with hard to heal acute and chronic wounds	Treadwell et al did not explicitly state whether this population of hard to heal acute and chronic wounds were infected and the percentage healed at 4 weeks was larger than other studies for other agents.

Agent	Study selected	Population	EAG comment on suitability
			Caution is advised when drawing comparisons because this population was small and may have a less-severe leg ulcer.
PHMB	Vallejo et al (2022) (Vallejo et al. 2022)	25 hard-to-heal leg ulcers of >6 weeks duration with mixed aetiologies. Typical clinical signs of infection were absent in study participants at baseline, despite presence of bacteria and high colony-forming units.	Other studies eligibility criteria included 1 sign of clinical infection, which was absent from this population, however, the population did have a local infection (identified by bacterial load). The population size is small and may not adhere completely to the decision problem. Therefore, caution is advised when drawing comparisons.
DACC	N/A	N/A	N/A
Enzyme alginogel	N/A	N/A	N/A
Chitosan	Mo et al (2015) (Mo et al. 2015)	A subgroup of 35 infected unhealed chronic wounds including pressure ulcers, vascular ulcers, diabetic foot ulcers	Out of a total population of 45 wounds, a sub-group of 35 wounds with a local infection informed the model as per the decision problem. The ulcer aetiologies vary and include ulcers outside of the decision problem. Because of this and the small sample size, caution is advised when drawing comparisons.
Octendine	N/A	N/A	N/A

Abbreviations: DACC – Dialkylcarbamoyl chloride; EAG – External assessment group; NA – Not applicable; PHMB – Polyhexamethylene biguanide; RCT – Randomised controlled trial; UK – United Kingdom.

Table 7.4: Efficacy data by agent

Agent	Maximum time agents are prescribed (as indicated by clinical guidelines)	Reference	Percentage 100% healed	Timepoint of 100% healing	Per week rate of infection resolution (transition from 'infected, unhealed' to 'non-infected, unhealed')	Per-week rate of healing (transition from 'non-infected, unhealed' to 'healed')	Reference and EAG comment of suitability
Silver	4 weeks	NHS Hertfordshire and West Essex. Integrated Care Board. Wound care products - Silver Dressings Guidance. This stated that that silver dressings "should be used for a maximum of 2-4 weeks of treatment (Brassington and Crotty 2024)	21.4%	4 weeks	0.2324	0.0603	Assumed equivalent the sub-agent with the smallest percentage healed (conservative assumption).
Silver salts and compounds	4 weeks		21.4%	4 weeks	0.2324	0.0603	Forlee et al (2014) (Forlee et al. 2014).
Elemental silver	4 weeks		22.6%	4 weeks	0.2463	0.0639	Miller et al (2010) (Miller et al. 2010).
Silver with anti-biofilm mechanisms	4 weeks		N/A	N/A	N/A	0.0000	No study reported the 4-week or 12-week percentage 100% healed for silver with anti-

Agent	Maximum time agents are prescribed (as indicated by clinical guidelines)	Reference	Percentage 100% healed	Timepoint of 100% healing	Per week rate of infection resolution (transition from 'infected, unhealed' to 'non-infected, unhealed')	Per-week rate of healing (transition from 'non-infected, unhealed' to 'healed')	Reference and EAG comment of suitability
							biofilm mechanisms.
Iodine	12 weeks	British National Formulary (2024) (BMJ Publishing Group Ltd and the Royal Pharmaceutical Society of Great Britain 2024). Iodine dressings. Accessed 02.10.2024.	26.3%	4 weeks	0.2943	0.0448	Assumed equivalent the sub-agent with the smallest percentage healed (conservative assumption).
Cadexomer iodine	12 weeks	It was stated that "Iodoflex and Iodosorb: max. duration up to 3 months in any single course of treatment."	26.3%	4 weeks	0.2943	0.0448	Miller et al (2010) (Miller et al. 2010).
Povidone iodine	12 weeks	In the absence of data specific to iodine-containing fabric dressings,	N/A	N/A	N/A	N/A	No study reported the 4-week or 12-week percentage 100% healed for povidone iodine.

Agent	Maximum time agents are prescribed (as indicated by clinical guidelines)	Reference	Percentage 100% healed	Timepoint of 100% healing	Per week rate of infection resolution (transition from 'infected, unhealed' to 'non-infected, unhealed')	Per-week rate of healing (transition from 'non-infected, unhealed' to 'healed')	Reference and EAG comment of suitability
		a maximum duration of use of 12 weeks has been applied to all iodine dressings.					
Honey	12 weeks	There were no clear UK clinical guidelines for honey dressings. Given that studies reported 12 week endpoints, it was assumed that people could remain on treatment for a maximum of 12 weeks.	13.3%	4 weeks	0.1379	0.0210	Assumed equivalent the sub-agent with the smallest percentage healed (conservative assumption).
Manuka honey	12 weeks		13.6%	4 weeks	0.1409	0.0214	Molle, et al (2023) (Molle et al. 2023).
Monofloral honey	12 weeks		13.3%	4 weeks	0.1379	0.0210	Moghazy et al (2010) (Moghazy et al. 2010).
Polyfloral honey	12 weeks		N/A	N/A	N/A	N/A	No study reported the 4-

Agent	Maximum time agents are prescribed (as indicated by clinical guidelines)	Reference	Percentage 100% healed	Timepoint of 100% healing	Per week rate of infection resolution (transition from 'infected, unhealed' to 'non-infected, unhealed')	Per-week rate of healing (transition from 'non-infected, unhealed' to 'healed')	Reference and EAG comment of suitability
							week or 12-week percentage 100% healed for polyfloral honey.
Chlorhexidine	12 weeks	Conservative assumption in the absence of data	N/A	N/A	N/A	N/A	No study reported the 4-week or 12-week percentage 100% healed for chlorhexidine.
Copper	4 weeks	There were no clear UK clinical guidelines for copper dressings. However, MedCU (a producer of copper dressings) states that "Reoccurring application of copper dressings	32%	4 weeks	0.3716	0.0964	Treadwell (2022) (Treadwell T et al. 2022).

Agent	Maximum time agents are prescribed (as indicated by clinical guidelines)	Reference	Percentage 100% healed	Timepoint of 100% healing	Per week rate of infection resolution (transition from 'infected, unhealed' to 'non-infected, unhealed')	Per-week rate of healing (transition from 'non-infected, unhealed' to 'healed')	Reference and EAG comment of suitability
		can continue for up to 30 days ". Therefore, it is assumed people can remain on copper dressings for 4 weeks (MedCu Technologies Ltd. 2021)					
PHMB	12 weeks	There were no clear UK clinical guidelines for PHMB dressings. Given that studies reported 12-week endpoints, it was assumed that people could remain on treatment for a maximum of 12 weeks	16%	12 weeks	0.0955	0.0145	Vallejo et al (2022) (Vallejo et al. 2022).

Agent	Maximum time agents are prescribed (as indicated by clinical guidelines)	Reference	Percentage 100% healed	Timepoint of 100% healing	Per week rate of infection resolution (transition from 'infected, unhealed' to 'non-infected, unhealed')	Per-week rate of healing (transition from 'non-infected, unhealed' to 'healed')	Reference and EAG comment of suitability
DACC	12 weeks	Conservative assumption in the absence of data	N/A	N/A	N/A	N/A	No study reported the 4-week or 12-week percentage 100% healed for DACC.
Enzyme alginogel	12 weeks	Conservative assumption in the absence of data	N/A	N/A	N/A	N/A	No study reported the 4-week or 12-week percentage 100% healed for enzyme alginogel.
Chitosan	4 weeks	There were no clear UK clinical guidelines for Chitosan dressings. Given that studies reported 4-week endpoints, it was assumed that people could	21.4%	4 weeks	0.2324	0.0603	Mo et al (2015) (Mo et al. 2015).

Agent	Maximum time agents are prescribed (as indicated by clinical guidelines)	Reference	Percentage 100% healed	Timepoint of 100% healing	Per week rate of infection resolution (transition from 'infected, unhealed' to 'non-infected, unhealed')	Per-week rate of healing (transition from 'non-infected, unhealed' to 'healed')	Reference and EAG comment of suitability
		remain on treatment for a maximum of 4-weeks					
Octenidine	12 weeks	Conservative assumption in the absence of data	N/A	N/A	N/A	N/A	No study reported the 4-week or 12-week percentage 100% healed for Octenidine.

Abbreviations: BMJ – British Medical Journal; DACC – Dialkylcarbamoyl chloride; EAG – External assessment group; NA – Not applicable; NHS – National Health Service; PHMB – Polyhexamethylene biguanide; UK – United Kingdom.

7.2.3.3 Recurrence of infection

In the absence of data to inform this parameter, it was assumed that there is no recurrence of infection.

7.2.3.4 Discontinuation

Clinical experts advised the EAG that they would expect a typical person with a leg ulcer to progress rapidly through a sequence of AMDs and other dressings. To adhere to what is observed in clinical practice, the model was designed to allow for discontinuation from the AMD applied at first line. However, there are no data to suggest the order of the sequence, nor the efficacy of specific antimicrobial dressings when used in different lines.

Therefore, it was assumed that, after discontinuation from the first line AMD, the cohort would move onto a “basket” of treatments as their second line. The efficacy of the mixed basket was informed by a published, peer-reviewed paper of 505 people identified from the UK-specific THIN database. The efficacy data associated with the second line treatment was assumed to be equivalent regardless of the AMD applied at first line. The per week rate of infection resolution was derived using the ratio from Gago et al (2008) as per the other AMDs (Gago et al. 2008).

Table 7.5: Second line basket efficacy data

Percentage 100% healed	Per week rate of infection resolution (transition from ‘infected, unhealed’ to ‘non-infected, unhealed’)	Per-week rate of healing (transition from ‘non-infected, unhealed’ to ‘healed’)	Reference
4 weeks: 22.0% 12 weeks: 35.5%	0.240	4 weeks: 0.0622 12 weeks: 0.0365	(Guest et al. 2018)

In clinical practice, discontinuation can occur for a variety of reasons, including local skin irritation and pain (Treadwell T et al. 2022). Given that people with leg ulcers can discontinue for multiple reasons, regardless of their healing status, it was assumed that, upon discontinuation of first line, the cohort would remain in the same health state for that cycle of the model.

The model considered 2 types of discontinuations.

1. A per cycle rate of discontinuation.
2. Discontinuation after a certain number of weeks as clinically indicated.

The percentage of the cohort discontinuing for personal preference or treatment-related adverse events was informed, where data was available, by the clinical trials from which the efficacy data was sourced. However, only 3 trials reported the percentage of the population who discontinued, therefore, where this data was missing, it was assumed that per-week discontinuation for adverse events was assumed to be 0. This data is presented in Table 7.6.

The second type of discontinuation was the maximum amount of time people could remain on the agent (the maximum prescription time), as indicated by clinical guidance. Where possible, clinical guidelines were used to inform the model. Where clinical guidance was unclear or unavailable, guidance from either the BNF or the manufacturer's website was used to inform the model. Where this was not available, the length of the clinical trial was used to inform this end point. Table 7.6 shows the parameters used in the base case of the model.

Table 7.6: Per week rate of discontinuation

Agent	Percentage discontinuing for patient preference or treatment-related adverse events	Time point	Reference	Per-week rate of discontinuation
Silver	0%	12 weeks	Assumed equivalent the sub-agent with the smallest percentage healed (conservative assumption)	0.0000
Silver salts and compounds	7.1%	6 weeks	(Forlee et al. 2014)	0.0124
Elemental silver	0%	12 weeks	No discontinuations were reported in Miller et al (2010) (Miller et al. 2010)	0.0000
Silver and anti-biofilm mechanisms	N/A	N/A	No study reported the 4-week or 12-week percentage 100% healed for silver with anti-biofilm mechanisms.	N/A
Iodine	0%	12 weeks	Assumed equivalent the sub-agent with the smallest percentage healed (conservative assumption)	0.0000
Cadexomer iodine	0%	12 weeks	No discontinuations were reported in Miller et al (2010) (Miller et al. 2010)	0.0000
Povidone iodine	N/A	N/A	No study reported the 4-week or 12-week percentage 100% healed for povidone iodine.	N/A

Agent	Percentage discontinuing for patient preference or treatment-related adverse events	Time point	Reference	Per-week rate of discontinuation
Honey	0%	4 weeks	Assumed equivalent the sub-agent with the smallest percentage healed (conservative assumption)	0.0000
Manuka honey	0%	4 weeks	No discontinuations were reported in Molle, et al. (Molle et al. 2023)	0.0000
Monofloral honey	0%	4 weeks	No discontinuations were reported in Moghazy et al (2010). (Moghazy et al. 2010)	0.0000
Polyfloral honey	N/A	N/A	No study reported the 4-week or 12-week percentage 100% healed for polyfloral honey.	N/A
Chlorhexidine	N/A	N/A	No study reported the 4-week or 12-week percentage 100% healed for chlorhexidine	N/A
Copper	12%	4 weeks	(Treadwell T et al. 2022)	0.0320
PHMB	4%	6 weeks	(Vallejo et al. 2022)	0.0068
DACC	N/A	N/A	No study reported the 4-week or 12-week percentage 100% healed for DACC	N/A
Enzyme alginogel	N/A	N/A	No study reported the 4-week or 12-week percentage 100% healed for enzyme alginogel	N/A

Agent	Percentage discontinuing for patient preference or treatment-related adverse events	Time point	Reference	Per-week rate of discontinuation
Chitosan	0%	4 weeks	No discontinuations were recorded in Mo et al (2015). (Mo et al. 2015)	0.0000
Octenidine	N/A	N/A	No study reported the 4-week or 12-week percentage 100% healed for enzyme Octenidine	N/A

Abbreviations: DACC – Dialkylcarbamoyl chloride; NA – Not applicable; PHMB – Polyhexamethylene biguanide.

7.2.4 *Resource use and cost parameters*

7.2.4.1 *Cost of AMDs*

AMD costs were sourced from Part IX of the Drug Tariff (NHS Business Services Authority 2024). To appropriately assess the cost differences of dressings associated with each agent and sub-agent, a weighted average cost and standard error of all dressings containing the agent or sub-agent of interest was calculated.

Given that not all AMDs are prescribed uniformly across the population of people with leg ulcers, it was not appropriate to use the mean cost over all dressings in a particular agent. Therefore, it was necessary to identify data to inform the market share.

A pragmatic literature search was performed to identify published studies to inform this. A study conducted by Urwin et al (2022) reported the agent market share over 570 people with venous leg ulcers in the Northwest of the UK over a 2-week period (Urwin et al. 2022). The EAG considered this study was not appropriate to inform the model, first, because the market share was by agent, rather than by a particular category or type of dressing, therefore, the final estimates for each agent would be a simple mean. Furthermore, use of this study would require additional assumptions, for example, that resource use in Northwest of England is representative of the English and Welsh population, and data collected in that 2-week period is generalisable over the total time horizon of the model.

A second study conducted by Phillips et al (2020) was identified. Phillips et al used the Secure Anonymised Information Linkage (SAIL) database to identify primary care data of 25,792 people with venous leg ulcers between 2007 to 2017. This is a large population and appropriate long follow-up (Phillips et al. 2020). However, the SAIL database is exclusive to Wales, therefore, use of this data would require an assumption that the market share in Wales was equivalent to the English and Welsh populations. Furthermore, use of this data would require categorisation of the dressings which would require additional assumptions. Ultimately, this study was not considered appropriate to inform the market share.

NICE provided the EAG with CPRD analysis, which reported the usage of AMDs between 01/10/2018 and 31/3/2024. Upon initial inspection, the CPRD data was deemed inappropriate because it did not distinguish between prophylactic and interventional use of AMDs, nor was it guaranteed that the AMD was prescribed for the ulcer itself. Furthermore, it did not capture community care data. Despite these limitations, the EAG considered that the CPRD data the most appropriate of all of the imperfect sources. Furthermore, the CPRD data reported market share of 303 different types and sizes of AMDs, 231 of these aligned with the AMDs included in the model. This allows for fewer assumptions between the categories and the costs.

However, 71 dressings were in the drug tariff and not reported in the CPRD data, furthermore, 20% of the market share in the CPRD was unaccounted for as the dressings were not aligned with those in the drug tariff. To adjust for this, 3 options were considered:

1. 20% market share is redistributed across treatments with shares.
2. 20% market share is redistributed across treatments without shares.
3. 20% market share is redistributed across all treatments.

Option 3 was considered most appropriate because it allowed for even distribution of the market share across AMDs and ensured that AMDs with data will always have a larger weight than those without data, as, if these did not appear in the CPRD data, it is reasonable to assume they are used less frequently. Furthermore, when the costs for the three approaches were compared, the ones using option three were central between the two other methods. We were able to derive standard errors, therefore, variation in the AMD cost will be accounted for in the PSA. Furthermore, the EAG performed a scenario analysis with the minimum and maximum costs for agents.

The weighted average cost, corresponding standard errors and the minimum and maximum costs associated with each agent and sub-agent is presented in Table 7.7. The costs for all dressings in Part IX of the Drug Tariff and the CPRD market share is presented in Appendix H: Cost and market share of AMDs. The number of dressings

per pack across the sub-agents was most commonly 1 or a certain amount of grams/millilitres for gels.

Table 7.7: Weighted average cost, standard errors and range of costs for each agent and sub-agent

Agent	Weighted average cost per pack	Standard error	Minimum, Maximum
Silver	£7.52	£0.62	£0.57 to £68.82
Silver salts and compounds	£6.65	£0.75	£0.57 to £68.82
Elemental silver	£9.89	£1.72	£1.70 to £50.58
Silver with anti-biofilm mechanisms	£7.83	£1.11	£1.67 to £24.96
Iodine	£1.45	£1.04	£0.29 to £14.37
Cadexomer iodine	£8.69	£1.79	£2.15 to £14.37
Povidone iodine	£0.39	£0.05	£0.29 to £0.51
Honey	£3.03	£0.42	£0.47 to £29.31
Manuka honey	£2.76	£0.51	£0.74 to £29.31
Monofloral honey	£3.60	£0.58	£0.47 to £7.75
Polyfloral honey	£5.65	£1.48	£2.10 to £23.09
Chlorhexidine	£0.51	£0.17	£0.33 to £0.68
Copper	£5.18	£1.12	£1.85 to £8.27
PHMB	£8.33	£1.31	£0.72 to £34.13
DACC	£4.34	£0.75	£1.80 to £25.04
Enzyme alginogel	£18.20	£5.63	£8.44 to £27.96
Chitosan	£4.75	£2.34	£0.72 to £31.79
Octendine	£16.13	£10.98	£5.15 to £27.10
Average over all dressings (applied in second line basket)	£5.27	£0.33	£0.29 to £68.82

Abbreviations: DACC – Dialkylcarbamoyl chloride; PHMB – Polyhexamethylene biguanide.

7.2.4.2 Frequency of dressing application

People with leg ulcers require regular dressing changes, particularly if their leg ulcer has a local infection. To appropriately identify the cost associated with each dressing, the number of dressing changes per week for each agent and sub-agent were required.

The number of dressings per week data was reported in the appropriate study (that is, the study informing the efficacy data), this information was used for the model. If wear time was not reported in the study, other studies identified in the clinical SLR were searched for the appropriate data. If not reported in the studies, clinical evidence was sought and used.

It was assumed that the cohort in the “infected, unhealed” health state would experience more dressing changes than those in the “non-infected, unhealed” health state. Therefore, if a range was reported for dressing changes, the higher value in the range was used for the “infected, unhealed” health state, and the lower value was used for the “non-infected, unhealed” health state. If a range was not reported (that is, only a single value was reported) a multiplier was applied to the maximum wear time to derive the number of dressings in the “infected, unhealed” health state. The multiplier (1.79) was derived from Meaume et al (2005) who reported different wear times for weeks 1 and 2, compared to subsequent weeks (Meaume et al. 2005). This was a UK study of 99 UK people with either a venous leg ulcer or a pressure ulcer and, therefore, considered to be appropriate to the UK clinical setting. The values used in the base case of the model are summarised in Table 7.8.

Table 7.8: Number of dressings required per week

Agent	Infected, unhealed	Non-infected, unhealed	Reference and assumptions
Silver	1.49	1	Assumed equivalent to the Forlee et al paper (Forlee et al. 2014).
Silver salts and compounds	1.49	1	Forlee et al reported that wear time had a mean of 6.4 days (range 4.7 to 7.0) (Forlee et al. 2014). Therefore, it was assumed that infected, unhealed leg ulcers would require $7/4.7 = 1.49$ dressing changes per week, and non-infected, unhealed leg ulcers would require $7/7 = 1$ dressing per week.
Elemental silver	5.00	2.8	Meaume et al stated that in dressings were changed at least 5 times per week in weeks 1 and 2, which informed the value for the infected, unhealed cohort (Meaume et al. 2005). Dressings were changed at least every 2 to 3 days after week 2. The average of this was taken (2.5) to calculate $7/2.5 = 2.8$ dressings per week required for the non-infected, unhealed cohort.
Silver with anti-biofilm mechanisms	N/A	N/A	N/A.
Iodine	4.17	2.33	Assumed equivalent the sub-agent with the smallest percentage healed (conservative assumption).
Cadexomer iodine	4.17	2.33	Cadexomer iodine consists of Iodoflex paste dressing and Iodosorb ointment dressing (as per the drug tariff). Guidance states that Iodoflex can be worn for a maximum of 3 days (NHS Somerset Clinical Commissioning Group 2020). This input was assumed to apply to non-infected, unhealed wounds, giving $7/3=2.33$ dressing changes per week. A multiplier was derived from Meaume et al, 2005 to determine how many dressings would be used for infected, unhealed wounds (Meaume et al. 2005).
Povidone iodine	N/A	N/A	N/A.
Honey	1.79	1.00	Guidance states that honey dressings can remain in situ for up to 7 days (NHS Somerset Clinical Commissioning Group 2020). The maximum is assumed for the non-infected, unhealed health state.

Agent	Infected, unhealed	Non-infected, unhealed	Reference and assumptions
			A multiplier was derived from Meaume et al, 2005 to determine how many dressings would be used for infected, unhealed wounds (Meaume et al. 2005).
Manuka honey	1.79	1.00	Guidance states that honey dressings can remain in situ for up to 7 days (NHS Somerset Clinical Commissioning Group 2020). The maximum is assumed for the non-infected, unhealed health state. A multiplier was derived from Meaume et al, 2005 to determine how many dressings would be used for infected, unhealed wounds (Meaume et al. 2005).
Monofloral honey	1.79	1.00	Guidance states that honey dressings can remain in situ for up to 7 days (NHS Somerset Clinical Commissioning Group 2020). The maximum is assumed for the non-infected, unhealed health state. A multiplier was derived from Meaume et al, 2005 to determine how many dressings would be used for infected, unhealed wounds (Meaume et al. 2005).
Polyfloral honey	N/A	N/A	N/A.
Chlorexidine	N/A	N/A	N/A.
Copper	2.33	1	Melamed et al reported the number of dressing changes in 6 of 10 case reports (Melamed et al. 2021). It was most common that, while infected, people had their dressing changed every 3 days. $7/3 = 2.33$ Treadwell et al report that in the cohort of hard to heal acute and chronic wounds, dressings were changed once per week (Treadwell T et al. 2022). This is assumed to apply to the non-infected, unhealed health state.
PHMB	1.4	1	Guidance indicates that PHMB dressings can be left in place for 5 to 7 days (NHS Harrogate and District Foundation Trust 2018). 5 days is assumed for the infected, unhealed health state ($7/5 = 1.4$ dressing changes per week). 7 days is assumed for the non-infected, unhealed health state ($7/7 = 1$ dressing change per week).
DACC	N/A	N/A	N/A.
Enzyme alginogel	4.17	4.17	N/A.

Agent	Infected, unhealed	Non-infected, unhealed	Reference and assumptions
Chitosan	2.33	1.75	Mo et al reported that dressing change frequency was every 3–4 days depending on the conditions of the wound following the hospital's standard protocols of care (Mo et al. 2015). 3 days were assumed for the infected, unhealed health state ($7/3 = 2.33$). 4 days were assumed for the non-infected, unhealed health state ($7/4 = 1.75$).
Octenidine	N/A	N/A	N/A.

Abbreviations: DACC – Dialkylcarbamoyl chloride; NA – Not applicable; NHS – National Health Service; PHMB – Polyhexamethylene biguanide.

7.2.4.3 *Unhealed ulcer resource use*

The model offers the user several options for resource use. 2 studies are included, which describe resource use for venous leg ulcers from 2017/18, 2019, 2020 and 2021 (Guest and Fuller 2023) and resource use for arterial, mixed or unspecified leg ulcers in 2017/18, respectively (Guest et al. 2020). For the base case, 2019 data from 1,263 people in the UK THIN database were selected (Guest and Fuller 2023) given that these data had the largest sample size and contain the most recent information that was not impacted by the COVID-19 pandemic. However, this data has its limitations. First, because the THIN database records primary care data whereas, clinical experts highlighted that the majority of leg ulcer care is delivered in a community setting and, therefore, some resource use may be under reported. Second, because peri- and post-pandemic, online GP appointments and virtual wards have become more common, these data may not be reflective of a post-pandemic NHS. Therefore, the EAG conducted a scenario analysis applying data from 2021.

47% of people in the cohort informing resource use developed an infected wound in 2019 (Guest and Fuller 2023). However, the study did not report resource use disaggregated by infection. Given that these data consisted of a mixed population, it was assumed that the same resource use was applicable to both the infected, unhealed and the non-infected, unhealed health state. However, clinical experts highlighted that there are expected resource use differences between the 'infected unhealed wound' health state and the 'non-infected unhealed wound' health state. Therefore, a scenario analysis was conducted to investigate the impact of a higher health state costs for the 'infected unhealed wound' health state than the 'non-infected unhealed wound' health state.

Table 7.9: Resource use parameters

Resource use	Annual resources needed per person (N)	Annual resources needed per person (SD)	Percentage of the population requiring each resource (%)
GP visits			
GP surgery visits	7.10	6.00	82.0%
GP telephone consultations	1.40	0.40	11.0%
GP home visit	0.00	0.00	0.0%
Nurse visits			
Practice nurse visits	10.40	9.40	80.0%
District nurse visits	29.20	26.40	78.0%
Practice nurse and district nurse visits combined	39.60	35.50	96.0%
Practice nurse telephone consultations	1.50	0.40	5.0%
Tissue viability nurse visits	2.00	0.40	2.0%
Visits to other staff			
Podiatry visits	1.30	0.30	2.0%
Hospital outpatient visits	1.80	0.80	21.0%
Healthcare assistant visit	0.00	0.00	0.0%
Other NHS services			

Resource use	Annual resources needed per person (N)	Annual resources needed per person (SD)	Percentage of the population requiring each resource (%)
Hospital inpatient admissions	1.60	0.40	21.0%
Accident and emergency attendances	1.30	0.30	31.0%
Ambulance services	0.00	0.00	0.0%
Concomitant interventions and diagnostic tests			
All compression	28.70	26.30	89.0%
Prescribed analgesics	12.30	11.10	65.0%
Prescribed antibiotics	5.30	4.30	71.0%
Doppler ultrasound scan	0.00	0.00	0.0%
Non-antimicrobial dressings	0.00	0.00	0.0%
Diagnostic tests	0.00	0.00	0.0%

Abbreviations: GP – General Practitioner; N – Number; NHS – National Health Service; SD – Standard deviation.

The resource unit costs were sourced from publicly available sources, including Personal Social Services Research Unit (PSSRU), NHS cost collection data and drugs and pharmaceutical electronic market information tool (e-MIT) database. These are described in Table 7.10. Where data were not available, inputs were derived from peer reviewed, published cost studies and inflated using CPI index from the PSSRU.

Table 7.10: Unit costs of resources

Resource cost	Base case value	Source
GP visits		
GP surgery visits	£49.00	Table 9.4.2: Unit costs for a GP (PSSRU 2023)(Jones et al. 2024).
GP telephone consultations	£20.27	Table 9.6.1: Costs and unit estimations for a telephone triage (Jones et al. 2024). The unit cost per intervention for a GP-led telephone triage is £20.27 (cost year 2022/23).
GP home visit	£247	Table 9.4.2: Unit costs for a GP (Jones et al. 2024). The unit cost for a GP, per hour of patient contact, including direct care staff costs and qualification costs, is £296 (cost year 2022/23). NICE guideline 94 indicates that home visits usually take 40 to 60 minutes. A duration of 50 minutes has been assumed. Therefore, the cost of a home visit is equal to: $£296 \times (50/60) = £247$.
Nurse visits		
Practice nurse visits	£53.00	Table 9.3.1: Costs and unit estimations for nurses working in a GP practice nurse (Band 5) (Jones et al. 2024). The unit cost for a GP practice nurse, including qualifications, is £53 per hour (cost year 2022/23).
District nurse visits	£55.80	It is understood that venous leg ulcers will be cared for by the district nursing team with the support of the tissue viability service where required. National Cost Collection 2022/23 (NHS England 2024) Area: Community Health Services. Weighted average over: Service code and description: 12 District nursing service

Resource cost	Base case value	Source
		Service code and description: 43 Tissue viability service Currency code and description: N02AF (District Nurse, Adult, Face to face)
Practice nurse and district nurse visits combined	£54.40	Average of practice & district nurses
Practice nurse telephone consultations	£9.04	Table 9.6.1: Costs and unit estimations for a telephone triage (Jones et al. 2024). The unit cost per intervention for a nurse-led telephone triage is £9.04 (cost year 2022/23).
Tissue viability nurse visits	£113	Weighted average over: Service code and description: 12 District nursing service Service code and description: 43 Tissue viability service Currency code and description: N25AF (Specialist Nursing, Tissue Viability Nursing/Liaison, Adult, Face to face) (NHS England 2024).
Visits to other staff		
Podiatry visits	£58.11	Weighted average over: Service code and description: 12 District nursing service Service code and description: 43 Tissue viability service Currency code and description: A09A Podiatrist, Tier 1, General Podiatry (NHS England 2024).
Hospital outpatient visits	£166.94	the following HRG codes in adults: YQ50: Skin Disorders with Interventions JD07: Peripheral Vascular Disorders NHS Digital. HRG4+ 2023/24 National Costs Grouper. Accessed October 2024. Available at: https://digital.nhs.uk/services/national-casemix-office/downloads-groupers-and-tools/hrg4-2023-24-national-costs-grouper it is assumed the relevant outpatient services are 330 - Dermatology Service

Resource cost	Base case value	Source
		107 - Vascular Surgery Service National Cost Collection 2022/23 (accessed 30/09/2024). Available at: https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/ A weighted average over these outpatient services were used to derive this cost.
Healthcare assistant visit	£30.36	The annual cost of NHS healthcare assistant visits for patients with venous leg ulcers (£458,110,000 in 2017/18 prices) was divided by the annual amount of these visits (n=17619780) to give a cost per visit of £26.00 (cost year 2017/18). This was inflated to £30.36 (cost year 2022/23).
Other NHS services		
Hospital inpatient admissions	£2,270	HRG codes in adults: YQ50: Skin Disorders with Interventions JD07: Peripheral Vascular Disorders NHS Digital. HRG4+ 2023/24 National Costs Grouper. Accessed October 2024. Available at: https://digital.nhs.uk/services/national-casemix-office/downloads-groupers-and-tools/hrg4-2023-24-national-costs-grouper Weighted average over Elective and Non-Elective Inpatients used to inform this cost. National Cost Collection 2022/23 (accessed 30/09/2024). Available at: https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/
Accident and emergency attendances	£263	A weighted average of emergency care attendances equated to a unit cost of £262.69. Included currency codes: - VB01Z to VB09Z - VB11Z

Resource cost	Base case value	Source
		Excluded: - Dental care (currency code VB10Z) - Patient dead on arrival (currency code VB99Z) (NHS England 2024)
Ambulance services	£244	National Schedule of NHS costs 2022-23 (NHS England 2024) A weighted average of ambulance services equated to a unit cost of £244.09. Included currency codes: - 01: Hear and treat. - 02: See and treat. - 03: See and convey. - 04: Other.
Concomitant interventions and diagnostic tests		
All compression	£12.81	A weighted average was calculated using: - The cost of Class 1, 2, 3 and Other compression hosiery, and the costs of compression and short stretch bandages from Appendix Table A1: Assigned unit costs. These costs were inflated from a cost year of 2019 to 2022/23. - The number of patients using each type of hosiery, sourced from Table 2: Summary statistics. (Urwin et al. 2022).
Prescribed analgesics	£0.70	A weighted average of the cost of 1 pack of simple analgesics (paracetamol) and non-steroidal anti-inflammatories (NSAIDs) is equal to £0.70. The average excluded: - Medicines formulated as a gel, suppository, solution for infusion or oral suspension, as these were less relevant to the scope of this project. - Diclofenac in combination with misoprostol, as the indication for this medicine is outside the scope of this project. - Medicines not on eMIT. - NSAIDs only licenced for indications outside the scope of this project.
Prescribed antibiotics	£2.20	eMIT 2023.

Resource cost	Base case value	Source
		A weighted average cost for a course of antibiotics used to treat venous leg ulcer infections is equal to £2.20.
Doppler ultrasound scan	£100	National Schedule of NHS costs 2022-23 (NHS England 2024). A weighted average of currency code RD47Z (Vascular Ultrasound Scan) from Diagnostic Imaging and Directly Accessed Diagnostic Services. Service codes that did not have a unit cost available were excluded from the calculation. The weighted average equals £99.63.
Non-antimicrobial dressings	£3.84	A weighted average was calculated using: - The cost of dressings from Appendix Table A1: Assigned unit costs. These costs were inflated from a cost year of 2019 to 2022/23. - The number of patients using each type of dressing, sourced from Table 2: Summary statistics. Only patients using honey, iodine, silver, other antimicrobial or non-antimicrobial dressings were included in the patient count, as these were the categories that costs were available for (Urwin et al. 2022). The weighted average equated to a cost of £4.82 per dressing (cost year 2022/23).
Diagnostic tests	£8.88	National Schedule of NHS costs 2022-23 (NHS England 2024) A weighted average of Directly Accessed Pathology Services, currency code DAPS07: Microbiology. This was chosen as it is assumed to represent the cost of microscopy, culture and sensitivity to process a wound swab. The service code 160 (Plastic Surgery Service) was excluded from the calculation as no unit cost was available. The weighted average equals £8.88.

Abbreviations: eMIT – Drugs and pharmaceutical electronic market information tool; GP – General Practitioner; HRG – Healthcare Resource Group; NHS – National Health Service; NICE – National Institute for Health and Care Excellence; NSAID – Non-steroidal anti-inflammatory drug; PSSRU – Personal Social Services Research Unit.

The resource use and associated costs in

Table 7.9 and Table 7.10 were used to derive the health state costs for the infected, unhealed and non-infected, unhealed health states. Guest et al (2018) reported that those with an unhealed ulcer cost 4.5 times more than those with a healed ulcer (Guest et al. 2018). Therefore, data from Guest et al (2023) was used for the model to derive a health state cost for people with an unhealed ulcer (Guest and Fuller 2023). A multiplier of (1/4.5) was applied to derive the cost for a “healed” leg ulcer.

The total health state costs are reported in Table 7.11.

Table 7.11: Health state costs

Health state	Derived per weekly cycle costs
Infected unhealed wound	£205.68
Non-infected unhealed wound	£205.68
Healed	£45.71

7.2.5 *Health state utilities*

The health state utility data was acquired from a study of 80 adult participants with a principal diagnosis of venous leg ulcer or mixed venous and arterial leg ulcer with predominantly venous origin (Cheng et al. 2019). Participants were recruited from 4 sites in Australia, including 2 community wound clinics, between November 2016 and September 2017. 59% of participants were female, and the average (mean) age was 75.13 years (standard deviation 13.88). These characteristics align well with the literature informing the baseline characteristics of the model, as both sources reported similar average ages and that the majority of participants were female (Cheng et al. 2019, Guest et al. 2018). Other utility studies, performed in the UK in 2005 and 2009, reported similar EQ-5D-3L utilities for leg ulcers that were "unhealed" and "healed" (Iglesias et al. 2005, Michaels et al. 2009). Iglesias et al reported 0.61 and 0.65 for unhealed, and between 0.74 and 0.78 for healed (Iglesias et al. 2005). Michaels et al

reported between 0.6474 for unhealed and 0.7531 for healed (Michaels et al. 2009). The selected study reports slightly marginally larger utilities, which may be more reflective of clinical practice today (Cheng et al. 2019). Therefore, this study was preferred over those that were 15 years old. EQ-5D-5L utility values, of 0.89 for a healed wound and 0.73 for an unhealed wound, were derived with a UK tariff were sourced from the study and converted to EQ-5D-3L utility values, of 0.78 for a healed wound and 0.64 for an unhealed wound for inclusion in the model, using the crosswalk method (Hernández Alava et al. 2020).

A limitation of this data is that it does not describe the utility associated with a locally-infected leg ulcer. Due to a paucity of data to inform this, it was assumed that the utility associated with a locally-infected leg ulcer is equal to the utility associated with a non-infected leg ulcer. This may overestimate the utility associated with a local leg ulcer infection, which would result in an underestimation of the QALY benefits of resolving such infections. The effects of this was explored in the DSA and PSA.

Population utility norms were sourced from standard utility data sources for the UK (Hernández Alava et al. 2022). Male and female EQ-5D-3L utility values were converted to a single weighted average using the proportion of participants assigned male at birth (Guest et al. 2018).

7.2.6 *Mortality*

Annual all-cause mortality probabilities were sourced from the Office for National Statistics (Office for National Statistics 2024). In line with NICE guidance, the National Life Tables from 2017-2019 were used instead of more recent data because of the as-yet-unknown impact of COVID-19 on long term mortality rates (Wailoo 2024). Male and female mortality values were converted to a single weighted average using the proportion of participants assigned male at birth, described in Section 7.2.2 Model population (Guest et al. 2018).

Equation 2 and Equation 3 were used to derive the sex-adjusted per cycle (1 week) probability of all-cause mortality.

Equation 2: Equation used to derive a per-cycle rate of all-cause mortality

$$R_c = \frac{-\ln(1 - P_a)}{t}$$

Equation 3: Equation used to derive a per-cycle probability of all-cause mortality (to use in the model)

$$P_c = 1 - e^{(-R_c)}$$

R_c is the per-cycle all-cause mortality rate

P_a is the annual probability of all-cause mortality (Office for National Statistics 2024)

P_c is the per-cycle probability of all-cause mortality

t is the number of cycles per year. Cycle length is weekly, therefore, $t = 52$

7.2.7 Fully incremental analysis

Results are presented in the form of a fully incremental analysis. The fully incremental analysis compares the agents sequentially in rank order of cost, as per NICE’s preference when comparing multiple mutually exclusive options (National Institute for Health and Care Excellence 2024a). Once ranked, the principal of strong dominance was applied. This identifies if a specific treatment is dominated by another treatment, meaning it is more costly and less effective. The principal of extended dominance was subsequently applied. This compares each intervention to the next most effective alternative by calculating the incremental cost-effectiveness ratio or ICER. Any intervention that has an ICER that is greater than that of a more effective intervention is extendedly dominated (U.S. Department of Veteran Affairs 2024). The dominating agents were then plotted on the efficacy frontier.

Once the dominant treatment was established, a pairwise analysis was conducted comparing all agents with the dominating agent.

7.2.8 Sensitivity analysis

The model includes both deterministic and probabilistic sensitivity analyses.

7.2.8.1 Probabilistic sensitivity analysis (PSA)

Probabilistic sensitivity analysis (PSA) assesses joint parameter uncertainty within the model. In the PSA, uncertain parameters in the model were each sampled from an appropriate distribution, fitted using the mean and SE associated with the uncertain parameter. In cases where the SE was unknown, it was assumed to be 10% of the mean value. For transition probabilities, Dirichlet distributions were used probabilities and utilities, beta distributions were used, while resource use parameters are fitted with gamma distributions (beta distributions are bound between the values of 0 and 1, whereas gamma distributions produce only non-negative values).

Table 7.12: PSA parameters

Parameter	Included in PSA	Distribution	Uncertainty estimate
Agent specific parameters: Costs and resource use			
Maximum time on treatment	No. This was informed by clinical guidelines where available and, therefore, not an area of uncertainty.	N/A	N/A
Number of AMDs required per weekly cycle	No. The average cost of the dressing itself was varied in the PSA. To avoid varying correlated inputs, this was not changed.	N/A	N/A
Cost of dressing	Yes.	Gamma	Standard errors calculated as described in Section 7.2.4.1.
Agent specific parameters: Efficacy			
Number of participants in first line study	No. Not an area of uncertainty.	N/A	N/A
Transitions from first line health state: infected, unhealed	Yes. Efficacy was a key area of uncertainty.	Dirichlet	Used the sample size to calculate the distribution across population and applied these is cumulative gamma or normal functions for studies with sample sizes less than or greater than 340 respectfully.

Parameter	Included in PSA	Distribution	Uncertainty estimate
Transitions from first line health state: non-infected, unhealed	Yes. Efficacy was a key area of uncertainty.	Dirichlet	See "Transitions from first line health state: infected, unhealed"
Transitions from first line healed	No. Once in the healed health state, it was assumed the population automatically transitioned to second line. No recurrence of leg ulcers within the time horizon was assumed.	N/A	N/A
Transitions from second line infected, unhealed	Yes. Efficacy was a key area of uncertainty.	Dirichlet	See "Transitions from first line health state: infected, unhealed"
Transitions from second line non-infected, unhealed	No. These were informed by a logarithmic curve derived by digitising a healing curve published by Guest et al (Guest et al. 2020) (see Section 7.2.3.1) rather than by fitting a curve to patient-level data. Therefore, uncertainty estimates were not available to vary the coefficients.	N/A	N/A
Resource use parameters			
Increase in dressings in infected, unhealed vs. non-infected, unhealed	Yes.	Gamma	Uncertainty estimate was not available; therefore, it was assumed to be 10% of the mean.
GP visits	Yes. Standard deviation published in Guest et al (2023). Please note that, given that the resources themselves were varied, the costs were not to avoid issues regarding correlation. If the costs were varied in addition to the resource use, the distribution will	Gamma	Standard error was derived from the standard deviation reported in Guest et al (2023) for the number of resources required per person.
Nurse visits		Gamma	
Visits to other staff		Gamma	
Other NHS services		Gamma	
Concomitant interventions and diagnostic tests		Gamma	

Parameter	Included in PSA	Distribution	Uncertainty estimate
	balance out to a more normal distribution.		
Cost parameters			
Health state costs	No. Derived from the resource use parameters. The costs were not to avoid issues regarding correlation.	N/A	N/A
Health state utility parameters			
Health state utility: Healed	Yes	Beta	Not reported therefore assumed to be 10% of the mean.
Health state utility: Non-infected unhealed	Yes	Beta	Not reported therefore assumed to be 10% of the mean.
Health state utility: Infected unhealed	Yes	Beta	Not reported therefore assumed to be 10% of the mean.

Abbreviations: AMD - Antimicrobial dressing; NA – Not applicable; NHS – National Health Service; PSA – Probabilistic sensitivity analysis.

7.2.8.2 ***Deterministic sensitivity analysis (DSA)***

Deterministic sensitivity analysis (DSA) accounts for first-order uncertainty regarding the data used for input parameter values. The model parameters included in the DSA are the number of AMDs required per weekly cycle for both unhealed health states, the cost of the AMD, the transitions from first and second line for each health state, the health state utility for each health state and the resource use. DSA involves altering the value used for individual parameters, within realistic ranges, to see the impact on the model results. The main output from the DSA was a tornado plot, which summarised the impact of changing each parameter on the model results and ranks the size of the individual impact from top to bottom. This enables the user to quickly identify the parameters that have the largest impact on the results when varied independently. In the DSA, where possible, parameters were varied based upon literature or their 95% confidence intervals. Where data was not available from literature to inform this, ranges

of +/- 20% were applied around the point estimate that was applied in the base case analysis.

Table 7.13: DSA parameters

Parameter	Included in DSA	Range (lower to upper value)	Description
Agent specific parameters: Costs and resource use			
Maximum time on treatment	No.	N/A	N/A
Number of AMDs required per weekly cycle	Yes	Varied depending upon agent	+/- 20% around the mean value
Cost of dressing	Yes.	Minimum to maximum costs (dependent on agent)	Part IX of the drug tariff informed the minimum and maximum cost for each agent. See Section 7.2.4.1 for the min and max costs.
Agent specific parameters: Efficacy			
Number of participants in first line study	No. Not an area of uncertainty.	N/A	N/A
Transitions from first line health state: infected, unhealed	Yes. Efficacy was a key area of uncertainty.	Varied depending upon agent	Used Dirichlet to vary +/- 20% around the mean value.
Transitions from first line health state: non-infected, unhealed	Yes. Efficacy was a key area of uncertainty.	Varied depending upon agent	Used Dirichlet to vary +/- 20% around the mean value.
Transitions from first line healed	No. Once in the healed health state, it was assumed the population automatically transitioned to second line. No recurrence of leg ulcers within the time horizon was assumed.	N/A	N/A
Transitions from second line infected, unhealed	Yes. Efficacy was a key area of uncertainty.	Varied depending upon the agent	Used Dirichlet to vary +/- 20% around the mean value.
Transitions from second line non-infected, unhealed	No. These were informed by a logarithmic curve derived by digitising a healing curve published	N/A	N/A

Parameter	Included in DSA	Range (lower to upper value)	Description
	by Guest et al (Guest et al. 2020) (see Section 7.2.3.1) rather than by fitting a curve to patient-level data. Therefore, uncertainty estimates were not available to vary the coefficients.		
Resource use parameters			
Increase in dressings in infected, unhealed vs. non-infected, unhealed	Yes.	1.43 to 2.14	Ratio was derived therefore no uncertainty estimate was available. Assumed to be +/- 20% around the mean.
GP surgery visits (cost per consult)	Yes (where data were available). Standard deviation published in Guest et al (2023). Please note that, given that the resources themselves were varied, health state costs were not varied in the DSA.	6.77 to 7.43	Standard error was derived from the standard deviation reported in Guest et al (2023) for the number of resources required per person. Calculate 95% CI using: $mean \pm 1.96 * SE$
GP telephone consultations		1.38 to 1.42	
GP home visit		N/A	
Practice nurse visits		N/A	
District nurse visits		9.88 to 10.92	
Practice nurse and district nurse visits combined		27.74 to 30.66	
Practice nurse telephone consultations		37.64 to 41.56	
Tissue viability nurse visits		1.48 to 1.52	
Podiatry visits		1.98 to 2.02	
Hospital outpatient visits		N/A	
Healthcare assistant visit		1.28 to 1.32	
Hospital inpatient admissions		1.76 to 1.84	
Accident and emergency attendances		N/A	
Ambulance services		N/A	
All compression		N/A	

Parameter	Included in DSA	Range (lower to upper value)	Description
Prescribed analgesics		N/A	
Prescribed antibiotics		1.58 to 1.62	
Doppler ultrasound scan		1.28 to 1.32	
Non-antimicrobial dressings		N/A	
Diagnostic tests		N/A	
Cost parameters			
Health state costs	No. Derived from the resource use parameters.	N/A	N/A
Health state utility parameters			
Health state utility: Healed	Yes	0.64 to 0.78	Assumed to be 20% of the mean while being bound above by the population norm or the next highest health state <i>and</i> bound below by 0 or the next lowest health state.
Health state utility: Non-infected unhealed	Yes	0.64 to 0.77	
Health state utility: Infected unhealed	Yes	0.51 to 0.64	

Abbreviations: AMD - Antimicrobial dressing; CI – Confidence interval; DSA – Deterministic sensitivity analysis; GP – General practitioner; NA – Not applicable; NHS – National Health Service.

7.3 Results from the economic modelling

The following section details results of the economic model. These outcomes are based on inputs and assumptions outlined in previous sections and should be interpreted within the context of the data uncertainty discussed in these earlier sections. See Section 7.3.5 for the EAG interpretation of the results within the context of the data available.

7.3.1 Base case results

In accordance with [NICE methods guidance](#), the base case cost-effectiveness results were derived from a probabilistic sensitivity analysis (PSA) to account for second order uncertainty around parameter values. Please see Section 7.2.8.1 for more details around the PSA. A deterministic summary and a presentation of disaggregated base

case results are presented for the base case in Section 7.3.2. Table 7.14 summarises the key model inputs used to generate the base case results for the model.

Table 7.14: Summary of key model inputs

Input	Value
Time horizon	1 year
Discount rate (costs)	3.5%
Discount rate (benefits)	3.5%
Cost-effectiveness threshold	£20,000 per QALY
Analysis type	Principal analysis

Abbreviations: QALY – Quality-adjusted life year.

7.3.1.1 Probabilistic base case

In order to account for second-order uncertainty around parameter values, the model included a PSA. [NICE’s health technology evaluations manual](#) states that estimates of the confidence around the model’s findings, and base case results, should be presented probabilistically when possible. It is worth noting that the ranges used to vary many of the inputs were not robust, and the addition of estimated ranges would have introduced uncertainty. By estimating a distribution using uncertain values, the PSA may be introducing more uncertainty to the results rather than accounting for it. As a result, the PSA results should be considered alongside the point-estimate in the deterministic base case.

2,000 PSA iterations over a 1-year time horizon were run to allow results to converge. In the model base case, convergence of the NMB occurred after approximately 1,000 PSA iterations, as presented in Appendix I: Additional probabilistic outcomes. All results were discounted at 3.5% annually for costs and QALYs as per the NICE reference case.

As referred to in Section 7.2.3.2, appropriate efficacy data was available for 6 of the 10 agents to inform the principal analysis. These agents were: chitosan; copper; honey

iodine; PHMB, and silver, Table 7.15 displays the results of the probabilistic fully incremental analysis.

The fully incremental analysis ranked Iodine as the agent that would generate the smallest costs per person, costing £6,494 (95% CI: £5,579 to £7,408) to the England and Welsh NHS over 1 year of treatment. It was also the most effective, accruing 0.70 (95% CI: 0.64 to 0.77) QALYs and, therefore, was the referent agent and dominated all other agents. Once the principals of dominance and extended dominance were applied, no other agent sat upon the efficacy frontier (Figure 7.5).

The negative NMBs and the large ICERs presented in Table 7.16 reinforce that Iodine is the most cost-effective treatment, as do the cost-effectiveness planes in Figure 7.6 to Figure 7.10. The deterministic results sit centrally in the distribution of points and distributions across all agents when compared to iodine. When accounting for uncertainty in the PSA, iodine was cost-effective in all cost-effectiveness thresholds (Appendix I: Additional probabilistic outcomes) in over 99% of iterations for all agents. However, the size of the ICERs, and the cost-effectiveness of iodine are largely driven by the very small incremental QALYs. However, overlapping confidence intervals in Table 7.16 indicate that there are no significant differences between the QALYs of any dressings. Therefore, with the evidence available, the EAG cannot conclude one agent is more efficacious / improves HRQoL over another agent and so the ICERs should be interpreted with this in mind.

Table 7.15: Mean (95% confidence interval) of discounted, patient-level, probabilistic, fully incremental base case results

	Efficacy data population details	Total cost (GBP) (95% confidence interval)	Total QALYs (95% confidence interval)	Dominance results
Iodine	Adults with a local infection of a lower leg ulcer (Miller et al. 2010).	£6,494 (95% CI: £5,579 to £7,408)	0.70 (95% CI: 0.64 to 0.77)	Referent
Copper	Adults with a range of wound types (including non-healing postoperative wounds, venous leg ulcers, diabetic foot ulcers and chronic traumatic wounds). Infection at baseline was not recorded (Treadwell T et al. 2022).	£6,887 (95% CI: £5,973 to £7,800)	0.70 (95% CI: 0.63 to 0.76)	Dominated
Chitosan	Adults with a range of chronic, non-healing wound types (including pressure ulcers, diabetic foot ulcers, venous leg ulcers and minor infected wounds). 35/45 (77.8%) people in the chitosan group had an infected wound at baseline (Mo et al. 2015).	£7,316 (95% CI: £6,505 to £8,127)	0.69 (95% CI: 0.63 to 0.75)	Dominated
Silver	Adults with a venous leg ulcer with one or more clinical signs of infection (Forlee et al. 2014).	£7,331 (95% CI: £6,433 to £8,229)	0.69 (95% CI: 0.63 to 0.75)	Dominated
Honey	Patients of all ages with diabetic foot ulcers. Local infection was not described as a binary outcome, however. 30/30 (100%) participants had inflammatory signs at baseline, and 23/30 (76.7%) participants had a foul/purulent exudate at baseline (Moghazy et al. 2010).	£7,512 (95% CI: £6,496 to £8,527)	0.69 (95% CI: 0.63 to 0.75)	Dominated
PHMB	Adults with hard-to-heal leg ulcers (duration >6 weeks). Local infection was not described as a binary outcome, rather, tissue type was described (for example, granulation, slough or necrosis). Spreading infection was an exclusion criteria and no participants had typical clinical signs of infection at baseline (Vallejo et al. 2022).	£7,834 (95% CI: £6,916 to £8,751)	0.68 (95% CI: 0.62 to 0.74)	Dominated

Abbreviations: CI – Confidence interval; GBP – Great British Pound; PHMB – Polyhexamethylene biguanide; QALY – Quality-adjusted life year.

Figure 7.3: Base case total QALYs

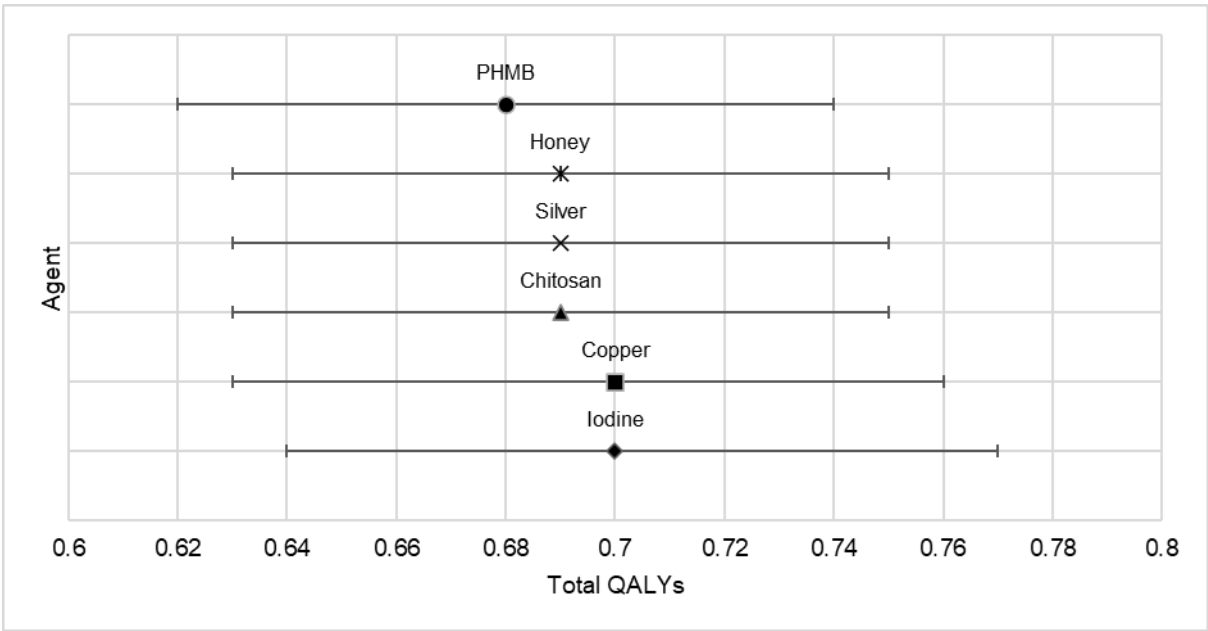


Figure 7.4: Base case total costs

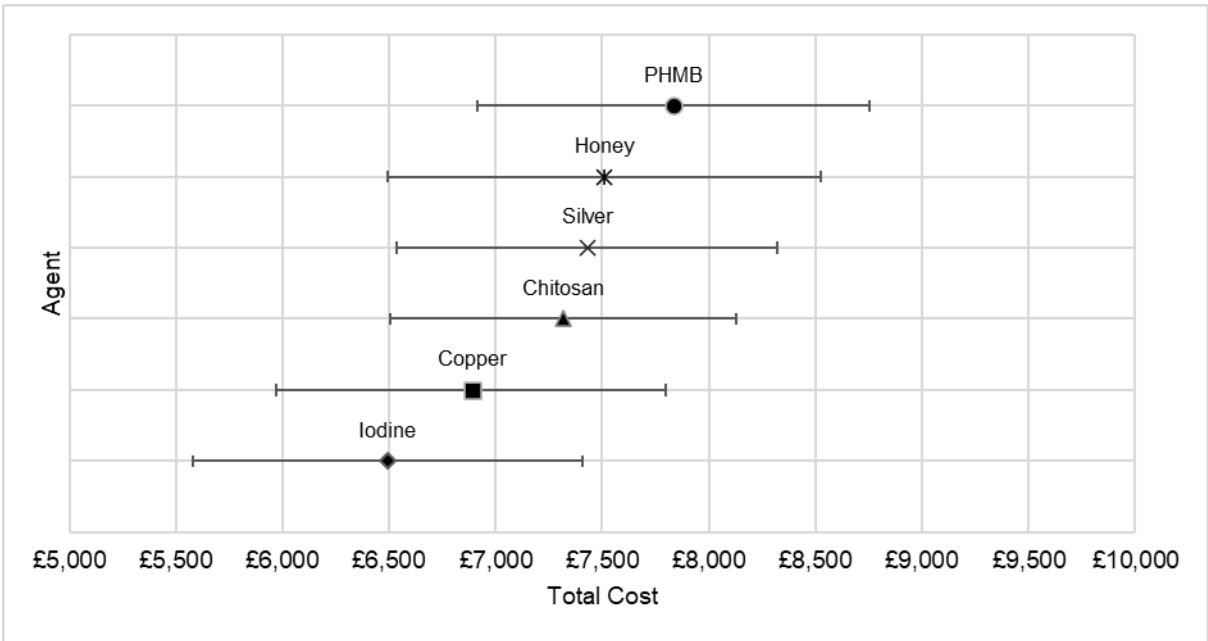


Figure 7.5: Probabilistic efficacy frontier

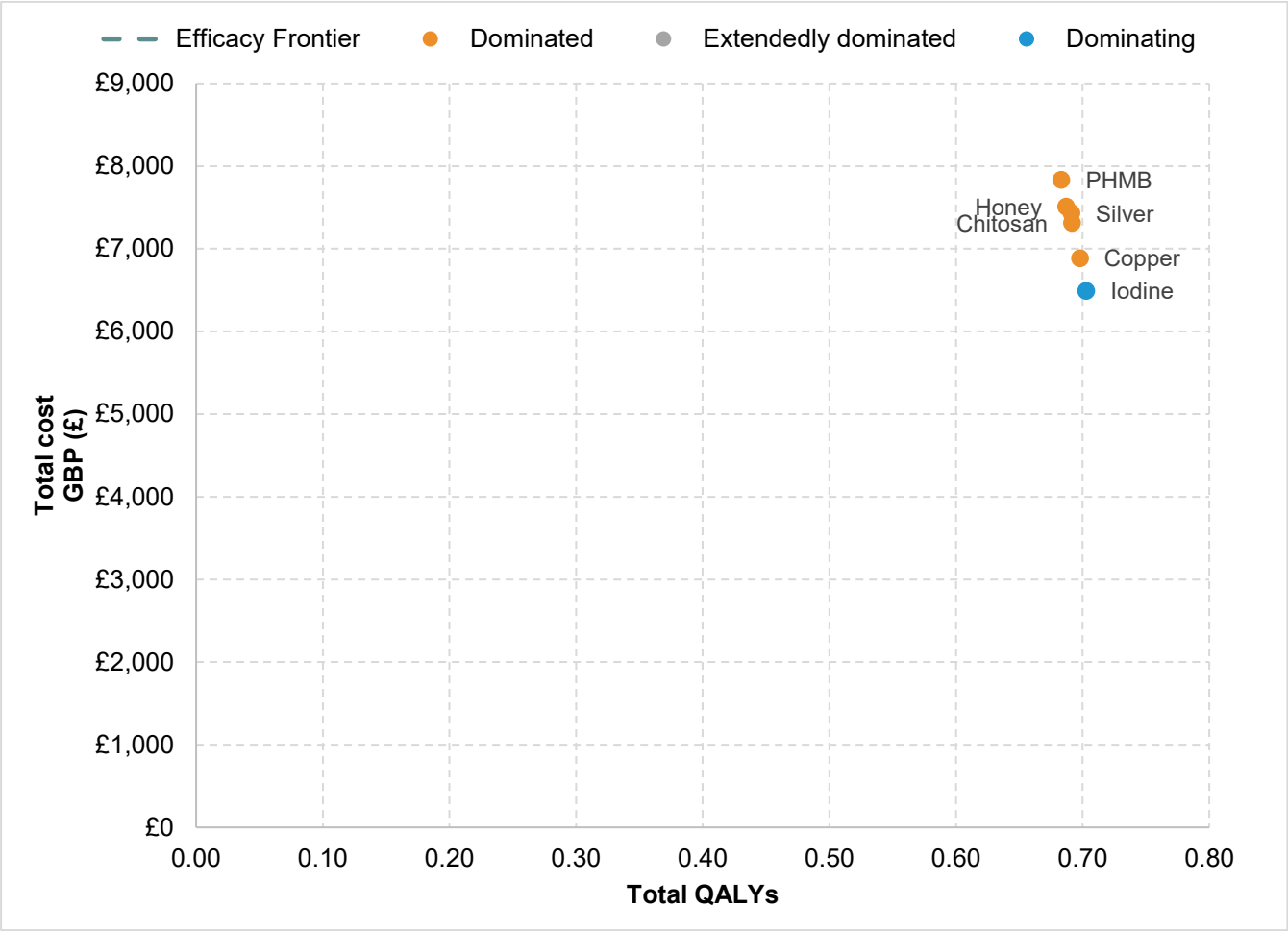


Table 7.16: Mean (95% confidence interval) pairwise analysis (compared to iodine)

	Iodine	Copper	Chitosan	Silver	Honey	PHMB
Total LYs	0.97 (95% CI: 0.97 to 0.97)	0.97 (95% CI: 0.97 to 0.97)	0.97 (95% CI: 0.97 to 0.97)	0.97 (95% CI: 0.97 to 0.97)	0.97 (95% CI: 0.97 to 0.97)	0.97 (95% CI: 0.97 to 0.97)
Total QALYs	0.70 (95% CI: 0.64 to 0.77)	0.70 (95% CI: 0.63 to 0.76)	0.69 (95% CI: 0.63 to 0.75)	0.69 (95% CI: 0.63 to 0.75)	0.69 (95% CI: 0.63 to 0.75)	0.68 (95% CI: 0.62 to 0.74)
Total cost GBP (£)	£6,494 (95% CI: £5,579 to £7,408)	£6,887 (95% CI: £5,973 to £7,800)	£7,316 (95% CI: £6,505 to £8,127)	£7,331 (95% CI: £6,433 to £8,229)	£7,512 (95% CI: £6,496 to £8,527)	£7,834 (95% CI: £6,916 to £8,751)
Incremental QALYs	-	0.00 (95% CI: 0.00 to 0.01)	0.01 (95% CI: 0.00 to 0.02)	0.01 (95% CI: 0.00 to 0.02)	0.02 (95% CI: 0.00 to 0.03)	0.02 (95% CI: 0.00 to 0.04)
Incremental costs	-	£-393 (95% CI: £-610 to £-176)	£-822 (95% CI: £-1,206 to £-438)	£-838 (95% CI: £-1,871 to £196)	£-1,018 (95% CI: £-1,358 to £-679)	£-1,340 (95% CI: £-1,776 to £-904)
ICER	-	£-81,222	£-72,693	£-72,219	£-64,112	£-67,928
Probability of cost-effectiveness at cost-effectiveness threshold of £20,000		99.5%	99.8%	72.5%	99.7%	100.0%
Incremental NMB	-	£490 (95% CI: £194 to £785)	£1,048 (95% CI: £503 to £1,594)	£1,070 (95% CI: £-1,373 to £3,512)	£1,336 (95% CI: £815 to £1,857)	£1,734 (95% CI: £1,061 to £2,407)

Abbreviations: CI – Confidence interval; GBP – Great British Pound; ICER – Incremental cost-effectiveness ratio; LY – Life years; NMB – Net monetary benefit; PHMB – Polyhexamethylene biguanide; QALY – Quality-adjusted life year.

Figure 7.6: Cost-effectiveness plane comparing chitosan (comparator) to iodine (intervention)

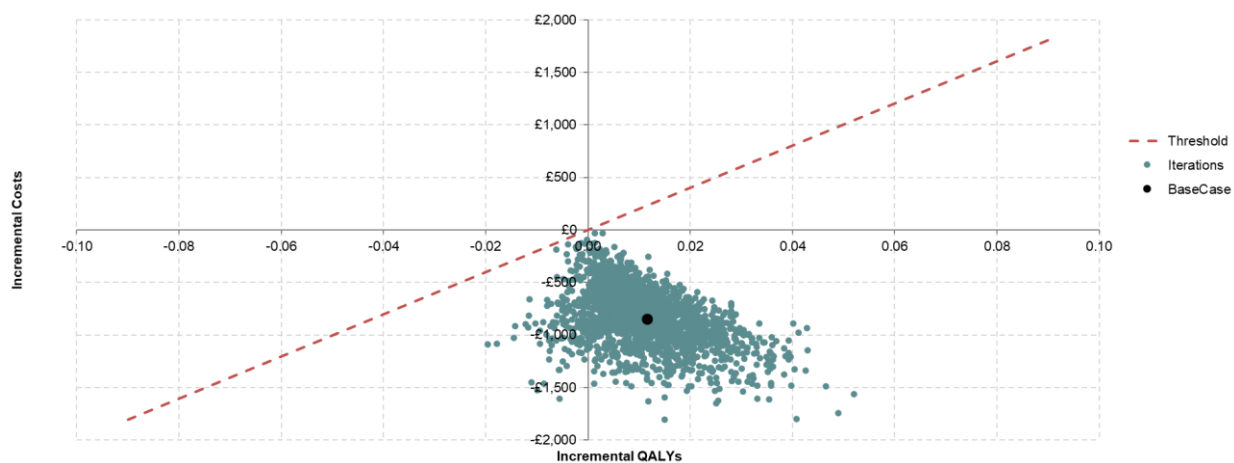


Figure 7.7: Cost-effectiveness plane comparing copper (comparator) to iodine (intervention)

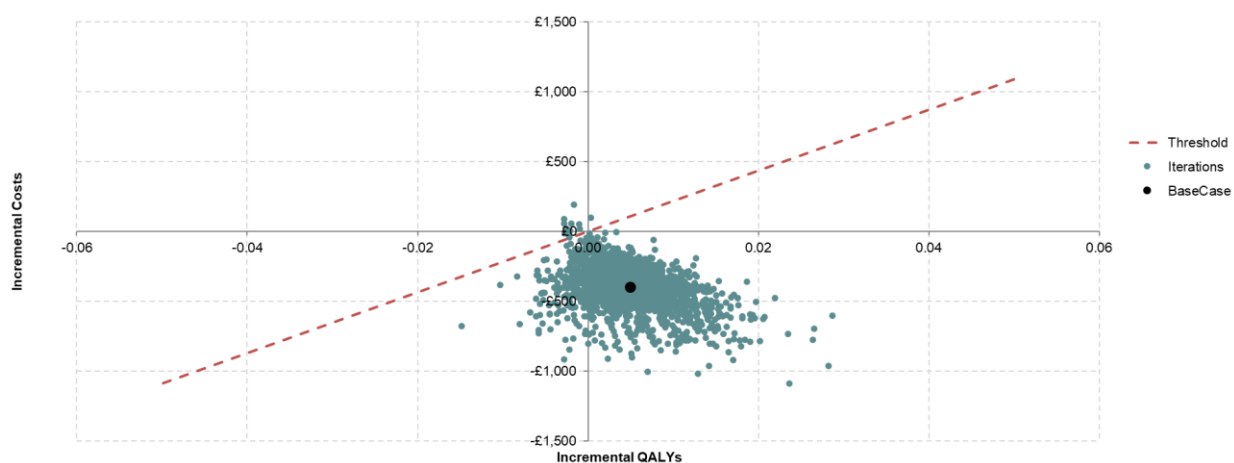


Figure 7.8: Cost-effectiveness plane comparing honey (comparator) to iodine (intervention)

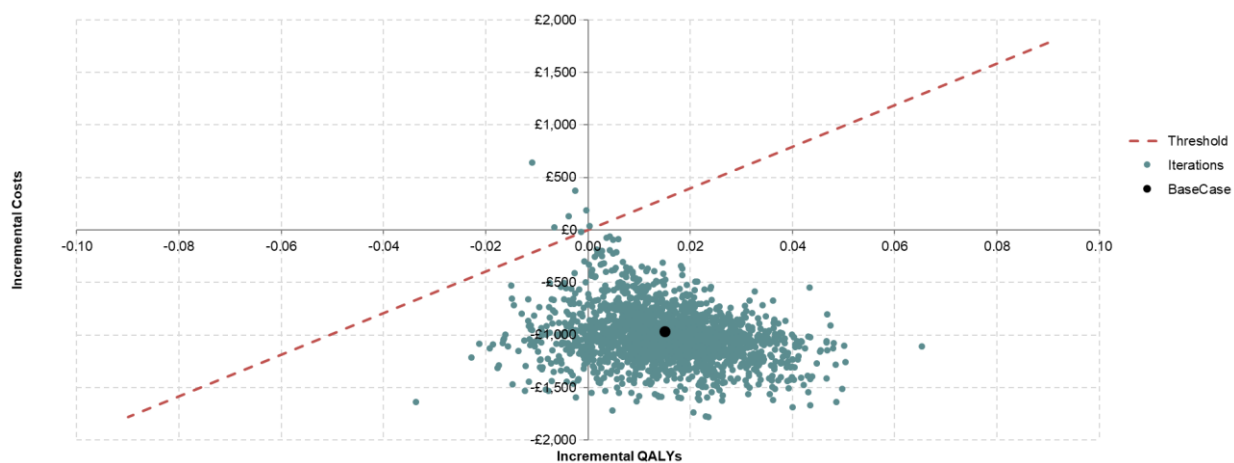


Figure 7.9: Cost-effectiveness plane comparing PHMB (comparator) to iodine (intervention)

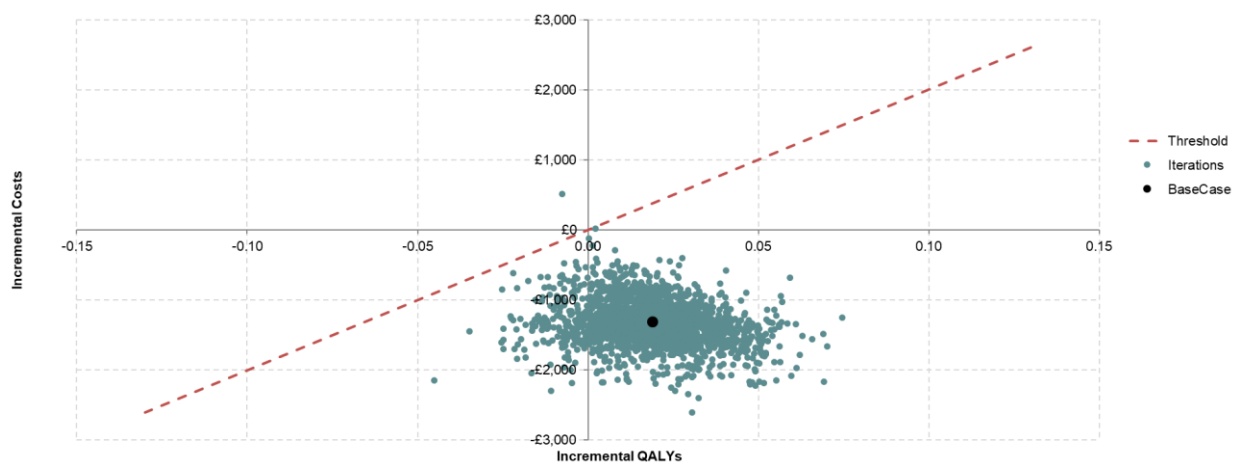
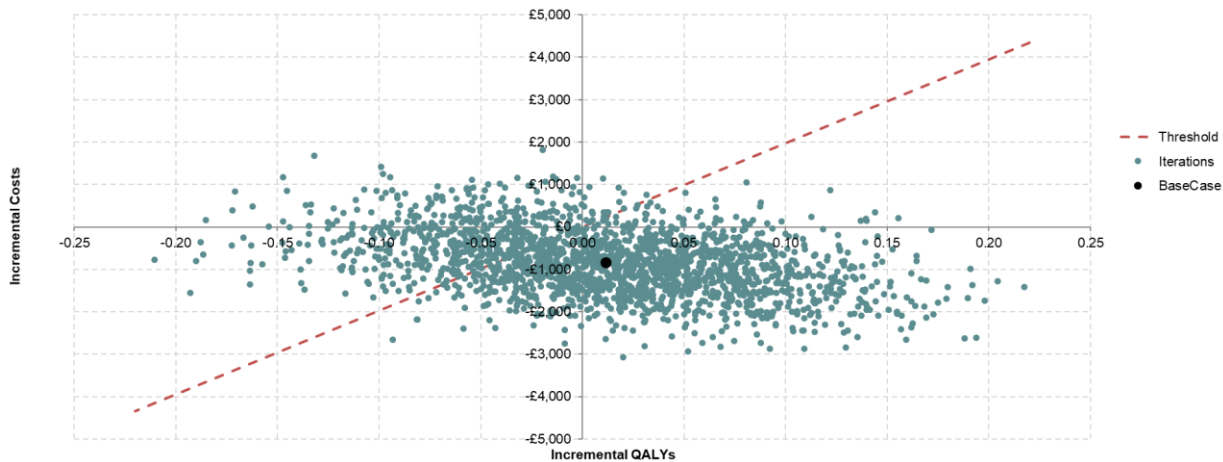


Figure 7.10: Cost-effectiveness plane comparing silver (comparator) to iodine (intervention)



7.3.1.2 Deterministic base case

The cost-effectiveness conclusions drawn from the deterministic base case results are equivalent to those in Section 7.3.1.1. These are presented in Table 7.17. The results show that iodine is the least costly and most effective agent, and therefore, dominates all other agents. Table 7.18 presents the incremental outcomes compared to iodine. Despite negative ICERs (which can be the consequence of cost savings with QALY gains or cost incurring with QALY loss), the positive NMBs show that iodine is cost-effective compared to all other agents, confirming the outcomes from the deterministic and probabilistic fully incremental analysis (Table 7.18).

The disaggregated life years, presented in Table 7.19, showed that the cohort with iodine dressings healed faster than other dressings and, therefore, spent less time in the more costly and more effective health states. It follows that those treated with iodine have the smallest costs and the largest QALYs. The disaggregated QALYs are presented in Table 7.20.

The model assumes time to infection resolution is proportional to the healing rate. Therefore, dressings containing agents with a slower healing rate spend more time in the ‘infected, unhealed’ health state and, therefore, have higher costs than other

agents. The agents associated with the highest cost were honey and PHMB. This suggests time spent in the infection health state is a key driver of costs.

Abbreviations: PHMB – Polyhexamethylene biguanide; QALY – Quality-adjusted life year.

Table 7.21 displays the discounted, patient-level, deterministic costs over 1 year, for each health state and agent. The largest proportion of total costs were attributable to the 'non-infected unhealed wound' health state, which contributed to between 62% (for PHMB) to 71% (copper) of the total costs. Comparatively, the 'infected unhealed wound' health state contributed to between 8% (copper) and 22% (PHMB) and the 'healed wound' health state to between 11% (PHMB) and 19% (iodine) of the total costs. AMD costs provided the smallest contribution to total costs, of between 3% (iodine) and 6% (silver).

Abbreviations: PHMB – Polyhexamethylene biguanide; QALY – Quality-adjusted life year.

Table 7.21 shows that interventions and technologies that allow for people to progress into the 'non-infected unhealed wound' health state faster (Table 7.19), and, thereby, have a lower cost than the 'infected unhealed wound' health state typically have a lower total cost overall. It is important to note that we have assumed that AMDs are still used in the non-infected, unhealed health state, which is not reflective of 'best practice'.

A substantial percentage of costs are accrued in the 'infected unhealed wound' and 'non-infected unhealed wound' health state. Therefore, this indicates that interventions and technologies that reduce the time taken for an infection to resolve, combined with an ongoing treatment effect to reduce the time taken for the ulcer to heal completely, could be a key criterion to consider when assessing the merits of AMDs. Indeed, this may substantially reduce the total costs of managing leg ulcers in an adult population.

Table 7.17: Discounted, patient-level, deterministic fully incremental analysis over 1 year

Agent	Total LYs	Total QALYs	Total cost GBP (£)	Dominance results
Iodine	0.97	0.70	£6,447	Referent
Copper	0.97	0.70	£6,845	Dominated
Chitosan	0.97	0.69	£7,294	Dominated
Silver	0.97	0.69	£7,295	Dominated
Honey	0.97	0.69	£7,417	Dominated
PHMB	0.97	0.68	£7,755	Dominated

Abbreviations: GBP – Great British Pound; LY – Life years; PHMB – Polyhexamethylene biguanide; QALY – Quality-adjusted life year.

Table 7.18: Pairwise cost-effectiveness analysis (compared to iodine)

	Incremental QALYs	Incremental costs	ICER	Incremental NMB
Chitosan	0.01	-£848	-£72,610	£1,081
Copper	0.00	-£398	-£80,480	£498
Honey	0.02	-£971	-£64,624	£1,271
PHMB	0.02	-£1,309	-£68,747	£1,690
Silver	0.01	-£849	-£72,507	£1,083

Abbreviations: ICER – Incremental cost-effectiveness ratio; NMB – Net monetary benefit; PHMB – Polyhexamethylene biguanide; QALY – Quality-adjusted life year.

Table 7.19: Discounted, patient-level, deterministic life years over 1 year

	Discounted life years (first line)			Discounted life years (second line)		
	Infected unhealed wound	Non-infected unhealed wound	Healed	Infected unhealed wound	Non-infected unhealed wound	Healed
Chitosan	0.05	0.03	0.00	0.03	0.44	0.42
Copper	0.04	0.04	0.00	0.01	0.42	0.46
Honey	0.11	0.12	0.00	0.01	0.34	0.39
Iodine	0.05	0.15	0.01	0.00	0.26	0.50
PHMB	0.14	0.09	0.00	0.02	0.35	0.36
Silver	0.05	0.03	0.00	0.03	0.44	0.42

Abbreviations: PHMB – Polyhexamethylene biguanide.

Table 7.20: Discounted, patient-level, deterministic QALYs over 1 year

	Infected unhealed wound	Non-infected unhealed wound	Healed	Total QALYs
Chitosan	0.051	0.311	0.330	0.692
Copper	0.032	0.298	0.368	0.699
Honey	0.080	0.298	0.311	0.688
Iodine	0.037	0.270	0.396	0.703
PHMB	0.105	0.292	0.288	0.684
Silver	0.051	0.311	0.330	0.692

Abbreviations: PHMB – Polyhexamethylene biguanide; QALY – Quality-adjusted life year.

Table 7.21: Discounted, patient-level, deterministic costs over 1 year

	Infected unhealed wound		Non-infected unhealed wound		Healed		Total AMD costs (line 1 and 2)		Total costs
	Cost	Percentage	Cost	Percentage	Cost	Percentage	Cost	Percentage	
Chitosan	£841	11.53%	£5,101	69.93%	£993	13.61%	£359	4.92%	£7,294
Copper	£529	7.72%	£4,893	71.49%	£1,109	16.20%	£314	4.59%	£6,845
Honey	£1,309	17.65%	£4,891	65.94%	£936	12.62%	£281	3.79%	£7,417
Iodine	£600	9.31%	£4,438	68.84%	£1,194	18.52%	£214	3.32%	£6,447
PHMB	£1,713	22.09%	£4,799	61.88%	£867	11.18%	£377	4.86%	£7,755
Silver	£841	11.52%	£5,103	69.95%	£993	13.61%	£358	4.91%	£7,295

Abbreviations: AMD – Antimicrobial dressing; PHMB – Polyhexamethylene biguanide.

7.3.2 *Deterministic sensitivity analysis results*

DSA was conducted by varying key input parameters using the ranges presented in Table 7.13. The results of the top parameters identified using the DSA as the parameters that had the greatest impact on the incremental NMB are shown in tornado plots in Figure 7.11 to Figure 7.15. All parameters allowed for iodine to be cost-effective within the NICE cost-effectiveness threshold of £20,000 per QALY gained. None of the DSA scenarios changed the conclusion of the deterministic results. Therefore, for all parameters varied in the DSA, iodine was cost-effective compared with other agents at a cost-effectiveness threshold of £20,000 per QALY.

Agents with large maximum costs of dressings compared with the weighted average, namely, silver and copper, show the use of the maximum cost as a large driver of cost effectiveness. In agents where there is less uncertainty across the cost of different products and brands, the cost of the AMD has less of an impact.

Transitions from the infected, unhealed to the non-infected, unhealed health state have a large impact on results, meaning that the rate at which infection is cleared is a key driver of cost-effectiveness. This data is, unfortunately, determined based on assumptions and many studies did not include it as an end point. More robust data is needed to make robust conclusions on the cost-effectiveness.

Decreasing the health state utility for the healed health state had a large impact on results. The cost-effectiveness of iodine stems from the time spent in the “healed” health state. It follows that there is less of a QALY difference between agents when this is lowered. There is very little impact when the utility is increased, because it is bound above by the population norms. This shows a key driver is the time spent in the “healed” health state, which is less costly and provides a large QALY benefit. The incremental QALYs observed in Sections 7.3.1.1 and 7.3.1.2 were extremely small therefore, it follows that changing the utility value associated with the healed health state will have a large impact on cost-effectiveness outcomes.

Figure 7.11: DSA tornado plot iodine (intervention) compared with chitosan (comparator)

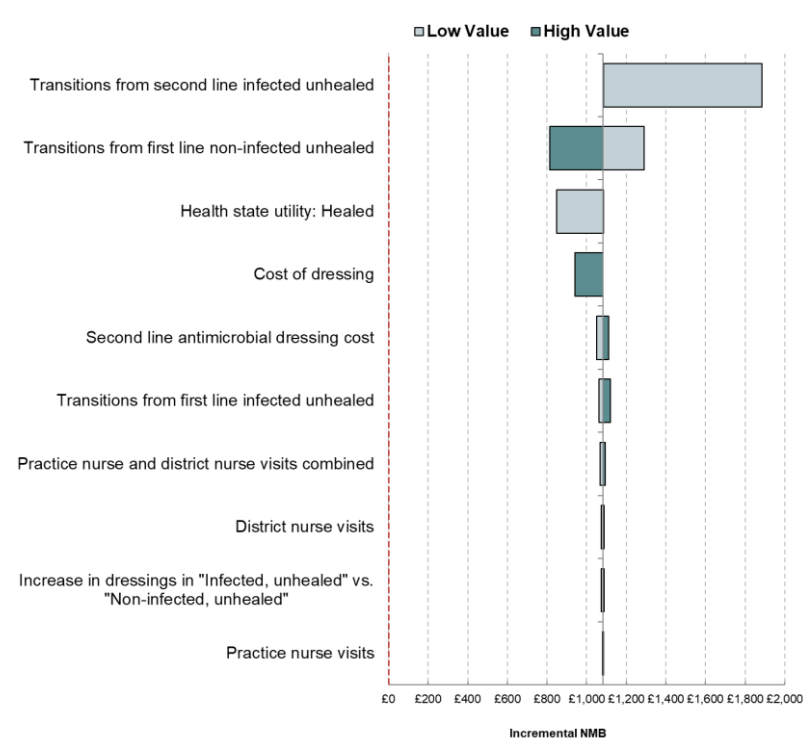


Figure 7.12: DSA tornado plot iodine (intervention) compared with copper (comparator)

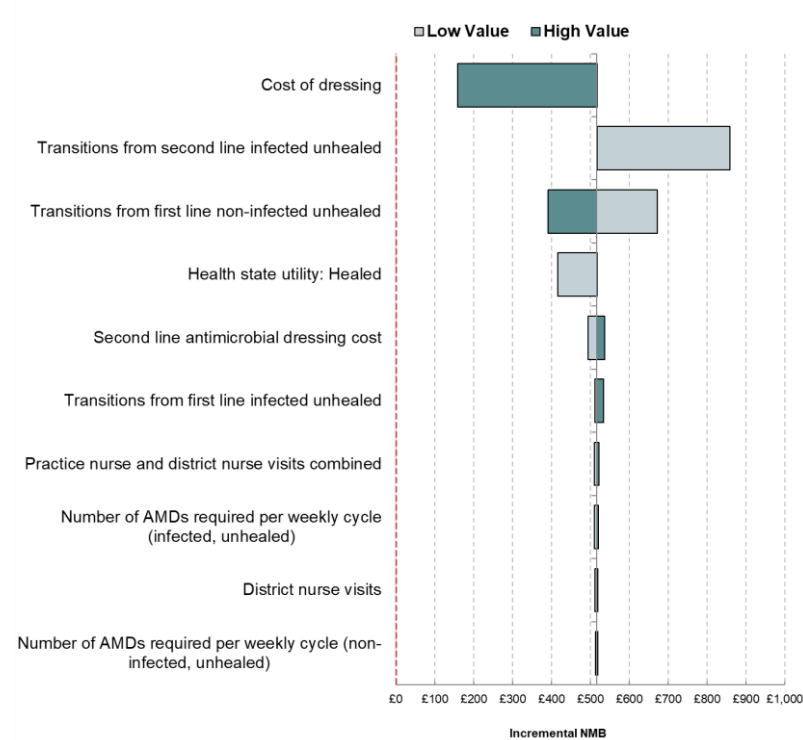


Figure 7.13: DSA tornado plot iodine (intervention) compared with honey (comparator)

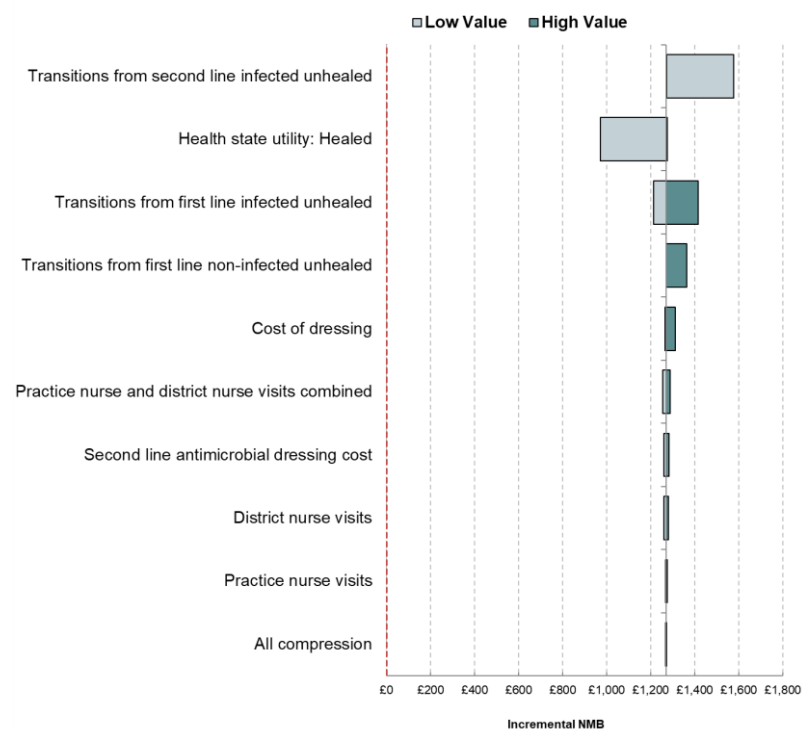


Figure 7.14: DSA tornado plot iodine (intervention) compared with PHMB (comparator)

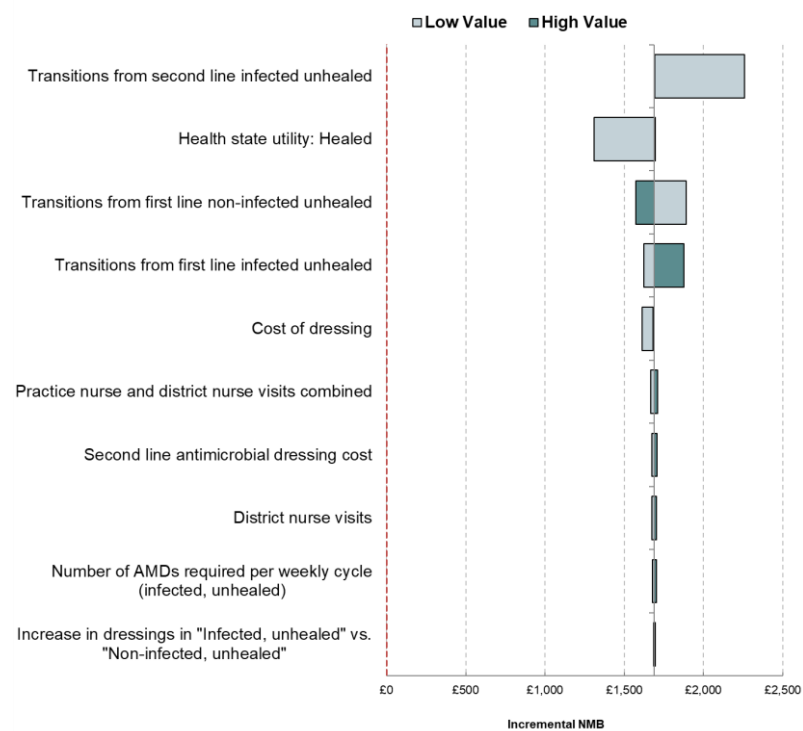
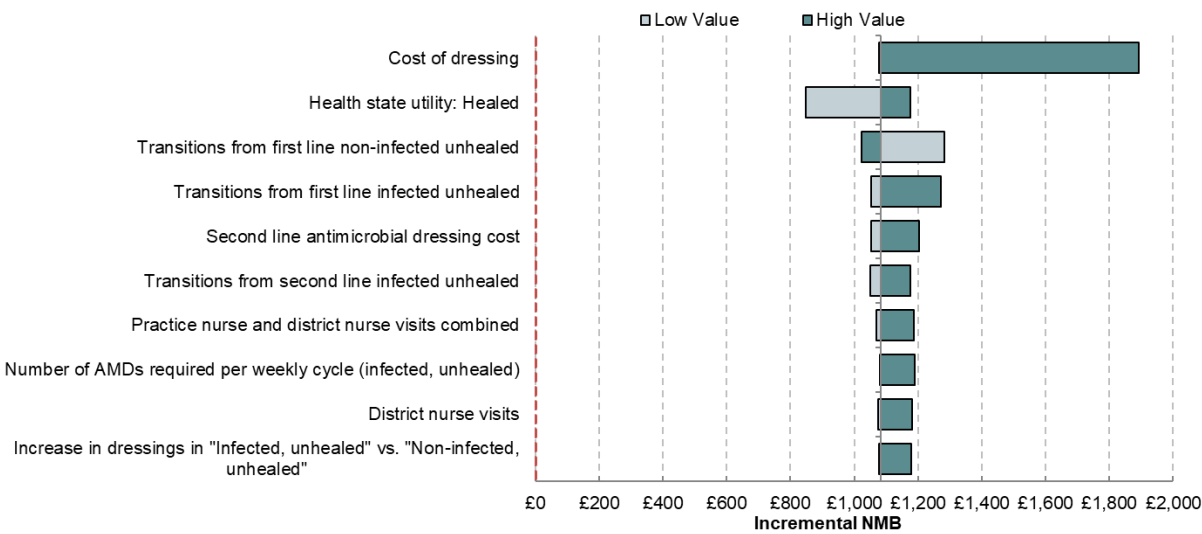


Figure 7.15: DSA tornado plot iodine (intervention) compared with silver (comparator)



7.3.3 Sub-agent analysis

This section summarises the results of the cost-effectiveness analysis of sub-agents within categories. The model was programmed to estimate results for the sub-agents for honey, iodine and silver (see Section 2.2). However, evidence was only available to inform silver and honey sub-agents to allow for a comparison.

7.3.3.1 Silver sub-agents

Silver sub-agents with available evidence were silver salts and compounds and elemental silver. As per the principal results (Section 7.3.1.1, 7.3.1.2 and 7.3.2) probabilistic and deterministic sensitivity analyses were undertaken for all base-case model inputs. Given that there were two silver sub-agents, a pairwise comparison of the agents was appropriate.

In the average PSA and the deterministic results, silver salts and compounds was found to be cost-effective compared with elemental silver. This was indicated by the positive incremental NMB of £81 in the deterministic analysis and £40 (95% CI: -£375 to £455) in the PSA. A complete table of deterministic and probabilistic results are presented in Table 7.22 and Table 7.23 respectively. While the NMBs are similar in the

probabilistic and deterministic outcomes, low incremental QALYs mean that the ICERs are unstable, resulting in the ICER being almost 3 times larger in the deterministic analysis compared with the probabilistic analysis. Therefore, in this analysis, the NMB is a more appropriate measure to use to assess cost-effectiveness.

The cost-effectiveness plane (Figure 7.16) shows a negative correlation with a large range of incremental costs suggesting there is more uncertainty in the costs than in the QALYs. Indeed, several probabilistic iterations caused in large incremental costs, in favour of silver salts and compounds (as observed in the lower right quadrant). The 95% confidence interval around the incremental costs was -£379 to £252, however, it is clear in Figure 7.16 that the range of incremental costs is broader. Indeed, the maximum incremental cost was £253 and the minimum was -£2,060. These outliers skewed the overall estimates of cost-effectiveness. This is shown in Table 7.23, which shows that the likelihood of silver salts and compounds being cost-effective compared with elemental silver is 39.1% at NICE's preferred threshold of £20,000 per QALY. Furthermore, the CEAC, as presented in Figure 7.17, shows that elemental silver was more likely to be cost-effective compared with silver salts and compounds across all thresholds of cost-effectiveness.

The DSA was an effective tool in explaining this apparent discrepancy. The DSA results identified that the key drivers of cost-effectiveness were the cost of the dressings themselves and the efficacy data from first line infected, unhealed and first line non-infected, unhealed. Modifying one or both of these parameters in the DSA changed the cost-effectiveness conclusion, as observed by the bars in the tornado plot crossing zero (Figure 7.18).

The PSA was programmed so that the overall dressing cost was sampled from a gamma distribution, therefore the number of dressings were not varied in the PSA. This was to avoid the central limit theorem biasing PSA results (i.e. final results to be normally distributed around the mean) which can occur when correlated parameters are varied. Given that the data informing the model suggests that elemental silver requires more frequent dressing changes (Section 7.2.4.2) and has a larger average cost with a

greater degree of uncertainty (Section 7.2.4.1) than silver salts and compounds, it follows that elemental silver has the potential to be more costly than silver salts and compounds in many PSA iterations. Outcomes in the scenario analysis (Section 7.3.4) showed the large cost differences per person when frequency of dressing changes was increased and decreased.

However, the AMD itself only makes up a small percentage of the overall cost (as presented in Abbreviations: PHMB – Polyhexamethylene biguanide; QALY – Quality-adjusted life year.

Table 7.21). Abbreviations: PHMB – Polyhexamethylene biguanide; QALY – Quality-adjusted life year.

Table 7.21 showed that the largest percentage of the cost was accrued in health state costs of the ‘infected unhealed wound’ and ‘non-infected unhealed wound’ health states. As such, the sub-agent with the highest efficacy (which, with the data available, was elemental silver in the model) is expected to accrue the lowest costs overall because the cohort are moving into the ‘healed wound’ health state faster. In the probabilistic iterations where this was not observed, silver salts and compounds was the cost-effective option. This, combined with high AMD costs in a percentage of the probabilistic iterations, likely caused the outliers. These drove silver salts and compounds to be more cost-effective than elemental silver in the average PSA results and the deterministic base case.

Table 7.22: Deterministic pairwise analysis of silver sub-agents

	Silver salts and compounds	Elemental silver
Total LYs*	0.97	0.97
Total QALYs*	0.69	0.69
Total cost GBP (£)	£7,290	£7,385
Incremental LYs*	-	0.00
Incremental QALYs*	-	0.00
Incremental costs	-	-£95
ICER	-	£142,188
Incremental NMB	-	£81

Abbreviations: GBP – Great British Pound; ICER – Incremental cost-effectiveness ratio; LY – Life years; NMB – Net monetary benefit; QALY – Quality-adjusted life year.

* All LY and QALY values have been rounded to 2 decimal places.

Table 7.23: Probabilistic pairwise analysis of silver sub-agents, mean (95% CI)

	Silver salts and compounds	Elemental silver
Total LYs*	0.97 (95% CI: 0.97 to 0.97)	0.97 (95% CI: 0.97 to 0.97)
Total QALYs*	0.69 (95% CI: 0.63 to 0.75)	0.69 (95% CI: 0.63 to 0.76)
Total cost GBP (£)	£7,332 (95% CI: £6,446 to £8,219)	£7,396 (95% CI: £6,631 to £8,161)
Incremental QALYs*	-	0.00 (95% CI: -0.01 to 0.01)
Incremental costs	-	-£64 (95% CI: -£379 to £252)
ICER	-	£54,305
Probability of cost-effectiveness		39.1%
Incremental NMB	-	£40 (95% CI: -£375 to £455)

Abbreviations: CI – Confidence interval; GBP – Great British Pound; ICER – Incremental cost-effectiveness ratio; LY – Life years; NMB – Net monetary benefit; QALY – Quality-adjusted life year.

* All LY and QALY values have been rounded to 2 decimal places.

Figure 7.16: Cost-effectiveness plane for silver salts and compound (intervention) compared with elemental silver (comparator)

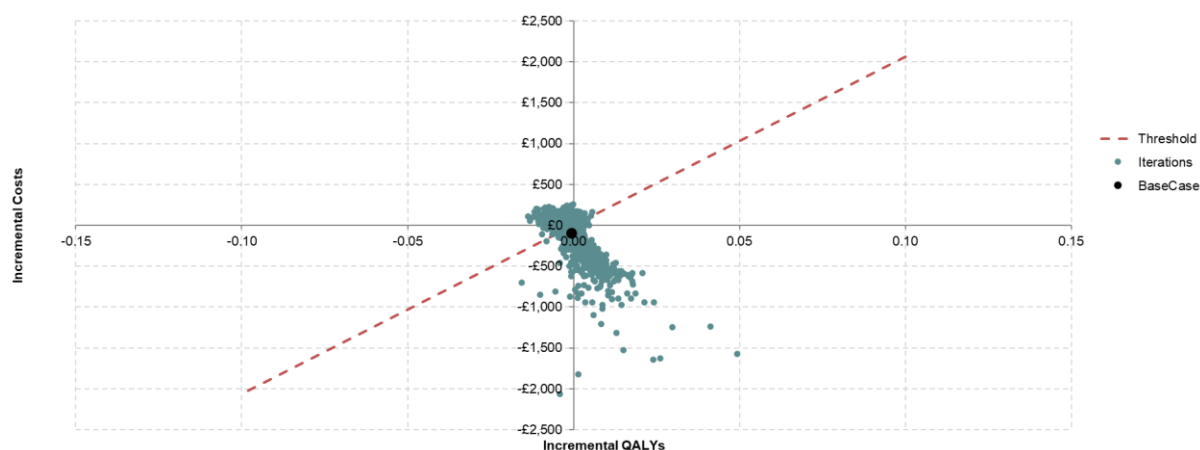


Figure 7.17: CEAC for silver salts and compound (intervention) compared with elemental silver (comparator)

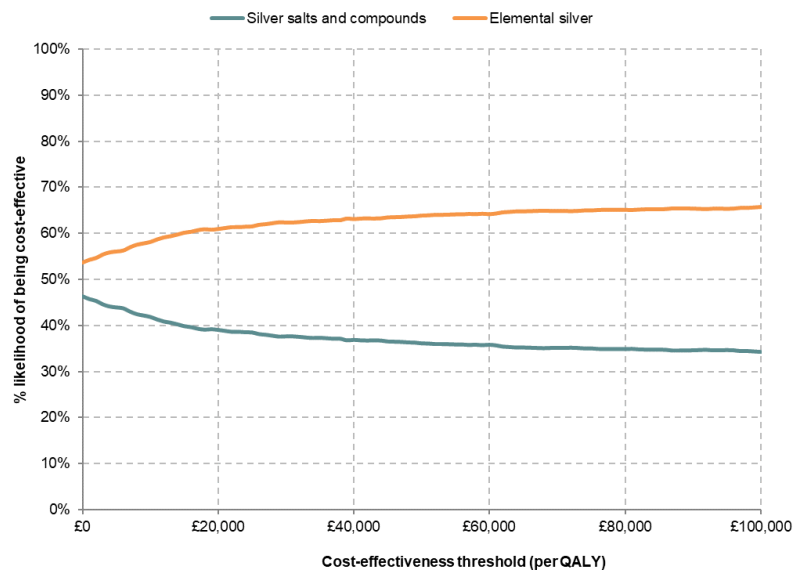
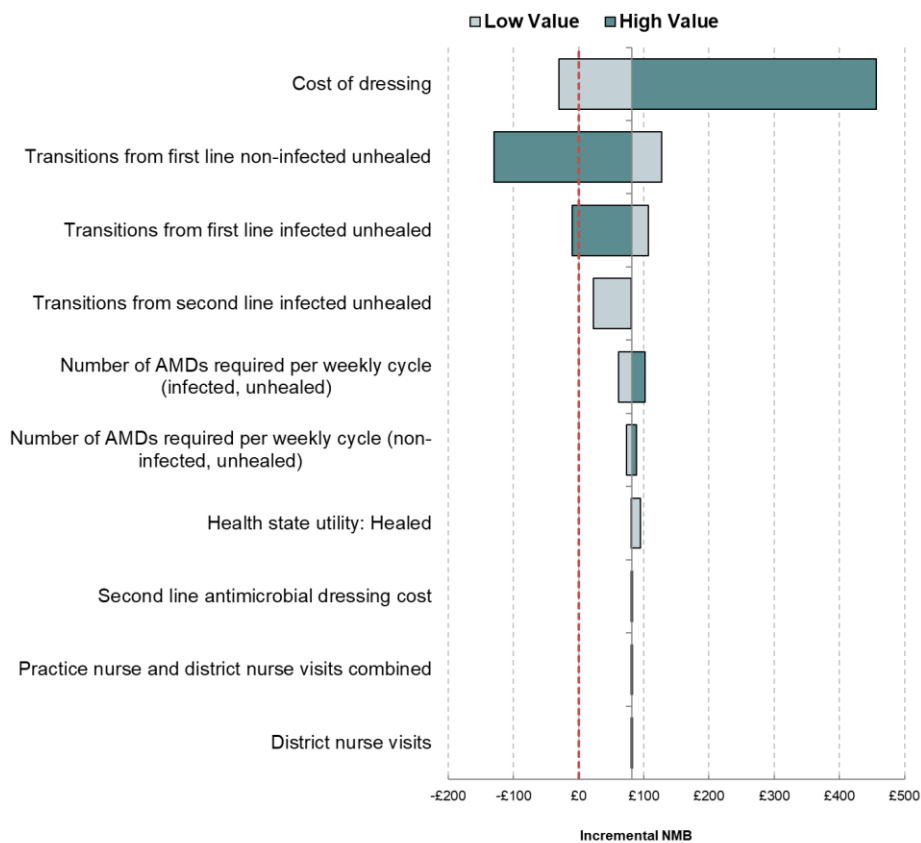


Figure 7.18: DSA tornado plot for silver salts and compound (intervention) compared with elemental silver (comparator)



7.3.3.2 Honey sub-agents

Honey sub-agents with available evidence were manuka and monofloral honey. As per the principal results (Section 7.3.1.1, 7.3.1.2 and 7.3.2) probabilistic and deterministic sensitivity analyses were undertaken for all base-case model inputs.

There are large differences in the ICERs for the deterministic analysis and probabilistic analyses. Incremental QALYs were extremely small, resulting in unstable and large ICERs as per the silver sub-agent analysis. Therefore, the incremental NMB is a more appropriate measure of cost-effectiveness, with manuka honey as the intervention and monofloral honey as the comparator.

The NMB is positive in the probabilistic analysis at £17 (95% CI: -£62 to £95). It is also positive for the deterministic analysis at £39. Therefore, the analysis suggests manuka honey is cost-effective when compared with monofloral honey at NICE's preferred threshold of £20,000 per QALY gained. This conclusion is drawn in 48.4% of PSA scenarios (Figure 7.20). As per the silver sub-agent analysis (Section 7.3.3.1), the distribution of points on the cost-effectiveness plane shows a negative correlation (Figure 7.19). The confidence intervals around the probabilistic incremental costs are from -£75 to £43. However, it is clear from Figure 7.19 that there are outliers in the South-East quadrant. These outliers skew the deterministic and probabilistic mean in favour of the agent which, based upon the available evidence base, has the comparatively lower rate of healing and the lower weighted average cost.

Key drivers of the cost-effectiveness, as highlighted in the DSA, are the cost of the AMD and the efficacy data from first line are the biggest drivers of cost-effectiveness. As per the principal analysis and the silver sub-agent analysis, the faster someone can progress to the healed health state the more likely it is that the outcome will be cost-effective because of a lower AMD cost, lower health state costs and higher QALYs. The analysis hints that this has a greater cost impact for manuka honey (based upon the available evidence base, this AMD has the numerically higher rate of healing and the higher weighted average cost) compared with monofloral honey. However, more evidence is needed before a firm conclusion on cost-effectiveness can be drawn.

Table 7.24: Deterministic pairwise analysis of honey sub-agents

	Manuka honey	Monofloral honey
Total LYs*	0.97	0.97
Total QALYs*	0.69	0.69
Total cost GBP (£)	£7,394	£7,427
Incremental LYs*	-	0.00
Incremental QALYs*	-	0.00
Incremental costs	-	-£33
ICER	-	-£113,234
Incremental NMB	-	£39

Abbreviations: GBP – Great British Pound; ICER – Incremental cost-effectiveness ratio; LY – Life years; NMB – Net monetary benefit; QALY – Quality-adjusted life year.

* All LY and QALY values have been rounded to 2 decimal places.

Table 7.25: Probabilistic pairwise analysis of honey sub-agents, mean (95% CI)

	Manuka honey	Monofloral honey
Total LYs*	0.97 (95% CI: 0.97 to 0.97)	0.97 (95% CI: 0.97 to 0.97)
Total QALYs*	0.69 (95% CI: 0.63 to 0.75)	0.69 (95% CI: 0.63 to 0.75)
Total cost GBP (£)	£7,505 (95% CI: £6,451 to £8,560)	£7,521 (95% CI: £6,505 to £8,538)
Incremental QALYs*	-	0.00 (95% CI: 0.00 to 0.00)
Incremental costs	-	-£16 (95% CI: -£75 to £43)
ICER	-	-£650,127
Probability of cost-effectiveness		48.4%
Incremental NMB	-	£17 (95% CI: -£62 to £95)

Abbreviations: CI – Confidence interval; GBP – Great British Pound; ICER – Incremental cost-effectiveness ratio; LY – Life years; NMB – Net monetary benefit; QALY – Quality-adjusted life year.

* All LY and QALY values have been rounded to 2 decimal places.

Figure 7.19: Cost-effectiveness plane for manuka honey (intervention) compared with monofloral honey (comparator)

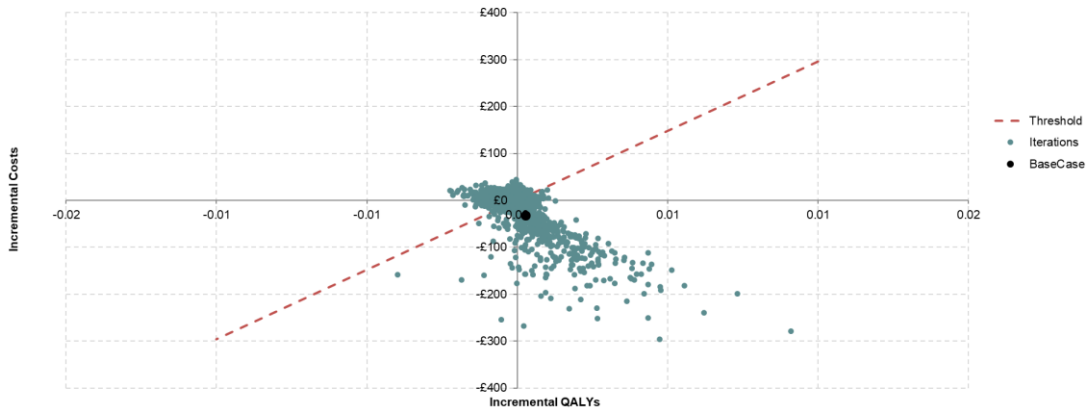


Figure 7.20: CEAC for manuka honey (intervention) compared with monofloral honey (comparator)

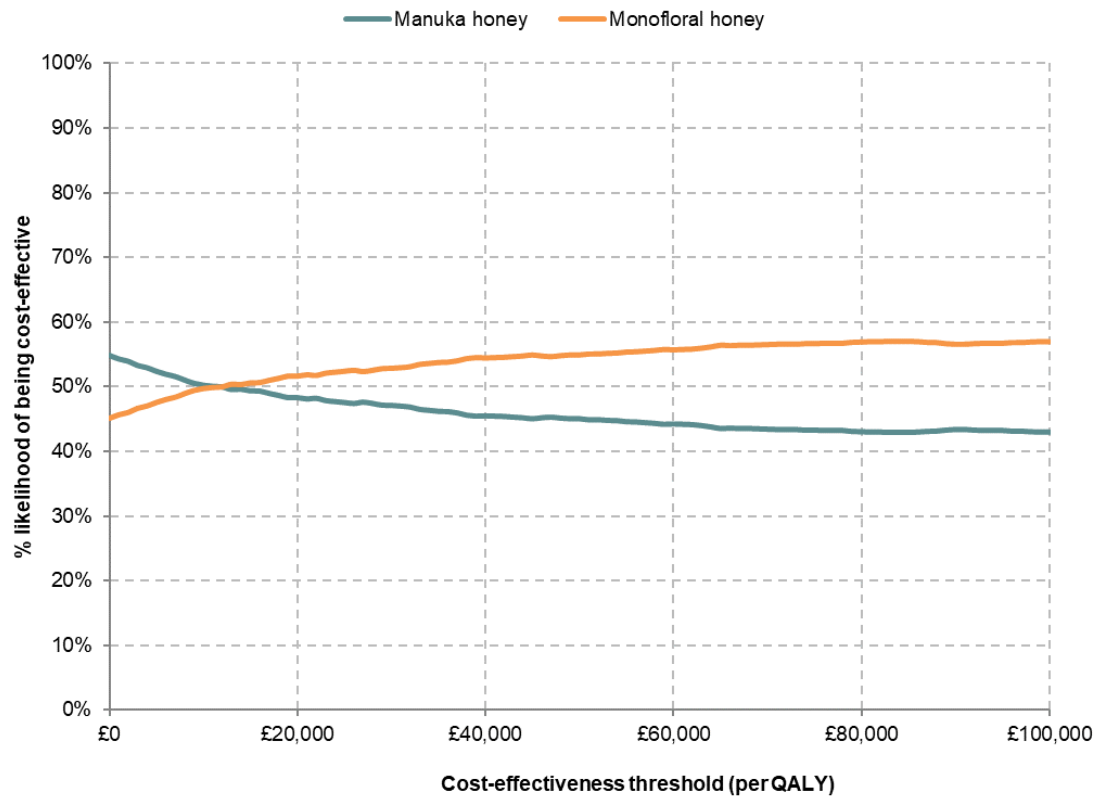
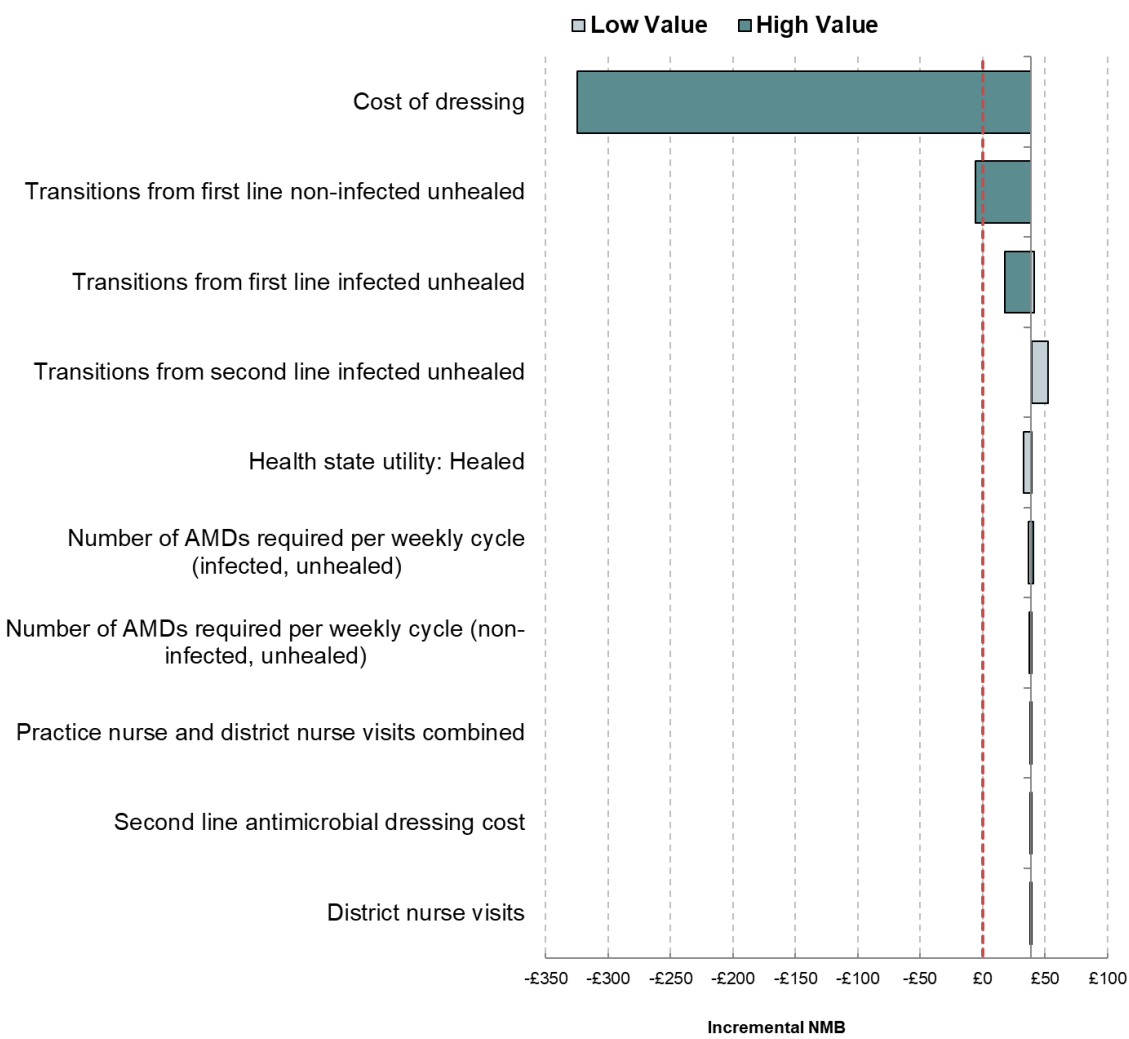


Figure 7.21: DSA tornado plot for manuka honey (intervention) compared with monofloral honey (comparator)



7.3.4 Scenario analysis

As highlighted throughout Section **Error! Reference source not found.**, there was a paucity of robust data available to inform some model parameters and, therefore, simplifying assumptions were required. The EAG conducted several scenario analyses to assess the impact of these assumptions. A description of each scenario and the respective outcome is reported in Table 7.26. The cost and QALY outcomes are

presented in Table 11.2 and Table 11.3 respectively (See Appendix J: Scenario analysis results). The referent treatment was identified as the intervention with the highest QALYs and lowest total cost. The NMB of the referent agent was compared with other agents at NICE's preferred cost-effectiveness threshold of £20,000 per QALY gained. The principals of dominance and extended dominance were applied (Table 7.27).

For many of the assumptions investigated by the EAG, the conclusion of cost-effectiveness did not change. Based upon the available evidence iodine was identified as the referent treatment. This conclusion was consistent across the use of maximum and minimum cost scenarios; variations in the frequency of dressing changes; resource use sources and health state cost assumptions; incorporating an assumed rate of reoccurrence of local infection and varying the health state utilities.

In these scenarios, there were observed variations in the costs and QALYs, described in more detail in Table 7.26. Of note, the total cost of a leg ulcer treated with a silver AMD was estimated to be £6,965 with the minimum costing silver AMD. This increased to £12,300 with the maximum costing silver AMD (difference of £5,335 per person in AMD costs). It is important to note that the data obtained from literature regarding frequency of silver dressing changes in the NHS are relatively high compared to others (see Table 7.8). When the frequency of dressing changes was reduced, the total cost was £6,948 when the minimum costing silver AMD was used and £9,006 when the maximum costing silver AMD was used (difference of £2,058 per person in AMD costs). This highlights the need for accurate data to inform the frequency of AMDs changes are needed to get an appropriate estimate of the total cost.

While there was a large shift towards other agents being cost-effective compared with iodine when the costs were lowered, the shift was not large enough for another agent to dominate iodine. These observations were consistent with the DSA. The maximum cost for the AMD caused costs to increase compared with the base case.

When a simple cost-comparison scenario was run, with the efficacy data were set to be equivalent, honey, which has a relatively low cost and resource use requirement,

became the referent treatment. Given that efficacy data was identified as key driver of cost-effectiveness, highlighted in Section 7.3.2, there is a need for robust, comparative efficacy data to inform the model for all agents, including agents for which data is currently missing, namely, chlorhexidine, DACC, enzyme alginogel and octenidine.

When the prescription times became equivalent, copper became the referent treatment. This is because copper is a relatively low costing agent, and the healing rate is higher compared with the other healing rates informing the model from clinical data available to inform the model. It is important to note that clinical experts raised a question over whether copper could be prescribed for longer than the 4-week period used in the model.

Longer prescription times allowed for the cohort to experience the treatment-effect of the AMD for longer for all agents. When the efficacy and prescription times were equivalent, increasing prescription time to 12 weeks allowed for costs to decrease and QALYs to increase compared with a prescription time of 12 weeks.

Discontinuation to second line without a sustained treatment effect associated with the AMD ('best practice') resulted in an increase in costs for low costing AMDs with a relatively high healing rate and a decrease in costs for other agents. This is likely because there is less time exposed to the more effective treatments. QALYs decreased for all treatments. Abbreviations: PHMB – Polyhexamethylene biguanide; QALY – Quality-adjusted life year.

Table 7.21 highlights the large costs associated the 'infected unhealed wound' and 'noninfected unhealed wound' health states. These outcomes support the principal analysis finding that key drivers of cost-effectiveness are the variables that can decrease the time spent in these 2 health states may be less costly overall.

The impact of changes in resource use were explored using data from during the COVID-19 pandemic. Applying resource use data from 2020 resulted in a cost reduction of almost 50% compared to the base case. The cost began to increase as the pandemic regulations began to ease (in 2021). However, it is difficult to conclude whether resources would have increased back to levels observed before the pandemic, especially with the move towards more virtual health care. Up-to-date resource use studies reflecting post-pandemic care are required to improve the accuracy of cost estimations. It is particularly important for this data to be disaggregated by health state to allow for a more detailed and accurate cost analysis.

Visits from practice and district nurses were in the top ten key drivers of cost-effectiveness identified in the DSA. These visits did not change the cost-effectiveness conclusion. These visits were incorporated in the resource use estimates informing the model

Table 7.9). To avoid double counting costs, it was assumed AMD changes occurred during these visits. However, this may have led to an underestimate of the health state cost of the 'infected unhealed wound' health state which was assumed to be equivalent to the 'non-infected unhealed wound' health state. An assumption of equivalence between the utilities of the 'infected unhealed wound' and the 'non-infected unhealed wound' was also required. Both assumptions were required because of a paucity of data specific to the 'infected unhealed wound' health state. However, it is unlikely these represent clinical practice. The EAG performed scenario analysis around this input and found that lowering the utilities and increasing the health state costs and saw no significant changes to the cost-effectiveness conclusions. Other key assumptions, including, reoccurrence of infection; and discontinuation of AMDs in the unhealed non-infected wound health state, did not change the overall cost-effectiveness conclusions.

Table 7.26: Cost-effectiveness scenario analysis outcomes

Scenario	Outcome
AMD cost scenarios	
Minimum cost of dressing containing agent.	• Iodine was the least costly, at £0.29 per pack. • Copper was the costliest, at £1.85 per pack • PHMB accrued the highest total costs for the year per person (£7,403) • Iodine accrued the lowest total cost for the year per person (£6,250) • No change in QALYs • Iodine was the referent agent. • All other agents became more cost-effective compared with iodine (decrease in incremental NMBs)
Maximum cost of dressing containing agent.	• When the maximum costs were used, copper was the least costly, at £8.27 per pack, and silver was the costliest at £68.82 per pack (see Table 7.7). • PHMB accrued the highest total costs for the year per person (£12,300) • Iodine accrued the lowest total cost for the year per person (£8,895) • No change in QALYs. • Iodine was the referent agent. • All other agents became less cost-effective compared with iodine (increase in incremental NMBs)
Assume all dressings changed once a week (regardless of infection status).	• Small decrease in costs where fewer dressing changes were required. • No change in QALYs. • Iodine was the referent agent • All other agents became more cost-effective compared with iodine (decrease in incremental NMBs)
Assume all dressings changed 3 times a week while infected, unhealed and once a week while non-infected, unhealed.	• Small decrease in costs where fewer dressing changes were required. • No change in QALYs. • Iodine was the referent agent. • PHMB became more cost-effective compared with iodine (increase in incremental NMB) • All other agents, apart from PHMB, became more cost-effective compared with iodine (decrease in incremental NMBs)

Scenario	Outcome
Assume all dressings changed 3 times a week while infected, unhealed and once a week while non-infected, unhealed with minimum cost.	• Small decrease in costs where fewer dressing changes were required. • Cost-effectiveness conclusion did not change • PHMB accrued the highest total costs for the year per person (£7,400). • Iodine accrued the lowest total cost for the year per person (£6,240). • Iodine was the referent agent • All other agents became more cost-effective compared with iodine (decrease in incremental NMBs)
Assume all dressings changed 3 times a week while infected, unhealed and once a week while non-infected, unhealed with maximum cost.	• PHMB accrued the highest total costs for the year per person (£9,577) • Iodine accrued the lowest total cost for the year per person (£7,398) • No change in QALYs. • Iodine was the referent agent. • All other agents became less cost-effective compared with iodine (increase in incremental NMBs)
Iodine cost to align with Cadaxomer iodine (to align with the efficacy)	• Cost for iodine changed from £1.45 to £8.69. • Iodine remained the referent treatment. • Costs for Iodine increased marginally. • Cost-effectiveness conclusion did not change (Iodine was the referent agent). • No change in QALYs
Resource use parameters	
Peri-pandemic resource use (2020) Published in Guest et al (2023) 1,153 people with venous leg ulcers in the THIN data base (Guest and Fuller 2023).	• Decrease in overall cost because of fewer resources being used during the pandemic. • Resource use has a very large impact on overall outcome, with costs decreasing by almost 50% in 2020. • No change in QALYs. • Iodine was the referent agent. • All other agents became more cost-effective compared with iodine (decrease in incremental NMBs)
Peri-pandemic resource use (2021) Published in Guest et al (2023). 733 people with venous leg ulcers in the THIN data base (Guest and Fuller 2023).	• Observed a rise in costs in 2021 compared with 2020 as lockdown measures began to ease. • No change in QALYs. • Iodine was the referent agent. • All other agents became more cost-effective compared with iodine (decrease in incremental NMBs)

Scenario	Outcome
Health state costs in the 'infected unhealed wound' health state 25% larger than the 'non-infected unhealed wound' health state (£216 per cycle)	• Increase in costs for all agents from base case. • Smallest increase in total costs for copper from the base case (£6,845 to £6,977). Increase in £132 overall. • Largest increase in total costs for PHMB from the base case (£7,755 to £8,184). Increase in £429 overall. • No change in QALYs. • Iodine was the referent agent. • All other agents, apart from copper, became less cost-effective compared with iodine (increase in incremental NMBs) • Copper became more cost-effective compared with iodine (decrease in incremental NMB)
Health state costs in the 'infected unhealed wound' health state 250% larger than the 'non-infected unhealed wound' health state (£514 per cycle)	• Increase in costs for all agents from base case. • Smallest increase in total costs for honey from the base case (£6,845 to £7,638). Increase in £793 overall. • Largest increase in total costs for PHMB from the base case (£7,755 to £10,325). Increase in £2,570 overall. • No change in QALYs • Iodine was the referent agent. • All other agents, apart from copper, became less cost-effective compared with iodine (increase in incremental NMBs) • Copper became more cost-effective compared with iodine (decrease in incremental NMB)
The cost of the infected unhealed health state 3.2 times more than that of an uninfected wound as per Guest et al (2018)	• Increase in costs for all agents from base case. • However, there was no change in the cost-effectiveness conclusion from base case (iodine remained the referent agent).
The cost of the healed health state set to £0	• Decrease in costs across all agents from base case. • No change in QALYs observed. • No change in cost-effectiveness conclusion from base case (iodine remained the referent agent).
The cost of the infected unhealed health state 3.2 times more than that of an uninfected wound as per Guest et al (2018) and the "healed" health state set to £0.	• Increase in costs for all agents from base case. • No change in cost-effectiveness conclusion from base case (iodine remained the referent agent).

Scenario	Outcome
Best practice scenarios	
Assumption that the people discontinue AMDs in the 'non-infected unhealed wound' health state and the treatment effect of AMDs remains (no AMD cost)	• Decrease in cost compared to base case, as AMD cost was no longer required. • Silver had the largest absolute difference in costs compared with the base case (-£320) • PHMB was the costliest overall (£7,488) • Iodine was the referent agent. • All other agents became less cost-effective compared with iodine (increase in incremental NMBs)
Assumption that the people discontinue AMDs in the 'non-infected unhealed wound' health state and automatically move onto second line basket	• Increase in cost compared to the scenario in which the treatment effect of the AMD was maintained in second line. • Decrease in cost compared to base case for all but copper and iodine, as AMD cost was no longer required. • With the clinical data available to inform the model, copper and iodine had the highest healing rate. • Copper had the largest absolute difference in costs compared with the base case (+£325) • PHMB was the costliest overall (£7,499) • Copper sat on the efficacy frontier. When iodine was compared with copper the incremental NMB was £9
Efficacy parameters and prescription time	
Equivalent efficacy data aligns with Table 7.5. No edits to the time for which the agent are prescribed (Guest et al. 2018).	• Assumed no per-week discontinuation for all agents. • Honey became the referent treatment. • Honey AMDs cost on average £3.03 despite being more costly per dressing than iodine (£1.45). However, honey has lower resource use requirements compared with iodine. • The treatment effect of the agent offsets the additional cost of the AMD.
Equivalent efficacy data aligns with Table 7.5 assuming all agents are prescribed for 4 weeks	• Assumed no per-week discontinuation for all agents. • All QALYs equivalent at 0.692 • Honey became the referent treatment. • Honey AMDs cost on average £3.03 despite being more costly per dressing than iodine (£1.45). However, honey has lower resource use requirements compared with iodine. • This is because the dressing change parameters informing the model suggest honey requires fewer dressing changes than iodine.
Equivalent efficacy data aligns with Table 7.5 assuming all	• All QALYs equivalent at 0.698

Scenario	Outcome
agents are prescribed for 12 weeks	- increased by 0.87% compared with the scenario where all agents were prescribed at 4 weeks with equivalent efficacy (from 0.692 to 0.698) - Honey became the referent treatment. - Honey AMDs cost on average £3.03 despite being more costly per dressing than iodine (£1.45). However, honey has lower resource use requirements compared with iodine. - This is because the dressing change parameters informing the model suggest honey requires fewer dressing changes than iodine.
Assumption that all agents are prescribed for 4 weeks	- Copper was the treatment with the highest efficacy, as reported in Table 7.4. - However, it was dominated in the case by iodine, because the product information indicated it could only be prescribed for 4 weeks (Table 7.4) - Copper became the referent treatment because it had the largest healing rate, and therefore, by model assumption, rate of infection resolution. - Increase in QALYs for PHMB compared with base case (0.684 to 0.687) - Decrease in QALYs for iodine compared with base case (0.703 to 0.695)
Assumption that all agents are prescribed for 12 weeks	- As per the previous scenario, copper became the referent treatment because it had the largest healing rate, and therefore, by model assumption, rate of infection resolution. - Increase in QALYs from base case for chitosan, copper and silver.
The intercept of the curve informing the 4 to 12 week conversion ratio was to account for the healing rate of infected people only (allowing for 11% to be healed at 4 weeks).	- The per-week conversion rate in the base case digitised data from figure 1, which looked at a combined population. - Figure 4 from Guest et al (2018) reported the time-to-healed for infected vs. non infected wounds. The proportional hazards assumption held, therefore, to derive the per-week healing curve for infected wounds, the intercept could be changed. - Halving the intercept allowed for 11% to be healed at 4 weeks which visually aligned with figure 4. - General decrease in cost across all agents, except PHMB - Minor changes in QALYs observed across most agents. - No change in cost-effectiveness conclusion from base case (iodine remained the referent agent).

Scenario	Outcome
Transition from "infected, unhealed wound" to "non-infected, unhealed wound" is informed by the healing rate and transition from "non-infected, unhealed wound" to "healed wound" is equivalent to Guest et al (2023)	• Increase in costs across all agents with the largest increased observed for Iodine. • Reduction in QALYs observed across all agents where the largest reduction was in PHMB. • Iodine was dominated with copper being the referent agent within this analysis.
Transition from "infected, unhealed wound" to "non-infected, unhealed wound" was equivalent	• Costs decreased for chitosan, honey, PHMB, and silver. • Minor changes in QALYs observed. • No change in cost-effectiveness conclusion from base case (iodine remained the referent agent).
Reoccurrence of local infection parameters	
Assumption that a per-week rate of 0.1 ulcer infections reoccur (move to infected unhealed wound from non-infected unhealed wound)	• Increase in costs across all agents • Decrease in QALYs across all agents. • Largest QALY decrease was chitosan and silver (-0.015) • Smallest QALY decrease was iodine and PHMB (-0.013) • Iodine was the referent agent. • All other agents became less cost-effective compared with iodine (increase in incremental NMBs)
Assumption that a per-week rate of 0.5 ulcer infections reoccur (move to infected unhealed wound from non-infected unhealed wound)	• Increase in costs across all agents. • Decrease in QALYs across all agents. • Largest QALY decrease was iodine (-0.037) • Smallest QALY decrease was PHMB (-0.032) • Iodine was the referent agent. • All other agents became more cost-effective compared with iodine (decrease in incremental NMBs)
Assumption that a per-week rate of 0.1 ulcer infections reoccur for first line, and a per-week rate	• Increase in costs across all agents. • Decrease in QALYs across all agents. • Largest QALY decrease was chitosan and silver (-0.015)

Scenario	Outcome
of 0.5 ulcer infections reoccur for second line	• Smallest QALY decrease was iodine (-0.026) • Iodine was the referent agent. • All other agents became less cost-effective compared with iodine (increase in incremental NMBs)
Discontinuation parameters	
Assumption that there is a per-week discontinuation rate of 0.25 from first line (infected AND non-infected, unhealed) to second line.	• Costs increased across all agents, except PHMB. • Minor changes in QALYs. • Iodine was dominated with copper being the referent agent within this analysis.
Utility parameters	
Health state utilities from Walzer et al (2018) (Walzer et al. 2018)	• Substantial decrease in health state utilities by over 1 QALY. • Largest QALY decrease was PHMB (-0.192) • Smallest QALY decrease was copper (-0.152) • No change to cost. • Iodine was the referent agent. • All other agents, apart from copper, became less cost-effective compared with iodine (increase in incremental NMBs) • Copper became more cost-effective compared with iodine (decrease in incremental NMB)
Health state utilities assuming 'infected unhealed wound' health state has utility 10% lower than 'non-infected unhealed' wound	• Small decrease in QALYs • Largest QALY decrease was PHMB (-0.010) • Smallest QALY decrease was iodine (-0.003) • No change to costs. • Iodine was the referent agent. • All other agents, apart from copper, became less cost-effective compared with iodine (increase in incremental NMBs) • Copper became more cost-effective compared with iodine (decrease in incremental NMB)

Abbreviations: AMD – Antimicrobial dressing; NMB – Net monetary benefit; PHMB – Polyhexamethylene biguanide; QALY – Quality-adjusted life year.

Table 7.27: Scenario results: NMB and dominance results

	Chitosan	Copper	Honey	Iodine	PHMB	Silver
Reference case	£1,081 (Dominated)	£498 (Dominated)	£1,271 (Dominated)	Referent	£1,690 (Dominated)	£1,083 (Dominated)
Cost scenarios						
Minimum cost of dressing containing agent	£942 (Dominated)	£407 (Dominated)	£1,207 (Dominated)	Referent	£1,533 (Dominated)	£941 (Dominated)
Maximum cost of dressing containing agent	£2,684 (Dominated)	£1,442 (Dominated)	£2,044 (Dominated)	Referent	£2,684 (Dominated)	£2,789 (Dominated)
Assume all dressings changed once a week (regardless of infection status)	£998 (Dominated)	£448 (Dominated)	£1,248 (Dominated)	Referent	£1,642 (Dominated)	£1,013 (Dominated)
Assume all dressings changed 3 time a week for infected unhealed wounds and once a week for non-infected unhealed wounds	£1,019 (Dominated)	£460 (Dominated)	£1,270 (Dominated)	Referent	£1,723 (Dominated)	£1,043 (Dominated)
Assume all dressings changed 3 time a week while infected, unhealed and once a week while non-infected, unhealed with minimum cost	£941 (Dominated)	£408 (Dominated)	£1,211 (Dominated)	Referent	£1,540 (Dominated)	£943 (Dominated)
Assume all dressings changed 3 time a week while infected, unhealed and once a week while non-infected, unhealed with maximum cost	£1,841 (Dominated)	£876 (Dominated)	£1,930 (Dominated)	Referent	£2,559 (Dominated)	£2,137 (Dominated)

	Chitosan	Copper	Honey	Iodine	PHMB	Silver
Iodine cost to align with Cadaxomer iodine (to align with the efficacy)	£863 (Dominated)	£302 (Dominated)	£1,053 (Dominated)	- (Referent)	£1,459 (Dominated)	£867 (Dominated)
Resource use						
Peri-pandemic resource use (2020) Published in Guest et al (2023) 1,153 people with venous leg ulcers in the THIN data base	£714 (Dominated)	£342 (Dominated)	£799 (Dominated)	Referent	£1,091 (Dominated)	£715 (Dominated)
Peri-pandemic resource use (2021) Published in Guest et al (2023). 733 people with venous leg ulcers in the THIN data base	£784 (Dominated)	£372 (Dominated)	£890 (Dominated)	Referent	£1,206 (Dominated)	£785 (Dominated)
Health state costs in the 'infected unhealed wound' health state 25% larger than the 'non-infected unhealed wound' health state	£1,141 (Dominated)	£480 (Dominated)	£1,448 (Dominated)	Referent	£1,968 (Dominated)	£1,143 (Dominated)
Health state costs in the 'infected unhealed wound' health state 250% larger than the 'non-infected unhealed wound' health state (£514 per cycle)	£1,442 (Dominated)	£390 (Dominated)	£2,335 (Dominated)	Referent	£3,359 (Dominated)	£1,444 (Dominated)
The cost of the infected unhealed health state 3.2 times more than that of an uninfected wound as per Guest et al (2018)	£1,611 (Dominated)	£340 (Dominated)	£2,831 (Dominated)	- (Referent)	£4,138 (Dominated)	£1,613 (Dominated)
The cost of the healed health state set to £0	£1,282 (Dominated)	£583 (Dominated)	£1,529 (Dominated)	- (Referent)	£2,017 (Dominated)	£1,284 (Dominated)

	Chitosan	Copper	Honey	Iodine	PHMB	Silver
The cost of the infected unhealed health state 3.2 times more than that of an uninfected wound as per Guest et al (2018) and the “healed” health state set to £0.	£1,812 (Dominated)	£426 (Dominated)	£3,090 (Dominated)	- (Referent)	£4,465 (Dominated)	£1,814 (Dominated)
Best practice scenarios						
Assumption that the people discontinue AMDs in the ‘non-infected unhealed wound’ health state and the treatment effect of AMDs remains (no AMD cost)	£979 (Dominated)	£416 (Dominated)	£1,232 (Dominated)	Referent	£1,618 (Dominated)	£982 (Dominated)
Assumption that the people discontinue AMDs in the ‘non-infected unhealed wound’ health state and automatically move onto second line basket	£107 (Dominated)	£9 (Not dominated)	£231 (Dominated)	Referent	£423 (Dominated)	£107 (Dominated)
Efficacy and prescription time						
Equivalent efficacy data aligns with Table 7.5. No edits to the time at which the agent are prescribed.	£628 (Dominated)	£625 (Dominated)	Referent	£5 (Extendedly Dominated)	£62 (Extendedly Dominated)	£627 (Dominated)
Equivalent efficacy data aligns with Table 7.5 in a world where all agents are prescribed for 4 weeks	£24 (Extendedly Dominated)	£21 (Extendedly Dominated)	Referent	£2 (Extendedly Dominated)	£26 (Extendedly Dominated)	£23 (Extendedly Dominated)
Equivalent efficacy data aligns with Table 7.5 in a world where all agents are prescribed for 12 weeks	£60 (Extendedly Dominated)	£40 (Extendedly Dominated)	Referent	£5 (Extendedly Dominated)	£62 (Extendedly Dominated)	£54 (Extendedly Dominated)

	Chitosan	Copper	Honey	Iodine	PHMB	Silver
Assumption that all agents are prescribed for 4 weeks	£584 (Dominated)	Referent	£890 (Dominated)	£309 (Dominated)	£1,037 (Dominated)	£585 (Dominated)
Assumption that all agents are prescribed for 12 weeks	£884 (Dominated)	Referent	£1,610 (Dominated)	£339 (Dominated)	£2,029 (Dominated)	£911 (Dominated)
The intercept of the curve informing the 4 to 12 week conversion ratio was to account for the healing rate of infected people only (allowing for 11% to be healed at 4 weeks).	£1,794 (Dominated)	£1,087 (Dominated)	£1,671 (Dominated)	- (Referent)	£2,609 (Dominated)	£1,797 (Dominated)
Transition from "infected, unhealed wound" to "non-infected, unhealed wound" is informed by the healing rate and transition from "non-infected, unhealed wound" to "healed wound" is equivalent to Guest et al (2023)	£105 (Dominated)	- (Referent)	£531 (Dominated)	£227 (Dominated)	£703 (Dominated)	£105 (Dominated)
Transition from "infected, unhealed wound" to "non-infected, unhealed wound" was equivalent	£911 (Dominated)	£678 (Dominated)	£834 (Dominated)	- (Referent)	£1,154 (Dominated)	£913 (Dominated)
Ulcer reoccurrence parameters						
Assumption that a per-week rate of 0.1 ulcer infections reoccur (move to infected unhealed wound from non-infected unhealed wound)	£1,175 (Dominated)	£545 (Dominated)	£1,323 (Dominated)	Referent	£1,716 (Dominated)	£1,273 178 (Dominated)

	Chitosan	Copper	Honey	Iodine	PHMB	Silver
Assumption that a per-week rate of 0.5 ulcer infections reoccur (move to infected unhealed wound from non-infected unhealed wound)	£910 (Dominated)	£341 (Dominated)	£1,031 (Dominated)	Referent	£1,309 (Dominated)	£914 1,016 (Dominated)
Assumption that a per-week rate of 0.1 ulcer infections reoccur for first line, and a per-week rate of 0.5 ulcer infections reoccur for second line	£1,721 (Dominated)	£970 (Dominated)	£1,587 (Dominated)	Referent	£2,038 (Dominated)	£1,726821 (Dominated)
Discontinuation parameters						
Assumption that there is a per-week discontinuation rate of 0.25 from first line (infected AND non-infected, unhealed) to second line.	£395 (Dominated)	- (Referent)	£595 (Dominated)	£211 (Dominated)	£712 (Dominated)	£394 (Dominated)
Utility parameters						
Health state utilities from Walzer et al (2018) (Walzer et al. 2018)	£1,208 (Dominated)	£421 (Dominated)	£1,733 (Dominated)	Referent	£2,435 (Dominated)	£1,209302 (Dominated)
Health state utilities assuming 'infected unhealed wound' health state has utility 10% lower than 'non-infected unhealed' wound	£1,110 (Dominated)	£489 (Dominated)	£1,358 (Dominated)	Referent	£1,825 (Dominated)	£1,112205 (Dominated)

Abbreviations: AMD – Antimicrobial dressing; PHMB – Polyhexamethylene biguanide; THIN – The Health Improvement Network.

7.3.5 *Summary and interpretation of the economic evidence*

Given the current evidence base available several simplifying assumptions were required to inform the model. This introduced a level of uncertainty into the analysis surrounding key parameters including the time taken for infection resolution and the time to healing. Therefore, it is essential to exercise caution when interpreting the model results.

The probabilistic base case analysis shows a large overlap between confidence intervals in the utilities and the costs (Section 7.3.1.1). This was also the case for the sub-agent PSA (Section 7.3.3). Therefore, with the available evidence, it is not possible conclude whether there are significant differences between the total cost and QALYs of the AMDs to use model results to rank the agents and/or sub-agents in terms of cost-effectiveness. Instead, outcomes from the analyses can be used to highlight which parameters were the key drivers of cost-effectiveness.

While this was not explored in the DSA, the prescription time was shown in the scenario analysis be a key driver of cost-effectiveness (Section 7.3.4). The model showed that a longer prescription time allowed for a prolonged treatment effect of the AMD. Therefore, the cohort was able to progress to the healed health state faster. A key finding from the principal analysis was that the faster the cohort progressed to the healed health state, the lower the costs because fewer AMDs and fewer resources were needed. As per this finding, the longer prescription time allowed for lower costs. QALYs also increased with a longer prescription time. Indeed, then efficacy was equivalent, the QALYs increased by 0.87% when prescription with was 12 weeks compared with a prescription length of 4 weeks.

There are likely other benefits to a longer prescription time that could not be captured in the model, particularly around TRAEs. TRAEs, for example allergic reactions, itching and general discomfort were captured indirectly with a per-cycle discontinuation rate and were not associated with a utility decrement. A clinical expert noted that regular dressing changes can lead to TRAEs. The model does not capture this and, therefore, likely underestimates the benefit to the patient experience if 1 dressing could be

prescribed for longer periods. Therefore, this parameter that may be important to consider when assessing the merits of AMDs. It is important to note here that prescription time in the model was informed by clinical practice guidelines where possible. Where guidelines were not available, assumptions were used. One clinical expert noted that they believed a copper dressing could be worn for a longer period than the 4 weeks used in the base case model. More information is required to inform the model appropriately.

Outcomes from the sub-agent analysis show that, in the base case, the least costly AMD was cost-effective in the base case deterministic and probabilistic analysis where efficacy data were similar (as observed in both analyses). Use of the less costly AMD had the potential to have greater incremental costs when compared with the more costly AMD creating outliers in the incremental PSA costs which drove the PSA mean. However, the more costly AMD had a greater likelihood of cost-effectiveness at NICE's willingness to pay threshold of £20,000 across the 1,000 probabilistic iterations. This is because the evidence base informing the efficacy for the more costly honey sub-agent had a numerically larger percentage healed than the less costly sub-agent. Where there was a greater difference in efficacy, the cost savings and QALY gains associated with moving to the healed health state faster offset the additional AMD costs. The cost of the AMD had less impact overall. The efficacy data is, therefore, a key driver of the cost-effectiveness in the model.

It is important to highlight the evidence base available to inform the model was disparate and heterogeneous. Complete healing data was transformed from a 4-week to 12-week rate using a multiplier derived from literature (Guest et al. 2018) assuming a healing rate following the trend of Equation 7.1. Data on time to infection resolution were sparse and required assumptions. Therefore, given the impact of efficacy data in the model, there is a need for robust, comparative evidence to appropriately assess the merits of AMDs and inform the model.

One scenario performed was a simple cost-comparison in which all efficacy data was set to be equivalent. In this scenario, the agent with a relatively low cost and low

frequency of dressing changes (honey) became the referent treatment. It is important to note that some clinical experts expressed surprise at the efficacy estimates for honey. They expressed uncertainty in the likelihood that, over the initial treatment period of 12 weeks, people prescribed honey AMDs would take longer to heal than other agents, for example, iodine (as indicated by the available efficacy data).

The AMD costs, combined with the frequency of dressing changes, contributed to only a small percentage of the overall cost (Abbreviations: PHMB – Polyhexamethylene biguanide; QALY – Quality-adjusted life year).

Table 7.21), however, use of the maximum cost caused a large shift in the incremental NMB. Subsequently, AMD costs were a key driver of cost-effectiveness identified in the DSA (Section 7.3.2). Use of the minimum AMD cost had a small impact on the ICER, suggesting that the current market share of AMDs in primary care (as indicated by the CPRD data) is more heavily weighted towards the lower costing AMDs.

The EAG acknowledge that there are key areas of uncertainty in the data and assumptions informing the economic model. Therefore, AMD specific cost and QALY results may not be appropriate to use to compare and assess the merits of AMDs. However, prescription time, efficacy (time to healing and time to infection resolution) and frequency of dressing changes combined with AMD costs were identified as key drivers of cost-effectiveness. The identification of these key parameters may help to direct future research from which a robust comparison can be performed.

7.3.6 *Limitations*

This section highlights key limitations associated with the data in the economic analysis.

Several key parameters were informed by large, UK-based studies of venous leg ulcer management reported by the THIN database use (Guest et al. 2018),(Guest and Fuller 2023). These parameters were the per-cycle ‘infected unhealed wound’ and the ‘non-infected unhealed wound’ health state resource use (Guest and Fuller 2023) and the multiplier to derive the per-cycle health state cost for the ‘healed wound’ health state (Guest et al. 2018). Furthermore, these data informed the non-linear equation to derive the percentage healed at different time point and the population inputs (Guest et al. 2018). A limitation of using Guest et al (2018) to derive the non-linear equation is that the healing rate for venous leg ulcers may differ from the healing rate of other types of leg ulcers included in our decision problem. One clinical expert highlighted that healing is slower for arterial leg ulcers and mixed arterial and venous leg ulcers than pure venous leg ulcers.

Resource use estimates were extracted from (Guest and Fuller 2023) and the market share applied to the costs were extracted from CPRD data. These data sources consisted of primary care data. It is important to acknowledge that that leg ulcer treatment and care is known to be provided in the community. This may have underestimated overall costs. The cost of AMDs can have a large impact on the cost-effectiveness as highlighted in Section 7.3.5. However, scenarios around the resource use did not impact the overall cost-effectiveness conclusions (Section 7.3.4), despite contributing to a substantial percentage of the overall health state costs (Abbreviations: PHMB – Polyhexamethylene biguanide; QALY – Quality-adjusted life year.

Table 7.21). The VenUS II and VenUS IV clinical trials were considered as alternate sources. However, the data is over 10 and 15 years old and, therefore, may not reflect clinical practice. Indeed, scenarios comparing resource use pre- and peri-the COVID-19 pandemic highlights the need for the resource use data to be reflective of today's clinical practice. Furthermore, neither the intervention or the comparator in the model were AMDs and the models did not include an infected health state.

Another key limitation of the cost-effectiveness analysis is the quality of evidence available. Indeed, there is a lack of comparative head-to-head randomized controlled trials and retrospective, observational studies on NHS data which could inform the model. The studies used to inform the model were from a variety of health care settings and not all treatment regimens align with those in the England and Wales NHS. An example of this is Forlee et al, whose participants remained on silver dressings for 8 weeks (Forlee et al. 2014), yet, guidance from the NHS recommends silver dressings should be used for a maximum of 4 weeks to avoid silver toxicity (Brassington and Crotty 2024).

Furthermore, there was limited data available on treatment-related adverse events (TRAEs), for example, allergic reactions and irritation caused by different AMDs. A comprehensive analysis comparing different agents in each of the different types of dressing and the associated TRAEs may be of interest in the future.

Furthermore, the location and aetiology of the wound varied amongst the studies. Indeed, the efficacy of honey dressings was informed by a population with infected diabetic foot ulcers, which is typically a more severe population (Moghazy et al. 2010). Subgroup analysis on the size, location and length of time the ulcer had persisted were not consistently available in literature. However, these factors were amongst those that were highlighted by clinical experts as being key to determining the rate of infection resolution and the healing rate. For this reason, some clinical experts disputed the simplifying assumption that the rate of infection resolution was equivalent to the rate of healing which was required for the model.

Recurrence of leg ulcers was not modelled as data was not available to demonstrate how AMD choice would impact recurrence, however it is acknowledged this is a significant issue when treating patients and an area to be considered if evidence becomes available. These limitations as well as the paucity of other large UK based studies to inform model inputs could lead to results that do not accurately align with the real world. However, sensitivity analysis was conducted to account for these uncertainties.

After discontinuation of the AMD, the cohort moved to a mixed basket of dressings. In clinical practice, it is expected that a person with a leg ulcer would cycle through different types of AMDs (i.e. experience a sequence of AMDs). There was a lack of evidence reporting a specific sequence that a patient would experience. This is thought to be because there will be heterogeneity between each patient and the resources available in a specific site. A patient-level simulation model would be required to accurately capture the unique sequence of AMDs. However, there is not enough evidence to inform the efficacy of each AMD at each point in the sequence. Building this functionality into a model would require a lot of assumptions and increase uncertainty.

8 Discussion

8.1 *Summary of clinical evidence*

The clinical evidence review did not identify evidence adequate to draw conclusions on the relative efficacy of AMDs when used to treat infected leg ulcers.

Included studies were heterogenous in the AMDs and sub-agents they evaluated, and consequently the evidence base for each intervention is small. In addition, studies were predominantly non-comparative with small sample sizes, were largely considered at moderate or high risk of bias and varied in their populations, outcome definitions and timepoints of measurement. The EAG therefore considers the evidence base to be uncertain.

Due to an absence of evidence, no conclusions can be identified for the relative efficacy of chlorhexidine, nor for 3 of the 14 sub-agents of interest (listed in Table 2.2, nanoparticulate silver, povidine iodine, and chlorhexidine).

Clinical opinion provided during the LSA scoping workshop identified key outcomes of importance as: complete healing, reduction of infection, wound-related pain and HRQoL. The discussion focuses on evidence for these outcomes.

Comparative evidence generally favours silver agents for achieving complete healing. However, comparisons between silver sub-agents are inconsistent and this observation may be due to the higher number of studies assessing silver than other agents. All agents/sub-agents evaluated by non-comparative studies were associated with improved rates of healing over time, with the exception of chitosan which showed a dip in performance at 4 weeks. Ionic silver and enzyme alginogel appeared to demonstrate the greatest improvement over time of the silver and non-silver agents or sub-agents respectively, while complete healing with monofloral honey was slower than for other non-silver sub-agents.

The EAG notes that 1 excluded RCT compared

[REDACTED]

[REDACTED] This finding is broadly consistent with the included body of evidence, although the lack of infection means the results may provide overestimates of effect when considering a population with infected wounds.

Interpretation of AMD impact on the clinical signs of infection was more difficult to interpret due to widely varying outcome definitions and the smaller number of studies reporting this outcome. Comparative evidence from 2 studies suggested ionic silver outperformed ionic silver complex, while Manuka honey outperformed an unspecified silver AMD for achieving improvement in infection. Non-comparative evidence may suggest ionic silver is associated with lower rates of infection by 4 to 7 weeks than

silver sulphadiazine. For non-silver agents/sub-agents, Octenidine gel with a wound contact layer showed a faster and greater improvement than Octenidine gel with foam or alginate.

No significant differences were found in pain and discomfort (1 comparative study) between use of DACC (Cutimed Sorbact) and ionic silver complex. Interpretation of non-comparative evidence is not possible due to the use of different measurement methods across studies reporting this outcome.

Insufficient evidence was available to interpret the impact of AMDs and sub-agents on 10 outcomes (each informed by 4 studies or fewer), preventing meaningful insights into relative treatment effects: severity of infection, signs of infection, recurrence of infection, time to wound healing, oedema, dressing changes, prescription of antibiotics, patient discomfort and HRQoL.

In terms of safety, the studies indicate that none of the assessed AMDs were associated with serious TRAEs, and the majority of TRAEs were pain or irritation on application or removal. However, the EAG notes that during 2024 the BNF updated caution notices for povidone iodine fabric dressings (Inadine) to list contraindications for patients with various conditions including kidney and thyroid diseases ([NICE 2024c](#)).

Several critical limitations of this evidence base suggest that conclusions drawn from the comparative and single-arm studies may not provide a reliable indication of relative efficacy. These are:

- The considerable heterogeneity in how outcomes were described and measured, and the timepoints at which they were measured.
- Differences in the study designs used to measure these outcomes; few studies directly compared different AMDs (4 of 34 included studies) while the design of non-comparative studies also varied.

- Concomitant care was poorly reported, so the causality of observed effects is highly uncertain. This issue is potentially exacerbated in older studies where the nature of concomitant care may be significantly different to current care.
- Scarce reporting of the statistical significance of outcomes, exacerbated in studies with small sample sizes. Only 3 studies (Vallejo et al. 2022)(Miller et al. 2010)(Gago et al. 2008) explicitly reported that they were adequately powered to detect differences in the primary outcome.

Clinically significant heterogeneity in study populations and settings, such that it is unclear whether observed treatment effects and differences in outcomes were due to the use of the AMD / sub-agent, or due to differences in patient population. This potential confounding is of particular concern when interpreting directional results across the non-comparative studies. Author reported infection was used to determine study eligibility, and the criteria used to define infection were not always reported. This may have introduced more variability between study populations included in this review, particularly for older studies. The EAG considers the generalisability of the evidence base to be poor due to the small number of UK studies (7 of 34 included studies) and variations in the setting of care, as well as the inclusion of evidence that did not fully satisfy the decision problem, due to a lack of relevant evidence. Although healthcare systems in some non-UK locations may be more similar to the UK NHS (such as some European countries), potential differences in the identification of infection and in treatment protocol mean the applicability of their findings to the UK NHS setting should be considered. Studies were included that assessed patients with non-infected wounds and infected wounds in locations other than the leg. Further, some AMDs in included studies may no longer be available for use (such as Aquacel Ag). Clinical interpretation will therefore be important to determine how generalisable the evidence is to people being treated in the NHS with infected leg ulcers.

Evidence was also unavailable to address 3 criteria stated during NICE's user preference workshop to be amongst the most important to users. The 5 criteria assessed were: (in order of priority to users) conformability, ease of removal,

application directions from manufacturer, cost (including cost of secondary and tertiary products, and the number and subsequent cost of dressing changes) and sustainability. Users agreed that all such outcomes were patient and situation specific, and that locally agreed infection control pathways should be prioritised. While data on ease of removal were captured as safety outcomes in the evidence base, no explicit data measuring conformability, application, or sustainability were identified. Costs data were captured by the economic evidence review.

8.2 *Summary of economic evidence*

The economic evidence review identified a limited number of economic evaluations of AMD agents, 6, to help guide the development of the de novo model. The review found only 1 study which was conducted in the UK, highlighting the novelty of the economic evaluation conducted by the EAG. Similar to the evidence base identified by the efficacy and safety review, the reported model populations and data sources used varied between studies, meaning that generalization of the available economic evidence to the scoped population and setting was uncertain.

The EAG recommend caution when interpreting model results because of the uncertainty around the model inputs and simplifying assumptions. Results from the economic model do not provide enough certainty to allow robust conclusions on the cost-effectiveness of AMDs when used to treat infected leg ulcers.

A key driver of cost-effectiveness was the efficacy data. However, as per the outcomes from the EAG's clinical review, the evidence base available to parameterise the efficacy data for the EAG's economic analysis had considerable heterogeneity. Robust comparative data on the time to infection resolution (and subsequent percentage of people healed, by agent) is needed to produce more reliable results. The economic model used published evidence and simplifying assumptions to calculate the rate of infection resolution and healing for each agent. Clinical evidence at these timepoints was lacking, with all but 1 (Koullias et al. 2022) of the included studies reporting outcomes at a timepoint of between 8 days and 12 weeks. Clinical experts highlighted the desirability of further clinical evidence to inform these parameters, and a need to

incorporate, where possible, other factors influencing healing rates. Efficacy data interacted with the prescribing time. It was found that a longer prescription time was associated with lower costs and higher QALYs overall.

Despite the acknowledged limitations associated with the underlying efficacy data, key drivers of cost-effectiveness and the direction of model results can be used to identify merits that can be used to assess choice of AMD for a locally infected leg ulcer. Prescription time and efficacy were key parameters that could be considered.

The modelling demonstrated that the largest proportion of costs incurred in the management of leg ulcers in this population was attributable to the 'infected unhealed wound' and the 'non-infected unhealed wound' health state (Abbreviations: PHMB – Polyhexamethylene biguanide; QALY – Quality-adjusted life year).

Table 7.21). Therefore, interventions and technologies that can reduce the amount of time spent in the 'infected unhealed wound' and provide a sustained treatment effect in the non-infected unhealed wound' health state (if best practice is assumed) may have substantial scope to reduce their total cost of treatment.

Conversely, the costs of AMDs contributed a small percentage of the total costs which, at first glance, suggests that interventions that solely reduce the cost of the AMDs (including number of dressing changes) have less scope to reduce the total cost of treatment. However, both the DSA and scenario analysis demonstrated that the use of high-cost AMDs attributed a substantial cost burden to the NHS (Table 7.27).

To further aid decision making, an analysis of NHS registry data or an appropriate observational evaluation could be considered to collect appropriate data on AMD efficacy to inform the model. However, questions exist over the value of this information; the overlapping QALY confidence intervals in the model suggest no significant differences between effectiveness of agents. An expected value of information (EVI) analysis may be a sensible approach to determine if the budgetary risk outweighs the benefit of collecting more evidence.

9 Conclusion

The current evidence base does not allow a clear assessment of the relative merits of different AMDs in UK patients with infected leg ulcers, so no conclusions on the relative efficacy on the range of AMDs can be drawn. Results from the economic model are not sufficiently certain to allow conclusions on the cost-effectiveness of AMDs in the scoped population and setting.

9.1 *Recommendations for further work*

The EAG recommends that further evidence should be collected to compare the performance of different agents and sub-agents within AMDs. Given that these dressings are in current use within the NHS, observational designs using hospital data

may provide pragmatic means of evaluation. These should focus on UK NHS patient populations with infected leg ulcers and clearly report the infection status of leg ulcers at baseline as well as how this was determined. Where possible, patients should be matched for key baseline characteristics that are likely to affect key treatment outcomes.

Future studies should gather data on the use of AMDs in clinical practice, including the use of secondary and tertiary products, and the number of dressing changes determined by nursing staff to be required. Outcomes should focus on those known to be of clinical value to patients and users (nursing staff), including those assessed in the user preference workshop which are currently not well represented in the evidence base. A research study (Cullum et al. 2016) conducted in the NHS between 2008 and 2012 gathered information on the outcomes most valued by patients and health professionals dealing with a range of chronic, complex wounds including leg ulcers. Though not specifically addressing infected wounds, the study identified healing (particularly time to healing) as a primary treatment outcome alongside other important outcomes measuring pain, infection and discomfort. Outcome data should be gathered over a sufficiently long term (informed by clinical input) to capture all instances of infection resolution and complete healing, as well as consequential risks of infection such as cellulitis, gangrene and amputation.

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11 Appendices

Use the appendices to describe additional data and information as needed.

List the titles of the appendices here.

11.1 *Appendix A: Clinical, technological and economic search strategies*

11.1.1 *Search strategies: Clinical, safety and economic evidence*

A single set of searches was conducted to identify evidence on clinical, safety and economic outcomes. Reflecting the NICE interim methods and process statement for LSA (National Institute for Health and Care Excellence 2024b), the search methods (including strategy design, selection of search resources and approach to strategy translation) incorporated some pragmatic elements, as appropriate to the LSA timeline and resource context. Database searches were conducted systematically; in other words, they were conducted in a methodical pre-planned way, were designed to be appropriately robust for the project context and are reported in a way that is appropriately transparent and reproducible.

Search strategy

A MEDLINE (OvidSP) search strategy was designed to identify studies of eligible dressings for infected leg ulcers. The search strategy was not restricted by outcome or study design and was therefore appropriate for identifying evidence on clinical, safety and economic outcomes. The final MEDLINE strategy used is presented below (A.1:).

The strategy comprised 3 main concepts:

- Leg ulcers (search lines 1 to 28).
- Non-specific antimicrobial/bacterial-binding dressings (search lines 29 to 38).
- Eligible agents (search lines 39 to 105).

The concepts were combined as follows: leg ulcers AND (non-specific antimicrobial/bacterial-binding dressings OR eligible agents).

The strategy was devised using a combination of subject indexing terms and free text search terms in the Title, Abstract and Keyword Heading Word fields. The search terms were identified through discussion within the research team, scanning background literature, browsing database thesauri and use of the [PubMed PubReminer tool](#).

The search terms for the leg ulcers concept were designed to retrieve studies on leg ulcers where the database record explicitly referred to either a specific leg ulcer context (search lines 1 to 16) or to non-specific venous, vasculitic or phlebolympoedema ulcers (search lines 17 to 27).

The search terms for the non-specific antimicrobial/bacterial-binding dressings concept (search lines 29 to 38) were included to retrieve studies on eligible agents where the database record did not explicitly refer to a specific eligible agent but only to a non-specific antimicrobial/bacterial-binding dressing context. The terms were designed to retrieve database records that referred to antimicrobial/bacterial-binding terms in close association with terms relating to dressings (for example dressing, alginate, film, foam, gauze, hydrogel, hydrocolloid) or topical application.

The search terms for the eligible agents concept (search lines 39 to 105) included generic terms and brand name terms for each specific agent. A pragmatic approach was used to identify the list of brand names for inclusion in the strategy. This approach and the list of included brand names were agreed with NICE.

The strategy excluded animal studies from MEDLINE using a standard algorithm (search line 109). The strategy also excluded some ineligible publication types which

were unlikely to yield relevant study reports (editorials, news items and case reports) and records with the phrase 'case report' in the title (search line 110).

Reflecting the eligibility criteria, the strategy was restricted to studies published in the English language (search line 112). No date limits were applied.

The protocol Ovid MEDLINE strategy was peer-reviewed before execution by a second Information Specialist. Peer review considered the appropriateness of the strategy for the review scope and eligibility criteria, inclusion of key search terms, errors in spelling, syntax and line combinations, and application of exclusions. Minor revisions suggested by the peer-review (to enhance potential sensitivity) and by final line-checking were incorporated, resulting in the final MEDLINE strategy as run.

Resources searched

We conducted the literature search in the databases shown in Table 10.1. The resources included sources of both clinical and economic studies.

Table 10.1: Databases and information sources searched

Resource	Interface / URL
Databases	
MEDLINE(R) ALL	OvidSP
Embase	OvidSP
Cochrane Database of Systematic Reviews (CDSR)	Cochrane Library/Wiley
Cochrane Central Register of Controlled Trials (CENTRAL)	Cochrane Library/Wiley
HTA Database	https://database.inahta.org/
Conference Proceedings Citation Index – Science (CPCI-S)	Web of Science
CINAHL Ultimate	EBSCOhost
NHS Economic Evaluation Database (NHS EED)	https://www.crd.york.ac.uk/CRDWeb/HomePage.asp
EconLit	OvidSP

Trials Registers	
ClinicalTrials.gov	https://clinicaltrials.gov/
WHO International Clinical Trials Registry Platform (ICTRP)	https://trialsearch.who.int/
Reference list checking	n/a
Company Submission Evidence	n/a

The trials register sources listed above (ClinicalTrials.gov and ICTRP) were searched to identify information on studies in progress. A number of data providers provide data to WHO for inclusion in ICTRP, including the EU Clinical Trials Register (EU-CTR).

Sources for identifying potentially eligible grey literature included Embase (for conference abstracts), CPCI-S, ClinicalTrials.gov, WHO ICTRP, HTA Database, reference-list checking and company submission evidence.

Reflecting the eligibility criteria, records indexed as preprints were excluded from Embase search results.

We also checked the included studies lists of retrieved relevant systematic reviews published in the last 5 years for any eligible studies that may have been missed by the database searches.

For details of how we used company submission evidence to identify eligible evidence, see Section 4.1.

Running the search strategies and downloading results

We conducted searches using each database or resource listed above, translating the agreed Ovid MEDLINE strategy appropriately. Translation included consideration of differences in database interfaces and functionality, in addition to variation in indexing languages and thesauri. A pragmatic approach was taken to some translations, as appropriate to the LSA methods context. The final translated database strategies were peer-reviewed by a second Information Specialist. Peer review considered the

appropriateness of the translation for the database being searched, errors in syntax and line combinations, and application of exclusions.

The full search strategies (including search dates) for all databases searched are shown below (A.1: to A.11:).

Where possible, the results of searches were downloaded in a tagged format and loaded into bibliographic software (EndNote) (Clarivate 2024). The results were deduplicated using several algorithms and the duplicate references held in a separate EndNote database for checking if required. Results from resources that did not allow export in a format compatible with EndNote were saved in Word or Excel documents as appropriate and manually deduplicated.

Literature search results

The searches were conducted between 31/07/2024 and 03/08/2024 and identified 4,378 records (Table 10.2). Following deduplication, 2,910 records were assessed for relevance.

Table 10.2: Literature search results

Resource	Number of records identified
Databases	
MEDLINE(R) ALL	698
Embase	1618
Cochrane Database of Systematic Reviews (CDSR)	14
Cochrane Central Register of Controlled Trials (CENTRAL)	416
HTA Database	24
Conference Proceedings Citation Index – Science (CPCI-S)	66
CINAHL Ultimate	653
NHS Economic Evaluation Database (NHS EED)	23
Econlit	6
Total records identified through database searching	3518
Trials Registers	

ClinicalTrials.gov.	227
WHO International Clinical Trials Registry Portal (ICTRP)	95
Total records identified through trials register searching	322
Other sources	
Reference list checking	11
Company submission evidence	527
Total additional records identified through other sources	538
Total number of records retrieved	4378
Total number of records after deduplication	2910

Search strategies

A.1: Source: MEDLINE ALL

Interface / URL: OvidSP

Database coverage dates: 1946 to July 30, 2024

Search date: 31/07/2024

Retrieved records: 698

Search strategy:

- 1 Leg Ulcer/ (8996)
- 2 (lower extremity/ or leg/) and (ulcer/ or skin ulcer/ or buruli ulcer/ or pressure ulcer/ or pyoderma gangrenosum/) (1246)
- 3 (ankle/ or knee/) and (ulcer/ or skin ulcer/ or buruli ulcer/ or pressure ulcer/ or pyoderma gangrenosum/) (122)
- 4 ((leg or legs) adj10 (ulcer* or ulcerus)).ti,ab,kf. (9874)
- 5 ((leg or legs) adj10 (bedsore* or decubital or decubitus or sore or sores)).ti,ab,kf. (215)
- 6 ((leg or legs) adj10 ((chronic* or longterm or long term or longlasting or long lasting) adj6 (lesion or lesions or wound or wounds))).ti,ab,kf. (545)
- 7 ((acurris or crural or cruris) adj10 (ulcer* or ulcerus)).ti,ab,kf. (628)
- 8 ((acurris or crural or cruris) adj10 (bedsore* or decubital or decubitus or sore or sores)).ti,ab,kf. (12)
- 9 ((acurris or crural or cruris) adj10 ((chronic* or longterm or long term or longlasting or long lasting) adj6 (lesion or lesions or wound or wounds))).ti,ab,kf. (12)
- 10 ((ankle* or calf or calves or gaiter* or knee or knees or shin or shins) adj10 (ulcer* or ulcerus)).ti,ab,kf. (1265)
- 11 ((ankle* or calf or calves or gaiter* or knee or knees or shin or shins) adj10 (bedsore* or decubital or decubitus or sore or sores)).ti,ab,kf. (107)

- 12 ((ankle* or calf or calves or gaiter* or knee or knees or shin or shins) adj10 ((chronic* or longterm or long term or longlasting or long lasting) adj6 (lesion or lesions or wound or wounds))).ti,ab,kf. (189)
- 13 (lower adj3 (extremity* or limb or limbs) adj10 (ulcer* or ulcerus)).ti,ab,kf. (3035)
- 14 (lower adj3 (extremity* or limb or limbs) adj10 (bedsore* or decubital or decubitus or sore or sores)).ti,ab,kf. (91)
- 15 (lower adj3 (extremity* or limb or limbs) adj10 ((chronic* or longterm or long term or longlasting or long lasting) adj6 (lesion or lesions or wound or wounds))).ti,ab,kf. (368)
- 16 or/1-15 (18335)
- 17 Varicose Ulcer/ (5474)
- 18 ((stasis or varicos* or varix or vein* or venous) adj10 (ulcer* or ulcerus)).ti,ab,kf. (8485)
- 19 ((stasis or varicos* or varix or vein* or venous) adj10 (bedsore* or decubital or decubitus or sore or sores)).ti,ab,kf. (309)
- 20 ((stasis or varicos* or varix or vein* or venous) adj10 ((chronic* or longterm or long term or longlasting or long lasting) adj6 (lesion or lesions or wound or wounds))).ti,ab,kf. (711)
- 21 (vascul* adj10 (ulcer* or ulcerus)).ti,ab,kf. (3961)
- 22 (vascul* adj10 (bedsore* or decubital or decubitus or sore or sores)).ti,ab,kf. (86)
- 23 (vascul* adj10 ((chronic* or longterm or long term or longlasting or long lasting) adj6 (lesion or lesions or wound or wounds))).ti,ab,kf. (687)
- 24 ((lymphedem* or lymphoedem* or phlebolymp*) adj10 (ulcer* or ulcerus)).ti,ab,kf. (169)
- 25 ((lymphedem* or lymphoedem* or phlebolymp*) adj10 (bedsore* or decubital or decubitus or sore or sores)).ti,ab,kf. (4)
- 26 ((lymphedem* or lymphoedem* or phlebolymp*) adj10 ((chronic* or longterm or long term or longlasting or long lasting) adj6 (lesion or lesions or wound or wounds))).ti,ab,kf. (49)
- 27 or/17-26 (14708)
- 28 16 or 27 (26834)
- 29 (anti-infective agents/ or anti-bacterial agents/ or disinfectants/ or antisepsis/) and exp Bandages/ (2815)
- 30 ((antibacter* or anti bacter* or antibiofilm* or anti biofilm* or antibiotic* or anti biotic* or antiinfect* or anti infect* or antimicrob* or anti microb* or antimycobacter* or anti mycobacter* or antisept* or anti sept* or bacteriocid* or bactericid* or biocid* or microbicid*) adj6 (dressing or dressings)).ti,ab,kf. (3186)
- 31 ((bacteria* or microb* or mycobacteria*) adj3 bind* adj6 (dressing or dressings)).ti,ab,kf. (14)
- 32 ((antibacter* or anti bacter* or antibiofilm* or anti biofilm* or antibiotic* or anti biotic* or antiinfect* or anti infect* or antimicrob* or anti microb* or antimycobacter* or anti mycobacter* or antisept* or anti sept* or bacteriocid* or bactericid* or biocid* or microbicid*) adj6 (alginat* or balm or balms or bandage* or bead or beads or bioactive or biomaterial* or biosynthetic* or cellulose* or cloth or cloths or collagen* or cotton* or cream or creams or disc or discs or disk or disks or elastin* or fabric or fabrics or fiber or fibers or fibre or fibres or fibrous or film or films or fluid or fluids or foam or foams or gauze* or gel or gels or gelling or gelatin* or hyaluronic or hydrocellular* or hydro cellular* or hydrocolloid* or hydro colloid* or hydrofiber* or hydrofibre* or hydrogel* or

hydropolymer* or irrigat* or lint or lints or liquid or liquids or matrice* or matrix* or membrane* or mesh* or ointment or ointments or packing* or pad or pads or paste or pastes or patch or patches or plaster or plasters or polyamide* or polyester* or polymer* or polysaccharid* or polyurethane* or powder* or rayon* or ribbon* or rope or ropes or sachet or sachets or seaweed* or sea weed* or sheet or sheets or silicon* or sleeve or sleeves or solution or solutions or sponge or sponges or strip or strips or swab or swabs or tape or tapes or tulle or tulles or wash or washes or wrap or wraps or wrapping*)).ti,ab,kf. (52774)

33 ((bacteria* or microb* or mycobacteria*) adj3 bind* adj6 (alginat* or balm or balms or bandage* or bead or beads or bioactive or biomaterial* or biosynthetic* or cellulose* or cloth or cloths or collagen* or cotton* or cream or creams or disc or discs or disk or disks or elastin* or fabric or fabrics or fiber or fibers or fibre or fibres or fibrous or film or films or fluid or fluids or foam or foams or gauze* or gel or gels or gelling or gelatin* or hyaluronic or hydrocellular* or hydro cellular* or hydrocolloid* or hydro colloid* or hydrofiber* or hydrofibre* or hydrogel* or hydropolymer* or irrigat* or lint or lints or liquid or liquids or matrice* or matrix* or membrane* or mesh* or ointment or ointments or packing* or pad or pads or paste or pastes or patch or patches or plaster or plasters or polyamide* or polyester* or polymer* or polysaccharid* or polyurethane* or powder* or rayon* or ribbon* or rope or ropes or sachet or sachets or seaweed* or sea weed* or sheet or sheets or silicon* or sleeve or sleeves or solution or solutions or sponge or sponges or strip or strips or swab or swabs or tape or tapes or tulle or tulles or wash or washes or wrap or wraps or wrapping*)).ti,ab,kf. (706)

34 anti-Infective agents, local/ (18281)

35 (anti-infective agents/ or anti-bacterial agents/ or disinfectants/ or antisepsis/) and (administration, topical/ or administration, cutaneous/) (4255)

36 ((antibacter* or anti bacter* or antibiofilm* or anti biofilm* or antibiotic* or anti biotic* or antiinfect* or anti infect* or antimicrob* or anti microb* or antimycobacter* or anti mycobacter* or antisept* or anti sep* or bacteriocid* or bactericid* or biocid* or microbicid*) adj6 (cutaneous* or dermal* or skin or skins or topical* or transdermal*)).ti,ab,kf. (14365)

37 ((bacteria* or microb* or mycobacteria*) adj3 bind* adj6 (cutaneous* or dermal* or skin or skins or topical* or transdermal*)).ti,ab,kf. (11)

38 or/29-37 (86540)

39 Chlorhexidine/ (9771)

40 chlorhex*.ti,ab,kf,rn,nm,ot. (15436)

41 (chlorohex* or clohex* or clorhex* or mk 412a or mk412a).ti,ab,kf,rn,nm,ot. (429)

42 (chg or chx).ti,ab,kf,rn,nm,ot. (6509)

43 (18472-51-0 or 200-238-7 or 242-354-0 or 36466-50-9 or 3697-42-5 or 55-56-1 or 56-95-1 or 5908zuf22y or 74194-72-2 or e64xl9u38k or mor84mud8e or r4ko0dy52l).ti,ab,kf,rn,nm,ot. (9795)

44 or/39-43 (18815)

45 Copper/ (80681)

46 copper*.ti,ab,kf,rn,nm,ot. (165577)

47 (cuprum metallicum or nanocopper*).ti,ab,kf,rn,nm,ot. (77)

48 (cu or cuo or cuonp or cuonps or nanocuo or nanocuos).ti,ab,kf,rn,nm,ot. (140483)

49 (1344-70-3 or 15158-11-9 or 231-159-6 or 7440-50-8 or 789u1901c5).ti,ab,kf,rn,nm,ot.
(80618)

50 medcu*.ti,ab,kf,rn,nm,ot. (3)

51 or/45-50 (245950)

52 (dialkylcarb* or dialkyl carb*).ti,ab,kf,rn,nm,ot. (185)

53 dacc.ti,ab,kf,rn,nm,ot. (1093)

54 sorbact*.ti,ab,kf,rn,nm,ot. (37)

55 or/52-54 (1270)

56 Honey/ (5268)

57 (honey or honeys).ti,ab,kf,rn,nm,ot. (16598)

58 (hy1 or hy 1).ti,ab,kf,rn,nm,ot. (419)

59 (y9h1v576fh or 8028-66-8).ti,ab,kf,rn,nm,ot. (0)

60 Apitherapy/ (203)

61 apitherap*.ti,ab,kf,rn,nm,ot. (148)

62 (actibalm* or actilite* or activon* or algivon* or l-mesitran* or lmesitran* or manuka* or
medihoney* or melladerm* or melloxy* or revamil* or surgihoney*).ti,ab,kf,rn,nm,ot. (972)

63 or/56-62 (17791)

64 exp Iodine/ or exp Iodine Compounds/ (103336)

65 iodine*.ti,ab,kf,rn,nm,ot. (136199)

66 (cadexomeriodine* or iodate* or iodide* or iodine* or iodophor* or iodopovidone* or iosal*
or jodium* or povidoneiodine* or pvp-i or pvpi).ti,ab,kf,rn,nm,ot. (59388)

67 (25655-41-8 or 85h0hzu99m or 9679tc07x4 or 7553-56-2 or 94820-09-4).ti,ab,kf,rn,nm,ot.
(30803)

68 (inadine* or iodoflex* or iodisorb* or povitulle*).ti,ab,kf,rn,nm,ot. (35)

69 or/64-68 (186696)

70 Biguanides/ (3437)

71 (polyhexamethylene* or poly hexamethylene*).ti,ab,kf,rn,nm,ot. (955)

72 (polihexamethylene* or poli hexamethylene*).ti,ab,kf,rn,nm,ot. (0)

73 (polyhexanide* or poly hexanide* or polihexanide* or poli hexanide*).ti,ab,kf,rn,nm,ot. (707)

74 phmb*.ti,ab,kf,rn,nm,ot. (657)

75 (28757-47-3 or 32289-58-0 or 322u039gmf or 4xi6112496).ti,ab,kf,rn,nm,ot. (555)

76 (activheal* or celludress* or kendall* amd* or prontosan* or suprasorb*).ti,ab,kf,rn,nm,ot.
(84)

77 or/70-76 (4433)

78 Silver/ or exp Silver Compounds/ or Silver Sulfadiazine/ or Silver Proteins/ (38339)

79 silver*.ti,ab,kf,rn,nm,ot. (99612)

80 ag.ti,ab,kf,rn,nm,ot. (103506)

81 (agnp or agnps or argenti or argentum or nanosilver* or ssd or ssds).ti,ab,kf,rn,nm,ot.
(16942)

82 (22199-08-2 or 231-131-3 or 24342-30-1 or 3m4g523w1g or 41034-18-8 or 7440-22-4 or
7761-88-8 or 7783-90-6 or 95it3w8jze or w46jy43ejr).ti,ab,kf,rn,nm,ot. (36051)

83 (acticoat* or actisorb* or algicell* or algisite* or allevyn* or aquacel* or askina* calgitrol* or atrauman* or biatain* or durafiber* or exufiber* or granufoam* or kerracel* or kerracontact* or melgisorb* or mepilex* or polymem* or sorbsan* or tegaderm* alginate* or urgoclean* or urgosorb* or urgotul*).ti,ab,kf,rn,nm,ot. (760)

84 or/78-83 (185460)

85 Alginates/ and Hydrogels/ (2578)

86 Alginates/ and (Lactoperoxidase/ or Glucose Oxidase/) (57)

87 (alginogel* or alginogel*).ti,ab,kf,rn,nm,ot. (11)

88 ((biocatalyst* or catalyst* or enzym*) and (algin or alginic or alginat* or polymannur* or polymannur*)).ti,ab,kf,rn,nm,ot. (3198)

89 (((glucose adj2 oxidase*) or glucose aerodehydrogenase or glucose oxygen oxidoreductase or glucose oxyhydrase or glucosoxidase or god or gox or microcid or notatin*) and alginat*).ti,ab,kf,rn,nm,ot. (105)

90 ((lactoperoxidase* or lactoperoxydase*) and alginat*).ti,ab,kf,rn,nm,ot. (11)

91 ((algin or alginic or alginat* or polymannur* or polymannur*) and (gel* or hydrogel*)).ti,ab,kf,rn,nm,ot. (11398)

92 flaminol*.ti,ab,kf,rn,nm,ot. (18)

93 or/85-92 (13633)

94 Chitosan/ (31265)

95 chitosan*.ti,ab,kf,rn,nm,ot. (48417)

96 (deacetylchitin* or deacetylated chitin* or nanochitosan* or poliglucan*).ti,ab,kf,rn,nm,ot. (282)

97 (9012-76-4 or 42617-20-9 or 87582-10-3 or 82lks4qv2y).ti,ab,kf,rn,nm,ot. (31202)

98 maxicel*.ti,ab,kf,rn,nm,ot. (2)

99 or/94-98 (48509)

100 octenidine*.ti,ab,kf,rn,nm,ot. (484)

101 (las189962 or las-189962).ti,ab,kf,rn,nm,ot. (0)

102 (71251-02-0 or 70775-75-6 or 274-861-8 or 86767-75-1 or oze0372s5a or u84956nu4b or r337868tdw).ti,ab,kf,rn,nm,ot. (278)

103 octenilin*.ti,ab,kf,rn,nm,ot. (24)

104 or/100-103 (487)

105 44 or 51 or 55 or 63 or 69 or 77 or 84 or 93 or 99 or 104 (695050)

106 28 and 38 (649)

107 28 and 105 (665)

108 106 or 107 (1118)

109 exp animals/ not humans/ (5243854)

110 (news or editorial or case reports).pt. or case report.ti. (3393659)

111 108 not (109 or 110) (862)

112 limit 111 to english language (698)

A.2: Source: Embase

Interface / URL: OvidSP

Database coverage dates: 1974 to 2024 July 30

Search date: 31/07/2024

Retrieved records: 1618 (1203 records not indexed as conference abstracts + 415 records indexed as conference abstracts)

Search strategy:

- 1 leg ulcer/ (15519)
- 2 (lower limb/ or leg/ or lower leg/) and (ulcer/ or application site ulcer/ or injection site ulcer/ or skin ulcer/ or ulcer healing/ or exp decubitus/ or buruli ulcer/ or pyoderma gangrenosum/) (3517)
- 3 (ankle/ or knee/) and (ulcer/ or application site ulcer/ or injection site ulcer/ or skin ulcer/ or ulcer healing/ or exp decubitus/ or buruli ulcer/ or pyoderma gangrenosum/) (1159)
- 4 ((leg or legs) adj10 (ulcer* or ulcus)).ti,ab,kf,dq. (12445)
- 5 ((leg or legs) adj10 (bedsore* or decubital or decubitus or sore or sores)).ti,ab,kf,dq. (322)
- 6 ((leg or legs) adj10 ((chronic* or longterm or long term or longlasting or long lasting) adj6 (lesion or lesions or wound or wounds))).ti,ab,kf,dq. (781)
- 7 ((acurris or crural or cruris) adj10 (ulcer* or ulcus)).ti,ab,kf,dq. (572)
- 8 ((acurris or crural or cruris) adj10 (bedsore* or decubital or decubitus or sore or sores)).ti,ab,kf,dq. (13)
- 9 ((acurris or crural or cruris) adj10 ((chronic* or longterm or long term or longlasting or long lasting) adj6 (lesion or lesions or wound or wounds))).ti,ab,kf,dq. (22)
- 10 ((ankle* or calf or calves or gaiter* or knee or knees or shin or shins) adj10 (ulcer* or ulcus)).ti,ab,kf,dq. (2014)
- 11 ((ankle* or calf or calves or gaiter* or knee or knees or shin or shins) adj10 (bedsore* or decubital or decubitus or sore or sores)).ti,ab,kf,dq. (184)
- 12 ((ankle* or calf or calves or gaiter* or knee or knees or shin or shins) adj10 ((chronic* or longterm or long term or longlasting or long lasting) adj6 (lesion or lesions or wound or wounds))).ti,ab,kf,dq. (280)
- 13 (lower adj3 (extremity* or limb or limbs) adj10 (ulcer* or ulcus)).ti,ab,kf,dq. (4525)
- 14 (lower adj3 (extremity* or limb or limbs) adj10 (bedsore* or decubital or decubitus or sore or sores)).ti,ab,kf,dq. (162)
- 15 (lower adj3 (extremity* or limb or limbs) adj10 ((chronic* or longterm or long term or longlasting or long lasting) adj6 (lesion or lesions or wound or wounds))).ti,ab,kf,dq. (493)
- 16 or/1-15 (27354)
- 17 ulcer/ and (stasis or varicos* or varix or vein* or venous).ti,ab,kf,dq,hw. (4665)
- 18 ((stasis or varicos* or varix or vein* or venous) adj10 (ulcer* or ulcus)).ti,ab,kf,dq. (11356)
- 19 ((stasis or varicos* or varix or vein* or venous) adj10 (bedsore* or decubital or decubitus or sore or sores)).ti,ab,kf,dq. (475)
- 20 ((stasis or varicos* or varix or vein* or venous) adj10 ((chronic* or longterm or long term or longlasting or long lasting) adj6 (lesion or lesions or wound or wounds))).ti,ab,kf,dq. (1024)
- 21 (vascul* adj10 (ulcer* or ulcus)).ti,ab,kf,dq. (6621)
- 22 (vascul* adj10 (bedsore* or decubital or decubitus or sore or sores)).ti,ab,kf,dq. (129)

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- 23 (vascul* adj10 ((chronic* or longterm or long term or longlasting or long lasting) adj6 (lesion or lesions or wound or wounds))).ti,ab,kf,dq. (1045)
- 24 ((lymphedem* or lymphoedem* or phlebolymph*) adj10 (ulcer* or ulcerus)).ti,ab,kf,dq. (249)
- 25 ((lymphedem* or lymphoedem* or phlebolymph*) adj10 (bedsore* or decubital or decubitus or sore or sores)).ti,ab,kf,dq. (9)
- 26 ((lymphedem* or lymphoedem* or phlebolymph*) adj10 ((chronic* or longterm or long term or longlasting or long lasting) adj6 (lesion or lesions or wound or wounds))).ti,ab,kf,dq. (75)
- 27 or/17-26 (21624)
- 28 16 or 27 (40413)
- 29 antimicrobial dressing/ or antibacterial dressing/ or antimicrobial gauze/ or ((*antiinfective agent/ or *antiseptis/ or *antimycobacterial agent/ or *bactericide/ or *microbicide/ or *antibiotic agent/)) and ((*bandages and dressings"/ or exp *wound dressing/)) (1099)
- 30 ((antibacter* or anti bacter* or antibiofilm* or anti biofilm* or antibiotic* or anti biotic* or antiinfect* or anti infect* or antimicrob* or anti microb* or antimycobacter* or anti mycobacter* or antisept* or anti sept* or bacteriocid* or bactericid* or biocid* or microbicid*) adj6 (dressing or dressings)).ti,ab,kf,dq,tn,dv,my,ot. (4221)
- 31 ((bacteria* or microb* or mycobacteria*) adj3 bind* adj6 (dressing or dressings)).ti,ab,kf,dq,tn,dv,my,ot. (21)
- 32 ((antibacter* or anti bacter* or antibiofilm* or anti biofilm* or antibiotic* or anti biotic* or antiinfect* or anti infect* or antimicrob* or anti microb* or antimycobacter* or anti mycobacter* or antisept* or anti sept* or bacteriocid* or bactericid* or biocid* or microbicid*) adj6 (alginat* or balm or balms or bandage* or bead or beads or bioactive or biomaterial* or biosynthetic* or cellulose* or cloth or cloths or collagen* or cotton* or cream or creams or disc or discs or disk or disks or elastin* or fabric or fabrics or fiber or fibers or fibre or fibres or fibrous or film or films or fluid or fluids or foam or foams or gauze* or gel or gels or gelling or gelatin* or hyaluronic or hydrocellular* or hydro cellular* or hydrocolloid* or hydro colloid* or hydrofiber* or hydrofibre* or hydrogel* or hydropolymer* or irrigat* or lint or lints or liquid or liquids or matrice* or matrix* or membrane* or mesh* or ointment or ointments or packing* or pad or pads or paste or pastes or patch or patches or plaster or plasters or polyamide* or polyester* or polymer* or polysaccharid* or polyurethane* or powder* or rayon* or ribbon* or rope or ropes or sachet or sachets or seaweed* or sea weed* or sheet or sheets or silicon* or sleeve or sleeves or solution or solutions or sponge or sponges or strip or strips or swab or swabs or tape or tapes or tulle or tulles or wash or washes or wrap or wraps or wrapping*)).ti,ab,kf,dq,tn,dv,my,ot. (64860)
- 33 ((bacteria* or microb* or mycobacteria*) adj3 bind* adj6 (alginat* or balm or balms or bandage* or bead or beads or bioactive or biomaterial* or biosynthetic* or cellulose* or cloth or cloths or collagen* or cotton* or cream or creams or disc or discs or disk or disks or elastin* or fabric or fabrics or fiber or fibers or fibre or fibres or fibrous or film or films or fluid or fluids or foam or foams or gauze* or gel or gels or gelling or gelatin* or hyaluronic or hydrocellular* or hydro cellular* or hydrocolloid* or hydro colloid* or hydrofiber* or hydrofibre* or hydrogel* or hydropolymer* or irrigat* or lint or lints or liquid or liquids or matrice* or matrix* or membrane* or mesh* or ointment or ointments or packing* or pad or pads or paste or pastes or patch or patches or plaster or plasters or polyamide* or polyester* or polymer* or polysaccharid* or polyurethane*

or powder* or rayon* or ribbon* or rope or ropes or sachet or sachets or seaweed* or sea weed* or sheet or sheets or silicon* or sleeve or sleeves or solution or solutions or sponge or sponges or strip or strips or swab or swabs or tape or tapes or tulle or tulles or wash or washes or wrap or wraps or wrapping*)).ti,ab,kf,dq,tn,dv,my,ot. (775)

34 topical antiinfective agent/ or disinfectant agent/ (21810)

35 (*antiinfective agent/ or *antisepsis/ or *antimycobacterial agent/ or *bactericide/ or *microbicide/ or *antibiotic agent/) and (*topical drug administration/ or *cutaneous drug administration/ or *transdermal drug administration/) (28)

36 ((antibacter* or anti bacter* or antibiofilm* or anti biofilm* or antibiotic* or anti biotic* or antiinfect* or anti infect* or antimicrob* or anti microb* or antimycobacter* or anti mycobacter* or antisept* or anti sept* or bacteriocid* or bactericid* or biocid* or microbicid*) adj6 (cutaneous* or dermal* or skin or skins or topical* or transdermal*)).ti,ab,kf,dq,tn,dv,my,ot. (19819)

37 ((bacteria* or microb* or mycobacteria*) adj3 bind* adj6 (cutaneous* or dermal* or skin or skins or topical* or transdermal*)).ti,ab,kf,dq,tn,dv,my,ot. (16)

38 or/29-37 (104814)

39 *chlorhexidine/ or *chlorhexidine gluconate/ or *2 propanol plus chlorhexidine gluconate/ or *chlorhexidine acetate/ or *alcohol plus chlorhexidine gluconate/ or *benzalkonium chloride plus chlorhexidine digluconate/ (9015)

40 chlorhex*.ti,ab,kf,dq,tn,dv,my,ot. (16502)

41 (chlorohex* or clohex* or clorhex* or mk 412a or mk412a).ti,ab,kf,dq,tn,dv,my,ot. (705)

42 (chg or chx).ti,ab,kf,dq,tn,dv,my,ot. (6991)

43 (18472-51-0 or 200-238-7 or 242-354-0 or 36466-50-9 or 3697-42-5 or 55-56-1 or 56-95-1 or 5908zuf22y or 74194-72-2 or e64xl9u38k or mor84mud8e or r4ko0dy52l).ti,ab,kf,dq,tn,dv,my,ot. (4)

44 or/39-43 (22470)

45 *copper/ or *copper sulfate plus manganese sulfate plus selenious acid plus zinc sulfate/ or *copper chloride/ or *copper derivative/ or *copper 64/ or *copper sulfate/ or *copper transport protein/ or *glycinate copper/ or *copper protein/ or *copper dotatate cu 64/ or *copper chloride cu 64/ or *copper sulfide nanoparticle/ or *prezotide copper/ or *copper zinc superoxide dismutase/ or *copper oxide nanoparticle/ or *copper ion/ or *1,10 phenanthroline copper/ or *amine oxidase (copper containing)/ or *copper 62/ or *copper oxide/ or *doxorubicin copper/ or *nitritotriacetate copper/ or *copper 67/ or *bleomycin copper/ or *copper nanoparticle/ or *3,5 diisopropylsalicylate copper/ or *copper histidinate/ or *copper acetate/ or *gluconate copper/ or *acetylsalicylate copper/ or *copper transporter 1/ or *copper complex/ (84053)

46 copper*.ti,ab,kf,dq,tn,dv,my,ot. (151971)

47 (cuprum metallicum or nanocopper*).ti,ab,kf,dq,tn,dv,my,ot. (83)

48 (cu or cuo or cuonp or cuonps or nanocuo or nanocuos).ti,ab,kf,dq,tn,dv,my,ot. (152367)

49 (1344-70-3 or 15158-11-9 or 231-159-6 or 7440-50-8 or 789u1901c5).ti,ab,kf,dq,tn,dv,my,ot. (0)

50 medcu*.ti,ab,kf,dq,tn,dv,my,ot. (12)

51 or/45-50 (260145)

52 (dialkylcarb* or dialkyl carb*).ti,ab,kf,dq,tn,dv,my,ot. (239)

53 dacc.ti,ab,kf,dq,tn,dv,my,ot. (1692)
 54 sorbact*.ti,ab,kf,dq,tn,dv,my,ot. (92)
 55 or/52-54 (1951)
 56 honey-based wound dressing/ or exp *honey/ (5496)
 57 (honey or honeys).ti,ab,kf,dq,tn,dv,my,ot. (18781)
 58 (hy1 or hy 1).ti,ab,kf,dq,tn,dv,my,ot. (451)
 59 (y9h1v576fh or 8028-66-8).ti,ab,kf,dq,tn,dv,my,ot. (0)
 60 *apitherapy/ (185)
 61 apitherap*.ti,ab,kf,dq,tn,dv,my,ot. (187)
 62 (actibalm* or actilite* or activon* or algivon* or l-mesitran* or lmesitran* or manuka* or medihoney* or melladerm* or melloxy* or revamil* or surgihoney*).ti,ab,kf,dq,tn,dv,my,ot. (1359)
 63 or/56-62 (20017)
 64 exp iodine dressing/ or *iodine/ or *povidone iodine/ or *cadexomer iodine/ or *povacrylex iodine/ or *iodine 125/ or *iodine 124/ or *iodine derivative/ or *omburtamab iodine i 131/ or *povidone iodine i 125/ or *iodine 123/ or *iodine 129/ or *iodine evuzamitide i 124/ or *iodine 131/ (40658)
 65 iodin*.ti,ab,kf,dq,tn,dv,my,ot. (89054)
 66 (cadexomeriodine* or iodate* or iodide* or iodium* or iodophor* or iodopovidone* or iosal* or jodium* or povidoneiodine* or pvp-i or pvpi).ti,ab,kf,dq,tn,dv,my,ot. (57087)
 67 (25655-41-8 or 85h0hzu99m or 9679tc07x4 or 7553-56-2 or 94820-09-4).ti,ab,kf,dq,tn,dv,my,ot. (4)
 68 (inadine* or iodoflex* or iodisorb* or povitulle*).ti,ab,kf,dq,tn,dv,my,ot. (200)
 69 or/64-68 (155950)
 70 **"poly(hexamethylenebiguanide)"/ (356)
 71 (polyhexamethylene* or poly hexamethylene*).ti,ab,kf,dq,tn,dv,my,ot. (1101)
 72 (polihexamethylene* or poli hexamethylene*).ti,ab,kf,dq,tn,dv,my,ot. (0)
 73 (polyhexanide* or poly hexanide* or polihexanide* or poli hexanide*).ti,ab,kf,dq,tn,dv,my,ot. (515)
 74 phmb*.ti,ab,kf,dq,tn,dv,my,ot. (821)
 75 (28757-47-3 or 32289-58-0 or 322u039gmf or 4xi6112496).ti,ab,kf,dq,tn,dv,my,ot. (5)
 76 (activheal* or celludress* or kendall* amd* or prontosan* or suprasorb*).ti,ab,kf,dq,tn,dv,my,ot. (297)
 77 or/70-76 (2043)
 78 silver dressing/ or *silver nitrate/ or silver impregnation/ or *sulfadiazine silver/ or *silver chloride/ or *silver in situ hybridization/ or *sulfathiazole silver/ or *silver/ or *colloidal silver/ or *silver derivative/ or *silver protein/ or *silver nanoparticle/ (39738)
 79 silver*.ti,ab,kf,dq,tn,dv,my,ot. (97486)
 80 ag.ti,ab,kf,dq,tn,dv,my,ot. (206357)
 81 (agnp or agnps or argenti or argentum or nanosilver* or ssd or ssds).ti,ab,kf,dq,tn,dv,my,ot. (20686)
 82 (22199-08-2 or 231-131-3 or 24342-30-1 or 3m4g523w1g or 41034-18-8 or 7440-22-4 or 7761-88-8 or 7783-90-6 or 95it3w8jze or w46jy43ejr).ti,ab,kf,dq,tn,dv,my,ot. (4)

83 (acticoat* or actisorb* or algicell* or algisite* or allevyn* or aquacel* or askina* calgitrol* or atrauman* or biatain* or durafiber* or exufiber* or granufoam* or kerracel* or kerracontact* or melgisorb* or mepilex* or polymem* or sorbsan* or tegaderm* alginate* or urgoclean* or urgosorb* or urgotul*).ti,ab,kf,dq,tn,dv,my,ot. (2085)

84 or/78-83 (297624)

85 alginate dressing/ or (*alginic acid/ and *hydrogel/) (1969)

86 *alginic acid/ and (*lactoperoxidase/ or *glucose oxidase/) (20)

87 (alginogel* or alginogel*).ti,ab,kf,dq,tn,dv,my,ot. (20)

88 ((biocatalyst* or catalyst* or enzym*) and (algin or alginic or alginat* or polymannur* or polymannur*)).ti,ab,kf,dq,tn,dv,my,ot. (3699)

89 (((glucose adj2 oxidase*) or glucose aerodehydrogenase or glucose oxygen oxidoreductase or glucose oxyhydrase or glucosoxidase or god or gox or microcid or notatin*) and alginat*).ti,ab,kf,dq,tn,dv,my,ot. (100)

90 ((lactoperoxidase* or lactoperoxydase*) and alginat*).ti,ab,kf,dq,tn,dv,my,ot. (4)

91 ((algin or alginic or alginat* or polymannur* or poly mannur*) and (gel* or hydrogel*)).ti,ab,kf,dq,tn,dv,my,ot. (13274)

92 flaminol*.ti,ab,kf,dq,tn,dv,my,ot. (42)

93 or/85-92 (16039)

94 *chitosan/ or *chitosan nanoparticle/ or *chitosan derivative/ or *chitosan acetate/ (32056)

95 chitosan*.ti,ab,kf,dq,tn,dv,my,ot. (53351)

96 (deacetylchitin* or deacetylated chitin* or nanochitosan* or poliglusam*).ti,ab,kf,dq,tn,dv,my,ot. (312)

97 (9012-76-4 or 42617-20-9 or 87582-10-3 or 82lks4qv2y).ti,ab,kf,dq,tn,dv,my,ot. (3)

98 maxicel*.ti,ab,kf,dq,tn,dv,my,ot. (3)

99 or/94-98 (53900)

100 *octenidine plus phenoxyethanol/ or *octenidine/ or octenidine*.ti,ab,kf,dq,tn,dv,my,ot. (566)

101 (las189962 or las-189962).ti,ab,kf,dq,tn,dv,my,ot. (0)

102 (71251-02-0 or 70775-75-6 or 274-861-8 or 86767-75-1 or oze0372s5a or u84956nu4b or r337868tdw).ti,ab,kf,dq,tn,dv,my,ot. (1)

103 octenilin*.ti,ab,kf,dq,tn,dv,my,ot. (38)

104 or/100-103 (590)

105 44 or 51 or 55 or 63 or 69 or 77 or 84 or 93 or 99 or 104 (799834)

106 28 and 38 (817)

107 28 and 105 (1487)

108 106 or 107 (2057)

109 (animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/ (7052737)

110 editorial.pt. or case report.ti. (1229800)

111 preprint.pt. (129302)

112 108 not (109 or 110 or 111) (1899)

113 limit 112 to english language (1618)

114 conference abstract.pt. (5203257)
115 113 not 114 (1203)
116 113 and 114 (415)

Search note:

Reflecting the LSA methods context and review protocol, a pragmatic approach was taken to some elements of strategy translation for Embase. This was designed to reduce the impact of Embase indexing on increasing the number of records retrieved. For the intervention-related concepts (non-specific antimicrobial/bacterial-binding dressings and eligible agents):

- The majority of Emtree headings were searched as major descriptors only (for example, see line 39).
- The textword search lines did not search across the CAS Registry Numbers (rn) and Drug Index Terms Word (dy) fields (for example, see search line 40).

The use of this focused approach for just the intervention concept terms was informed by the CADTH report (Canadian Agency for Drugs and Technologies in Health 2015) exploring the impact of searching Emtree terms as major descriptors, which suggests that where this approach is used, it is safest to use it solely for the intervention concept.

The approach was discussed and agreed within the EAG team. Any risk of missing relevant studies was mitigated by:

- The reasonably sensitive approach taken to the range of textword terms included in the Embase search.
- The standard approach taken to index terms in the other database searches.
- The additional supplementary search activities conducted by the EAG (the check of company submitted evidence and the check of the included studies lists of retrieved relevant systematic reviews published in the last 5 years).

A.3: Source: CINAHL Ultimate

Interface / URL: EBSCOhost

Database coverage dates: 1937 to date

Search date: 31/07/2024

Retrieved records: 653

Search strategy:

Interface - EBSCOhost Research Databases

Search Screen - Advanced Search

Database - CINAHL Ultimate

Expanders - Apply equivalent subjects

Search modes - Proximity

External assessment group report: Topical antimicrobial dressings for infected leg ulcers in people aged 16 and over

Date: August 2024

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S1 (MH "Leg Ulcer") 4,234

S2 ((MH "Lower Extremity") OR (MH "Leg")) AND ((MH "Ulcer") OR (MH "Skin Ulcer") OR (MH "Buruli Ulcer") OR (MH "Fungating Wounds") OR (MH "Pyoderma Gangrenosum") OR (MH "Pressure Ulcer") OR (MH "Deep Tissue Injury")) 300

S3 ((MH "Ankle") OR (MH "Knee")) AND ((MH "Ulcer") OR (MH "Skin Ulcer") OR (MH "Buruli Ulcer") OR (MH "Fungating Wounds") OR (MH "Pyoderma Gangrenosum") OR (MH "Pressure Ulcer") OR (MH "Deep Tissue Injury")) 48

S4 (((TI leg OR AB leg) OR (TI legs OR AB legs)) N10 ((TI ulcer* OR AB ulcer*) OR (TI ulcus OR AB ulcus))) 4,337

S5 (((TI leg OR AB leg) OR (TI legs OR AB legs)) N10 ((TI bedsore* OR AB bedsore*) OR (TI decubital OR AB decubital) OR (TI decubitus OR AB decubitus) OR (TI sore OR AB sore) OR (TI sores OR AB sores))) 67

S6 (((TI leg OR AB leg) OR (TI legs OR AB legs)) N10 (((TI chronic* OR AB chronic*) OR (TI longterm OR AB longterm) OR (TI "long term" OR AB "long term") OR (TI longlasting OR AB longlasting) OR (TI "long lasting" OR AB "long lasting"))) N6 ((TI lesion OR AB lesion) OR (TI lesions OR AB lesions) OR (TI wound OR AB wound) OR (TI wounds OR AB wounds))) 286

S7 (((TI acuris OR AB acuris) OR (TI crural OR AB crural) OR (TI cruris OR AB cruris)) N10 ((TI ulcer* OR AB ulcer*) OR (TI ulcus OR AB ulcus))) 27

S8 (((TI acuris OR AB acuris) OR (TI crural OR AB crural) OR (TI cruris OR AB cruris)) N10 ((TI bedsore* OR AB bedsore*) OR (TI decubital OR AB decubital) OR (TI decubitus OR AB decubitus) OR (TI sore OR AB sore) OR (TI sores OR AB sores))) 0

S9 (((TI acuris OR AB acuris) OR (TI crural OR AB crural) OR (TI cruris OR AB cruris)) N10 (((TI chronic* OR AB chronic*) OR (TI longterm OR AB longterm) OR (TI "long term" OR AB "long term") OR (TI longlasting OR AB longlasting) OR (TI "long lasting" OR AB "long lasting"))) N6 ((TI lesion OR AB lesion) OR (TI lesions OR AB lesions) OR (TI wound OR AB wound) OR (TI wounds OR AB wounds))) 1

S10 (((TI ankle* OR AB ankle*) OR (TI calf OR AB calf) OR (TI calves OR AB calves) OR (TI gaiter* OR AB gaiter*) OR (TI knee OR AB knee) OR (TI knees OR AB knees) OR (TI shin OR AB shin) OR (TI shins OR AB shins)) N10 ((TI ulcer* OR AB ulcer*) OR (TI ulcus OR AB ulcus))) 403

S11 (((TI ankle* OR AB ankle*) OR (TI calf OR AB calf) OR (TI calves OR AB calves) OR (TI gaiter* OR AB gaiter*) OR (TI knee OR AB knee) OR (TI knees OR AB knees) OR (TI shin OR AB shin) OR (TI shins OR AB shins)) N10 ((TI bedsore* OR AB bedsore*) OR (TI decubital OR AB decubital) OR (TI decubitus OR AB decubitus) OR (TI sore OR AB sore) OR (TI sores OR AB sores))) 39

S12 (((TI ankle* OR AB ankle*) OR (TI calf OR AB calf) OR (TI calves OR AB calves) OR (TI gaiter* OR AB gaiter*) OR (TI knee OR AB knee) OR (TI knees OR AB knees) OR (TI shin OR AB shin) OR (TI shins OR AB shins)) N10 (((TI chronic* OR AB chronic*) OR (TI longterm OR AB longterm) OR (TI "long term" OR AB "long term") OR (TI longlasting OR AB longlasting) OR (TI "long lasting" OR AB "long lasting"))) N6 ((TI lesion OR AB lesion) OR (TI lesions OR AB lesions) OR (TI wound OR AB wound) OR (TI wounds OR AB wounds)))) 99

S13 ((TI lower OR AB lower) N3 ((TI extremity* OR AB extremity*) OR (TI limb OR AB limb) OR (TI limbs OR AB limbs)) N10 ((TI ulcer* OR AB ulcer*) OR (TI ulcer OR AB ulcer))) 1,170

S14 ((TI lower OR AB lower) N3 ((TI extremity* OR AB extremity*) OR (TI limb OR AB limb) OR (TI limbs OR AB limbs)) N10 ((TI bedsore* OR AB bedsore*) OR (TI decubital OR AB decubital) OR (TI decubitus OR AB decubitus) OR (TI sore OR AB sore) OR (TI sores OR AB sores))) 17

S15 ((TI lower OR AB lower) N3 ((TI extremity* OR AB extremity*) OR (TI limb OR AB limb) OR (TI limbs OR AB limbs)) N10 (((TI chronic* OR AB chronic*) OR (TI longterm OR AB longterm) OR (TI "long term" OR AB "long term") OR (TI longlasting OR AB longlasting) OR (TI "long lasting" OR AB "long lasting"))) N6 ((TI lesion OR AB lesion) OR (TI lesions OR AB lesions) OR (TI wound OR AB wound) OR (TI wounds OR AB wounds)))) 204

S16 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 7,845

S17 (MH "Venous Ulcer") 3,160

S18 (((TI stasis OR AB stasis) OR (TI varicos* OR AB varicos*) OR (TI varix OR AB varix) OR (TI vein* OR AB vein*) OR (TI venous OR AB venous)) N10 ((TI ulcer* OR AB ulcer*) OR (TI ulcer OR AB ulcer))) 3,871

S19 (((TI stasis OR AB stasis) OR (TI varicos* OR AB varicos*) OR (TI varix OR AB varix) OR (TI vein* OR AB vein*) OR (TI venous OR AB venous)) N10 ((TI bedsore* OR AB bedsore*) OR (TI decubital OR AB decubital) OR (TI decubitus OR AB decubitus) OR (TI sore OR AB sore) OR (TI sores OR AB sores))) 112

S20 (((TI stasis OR AB stasis) OR (TI varicos* OR AB varicos*) OR (TI varix OR AB varix) OR (TI vein* OR AB vein*) OR (TI venous OR AB venous)) N10 (((TI chronic* OR AB chronic*) OR (TI longterm OR AB longterm) OR (TI "long term" OR AB "long term") OR (TI longlasting OR AB longlasting) OR (TI "long lasting" OR AB "long lasting"))) N6 ((TI lesion OR AB lesion) OR (TI lesions OR AB lesions) OR (TI wound OR AB wound) OR (TI wounds OR AB wounds)))) 301

S21 ((TI vascul* OR AB vascul*) N10 ((TI ulcer* OR AB ulcer*) OR (TI ulcer OR AB ulcer))) 890

S22 ((TI vascul* OR AB vascul*) N10 ((TI bedsore* OR AB bedsore*) OR (TI decubital OR AB decubital) OR (TI decubitus OR AB decubitus) OR (TI sore OR AB sore) OR (TI sores OR AB sores))) 17

S23 ((TI vascul* OR AB vascul*) N10 (((TI chronic* OR AB chronic*) OR (TI longterm OR AB longterm) OR (TI "long term" OR AB "long term") OR (TI longlasting OR AB longlasting) OR (TI "long lasting" OR AB "long lasting"))) N6 ((TI lesion OR AB lesion) OR (TI lesions OR AB lesions) OR (TI wound OR AB wound) OR (TI wounds OR AB wounds)))) 131

S24 (((TI lymphedem* OR AB lymphedem*) OR (TI lymphoedem* OR AB lymphoedem*) OR (TI phlebolymp* OR AB phlebolymp*)) N10 ((TI ulcer* OR AB ulcer*) OR (TI ulcer OR AB ulcer))) 56

S25 (((TI lymphedem* OR AB lymphedem*) OR (TI lymphoedem* OR AB lymphoedem*) OR (TI phlebolymp* OR AB phlebolymp*)) N10 ((TI bedsore* OR AB bedsore*) OR (TI decubital OR AB decubital) OR (TI decubitus OR AB decubitus) OR (TI sore OR AB sore) OR (TI sores OR AB sores))) 0

S26 (((TI lymphedem* OR AB lymphedem*) OR (TI lymphoedem* OR AB lymphoedem*) OR (TI phlebolymp* OR AB phlebolymp*)) N10 (((TI chronic* OR AB chronic*) OR (TI longterm OR AB longterm) OR (TI "long term" OR AB "long term") OR (TI longlasting OR AB longlasting) OR (TI "long lasting" OR AB "long lasting"))) N6 ((TI lesion OR AB lesion) OR (TI lesions OR AB lesions) OR (TI wound OR AB wound) OR (TI wounds OR AB wounds)))) 20

S27 S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26
5,880

S28 S16 OR S27 10,623

S29 (MH "Antimicrobial Dressings") OR ((MH "Antiinfective Agents") OR (MH "Antibiotics")) AND (MH "Bandages and Dressings+") 1,213

S30 (((TI antibacter* OR AB antibacter*) OR (TI "anti bacter*" OR AB "anti bacter*") OR (TI antibiofilm* OR AB antibiofilm*) OR (TI "anti biofilm*" OR AB "anti biofilm*") OR (TI antibiotic* OR AB antibiotic*) OR (TI "anti biotic*" OR AB "anti biotic*") OR (TI antiinfect* OR AB antiinfect*) OR (TI "anti infect*" OR AB "anti infect*") OR (TI antimicrob* OR AB antimicrob*) OR (TI "anti microb*" OR AB "anti microb*") OR (TI antimycobacter* OR AB antimycobacter*) OR (TI "anti mycobacter*" OR AB "anti mycobacter*") OR (TI antisept* OR AB antisept*) OR (TI "anti sept*" OR AB "anti sept*") OR (TI bacteriocid* OR AB bacteriocid*) OR (TI bactericid* OR AB bactericid*) OR (TI biocid* OR AB biocid*) OR (TI microbicid* OR AB microbicid*)) N6 ((TI dressing OR AB dressing) OR (TI dressings OR AB dressings))) 893

S31 (((TI bacteria* OR AB bacteria*) OR (TI microb* OR AB microb*) OR (TI mycobacteria* OR AB mycobacteria*)) N3 (TI bind* OR AB bind*) N6 ((TI dressing OR AB dressing) OR (TI dressings OR AB dressings))) 27

S32 (((TI antibacter* OR AB antibacter*) OR (TI "anti bacter*" OR AB "anti bacter*") OR (TI antibiofilm* OR AB antibiofilm*) OR (TI "anti biofilm*" OR AB "anti biofilm*") OR (TI antibiotic* OR AB antibiotic*) OR (TI "anti biotic*" OR AB "anti biotic*") OR (TI antiinfect* OR AB antiinfect*) OR (TI "anti infect*" OR AB "anti infect*") OR (TI antimicrob* OR AB antimicrob*) OR (TI "anti microb*" OR AB "anti microb*") OR (TI antimycobacter* OR AB antimycobacter*) OR (TI "anti mycobacter*" OR AB "anti mycobacter*") OR (TI antisept* OR AB antisept*) OR (TI "anti sept*" OR AB "anti sept*") OR (TI bacteriocid* OR AB bacteriocid*) OR (TI bactericid* OR AB bactericid*) OR (TI biocid* OR AB biocid*) OR (TI microbicid* OR AB microbicid*)) N6 ((TI alginat* OR AB alginat*) OR (TI balm OR AB balm) OR (TI balms OR AB balms) OR (TI bandage* OR AB bandage*) OR (TI bead OR AB bead) OR (TI beads OR AB beads) OR (TI bioactive OR AB bioactive) OR (TI biomaterial* OR AB biomaterial*) OR (TI biosynthetic* OR AB biosynthetic*) OR (TI cellulose* OR AB cellulose*) OR (TI cloth OR AB cloth) OR (TI cloths OR AB cloths) OR (TI collagen* OR AB collagen*) OR (TI cotton* OR AB cotton*) OR (TI cream OR AB cream) OR (TI creams OR AB creams) OR (TI disc OR AB disc) OR (TI discs OR AB discs) OR (TI disk OR AB disk) OR (TI disks OR AB disks) OR (TI elastin* OR AB elastin*) OR (TI fabric OR AB fabric) OR (TI fabrics OR AB fabrics) OR (TI fiber OR AB fiber) OR (TI fibers OR AB fibers) OR (TI fibre OR AB fibre) OR (TI fibres OR AB fibres) OR (TI fibrous OR AB fibrous) OR (TI film OR AB film) OR (TI films OR AB films) OR (TI fluid OR AB fluid) OR (TI fluids OR AB fluids) OR (TI foam OR AB foam) OR (TI foams OR AB foams) OR (TI gauze* OR AB gauze*) OR (TI gel OR AB gel) OR (TI gels OR AB gels) OR (TI gelling OR AB gelling) OR (TI gelatin* OR AB gelatin*) OR (TI hyaluronic OR AB hyaluronic) OR (TI hydrocellular* OR AB hydrocellular*) OR (TI "hydro cellular*" OR AB "hydro cellular*") OR (TI hydrocolloid* OR AB hydrocolloid*) OR (TI "hydro colloid*" OR AB "hydro colloid*") OR (TI hydrofiber* OR AB hydrofiber*) OR (TI hydrofibre* OR AB hydrofibre*) OR (TI hydrogel* OR AB hydrogel*) OR (TI hydropolymer* OR AB hydropolymer*) OR (TI irrigat* OR AB irrigat*) OR (TI lint OR AB lint) OR (TI lints OR AB lints) OR (TI liquid OR AB liquid) OR (TI liquids OR AB liquids) OR (TI matrice* OR AB matrice*) OR (TI matrix* OR AB matrix*) OR (TI membrane* OR AB membrane*) OR (TI mesh* OR AB mesh*) OR (TI ointment OR AB ointment) OR (TI ointments OR AB ointments)))

ointments) OR (TI packing* OR AB packing*) OR (TI pad OR AB pad) OR (TI pads OR AB pads) OR (TI paste OR AB paste) OR (TI pastes OR AB pastes) OR (TI patch OR AB patch) OR (TI patches OR AB patches) OR (TI plaster OR AB plaster) OR (TI plasters OR AB plasters) OR (TI polyamide* OR AB polyamide*) OR (TI polyester* OR AB polyester*) OR (TI polymer* OR AB polymer*) OR (TI polysaccharid* OR AB polysaccharid*) OR (TI polyurethane* OR AB polyurethane*) OR (TI powder* OR AB powder*) OR (TI rayon* OR AB rayon*) OR (TI ribbon* OR AB ribbon*) OR (TI rope OR AB rope) OR (TI ropes OR AB ropes) OR (TI sachet OR AB sachet) OR (TI sachets OR AB sachets) OR (TI seaweed* OR AB seaweed*) OR (TI "sea weed*" OR AB "sea weed*") OR (TI sheet OR AB sheet) OR (TI sheets OR AB sheets) OR (TI silicon* OR AB silicon*) OR (TI sleeve OR AB sleeve) OR (TI sleeves OR AB sleeves) OR (TI solution OR AB solution) OR (TI solutions OR AB solutions) OR (TI sponge OR AB sponge) OR (TI sponges OR AB sponges) OR (TI strip OR AB strip) OR (TI strips OR AB strips) OR (TI swab OR AB swab) OR (TI swabs OR AB swabs) OR (TI tape OR AB tape) OR (TI tapes OR AB tapes) OR (TI tulle OR AB tulle) OR (TI tulles OR AB tulles) OR (TI wash OR AB wash) OR (TI washes OR AB washes) OR (TI wrap OR AB wrap) OR (TI wraps OR AB wraps) OR (TI wrapping* OR AB wrapping*)) 5,510

S33 (((TI bacteria* OR AB bacteria*) OR (TI microb* OR AB microb*) OR (TI mycobacteria* OR AB mycobacteria*)) N3 (TI bind* OR AB bind*) N6 ((TI alginat* OR AB alginat*) OR (TI balm OR AB balm) OR (TI balms OR AB balms) OR (TI bandage* OR AB bandage*) OR (TI bead OR AB bead) OR (TI beads OR AB beads) OR (TI bioactive OR AB bioactive) OR (TI biomaterial* OR AB biomaterial*) OR (TI biosynthetic* OR AB biosynthetic*) OR (TI cellulose* OR AB cellulose*) OR (TI cloth OR AB cloth) OR (TI cloths OR AB cloths) OR (TI collagen* OR AB collagen*) OR (TI cotton* OR AB cotton*) OR (TI cream OR AB cream) OR (TI creams OR AB creams) OR (TI disc OR AB disc) OR (TI discs OR AB discs) OR (TI disk OR AB disk) OR (TI disks OR AB disks) OR (TI elastin* OR AB elastin*) OR (TI fabric OR AB fabric) OR (TI fabrics OR AB fabrics) OR (TI fiber OR AB fiber) OR (TI fibers OR AB fibers) OR (TI fibre OR AB fibre) OR (TI fibres OR AB fibres) OR (TI fibrous OR AB fibrous) OR (TI film OR AB film) OR (TI films OR AB films) OR (TI fluid OR AB fluid) OR (TI fluids OR AB fluids) OR (TI foam OR AB foam) OR (TI foams OR AB foams) OR (TI gauze* OR AB gauze*) OR (TI gel OR AB gel) OR (TI gels OR AB gels) OR (TI gelling OR AB gelling) OR (TI gelatin* OR AB gelatin*) OR (TI hyaluronic OR AB hyaluronic) OR (TI hydrocellular* OR AB hydrocellular*) OR (TI "hydro cellular*" OR AB "hydro cellular*") OR (TI hydrocolloid* OR AB hydrocolloid*) OR (TI "hydro colloid*" OR AB "hydro colloid*") OR (TI hydrofiber* OR AB hydrofiber*) OR (TI hydrofibre* OR AB hydrofibre*) OR (TI hydrogel* OR AB hydrogel*) OR (TI hydropolymer* OR AB hydropolymer*) OR (TI irrigat* OR AB irrigat*) OR (TI lint OR AB lint) OR (TI lints OR AB lints) OR (TI liquid OR AB liquid) OR (TI liquids OR AB liquids) OR (TI matrice* OR AB matrice*) OR (TI matrix* OR AB matrix*) OR (TI membrane* OR AB membrane*) OR (TI mesh* OR AB mesh*) OR (TI ointment OR AB ointment) OR (TI ointments OR AB ointments) OR (TI packing* OR AB packing*) OR (TI pad OR AB pad) OR (TI pads OR AB pads) OR (TI paste OR AB paste) OR (TI pastes OR AB pastes) OR (TI patch OR AB patch) OR (TI patches OR AB patches) OR (TI plaster OR AB plaster) OR (TI plasters OR AB plasters) OR (TI polyamide* OR

AB polyamide*) OR (TI polyester* OR AB polyester*) OR (TI polymer* OR AB polymer*) OR (TI polysaccharid* OR AB polysaccharid*) OR (TI polyurethane* OR AB polyurethane*) OR (TI powder* OR AB powder*) OR (TI rayon* OR AB rayon*) OR (TI ribbon* OR AB ribbon*) OR (TI rope OR AB rope) OR (TI ropes OR AB ropes) OR (TI sachet OR AB sachet) OR (TI sachets OR AB sachets) OR (TI seaweed* OR AB seaweed*) OR (TI "sea weed*" OR AB "sea weed*") OR (TI sheet OR AB sheet) OR (TI sheets OR AB sheets) OR (TI silicon* OR AB silicon*) OR (TI sleeve OR AB sleeve) OR (TI sleeves OR AB sleeves) OR (TI solution OR AB solution) OR (TI solutions OR AB solutions) OR (TI sponge OR AB sponge) OR (TI sponges OR AB sponges) OR (TI strip OR AB strip) OR (TI strips OR AB strips) OR (TI swab OR AB swab) OR (TI swabs OR AB swabs) OR (TI tape OR AB tape) OR (TI tapes OR AB tapes) OR (TI tulle OR AB tulle) OR (TI tulles OR AB tulles) OR (TI wash OR AB wash) OR (TI washes OR AB washes) OR (TI wrap OR AB wrap) OR (TI wraps OR AB wraps) OR (TI wrapping* OR AB wrapping*)) 25

S34 (MH "Antiinfective Agents, Local") OR (MH "Disinfectants") 7,436

S35 ((MH "Antiinfective Agents") OR (MH "Antibiotics")) AND (MH "Administration, Topical") 996

S36 (((TI antibacter* OR AB antibacter*) OR (TI "anti bacter*" OR AB "anti bacter*") OR (TI antibiofilm* OR AB antibiofilm*) OR (TI "anti biofilm*" OR AB "anti biofilm*") OR (TI antibiotic* OR AB antibiotic*) OR (TI "anti biotic*" OR AB "anti biotic*") OR (TI antiinfect* OR AB antiinfect*) OR (TI "anti infect*" OR AB "anti infect*") OR (TI antimicrob* OR AB antimicrob*) OR (TI "anti microb*" OR AB "anti microb*") OR (TI antimycobacter* OR AB antimycobacter*) OR (TI "anti mycobacter*" OR AB "anti mycobacter*") OR (TI antisept* OR AB antisept*) OR (TI "anti sept*" OR AB "anti sept*") OR (TI bacteriocid* OR AB bacteriocid*) OR (TI bactericid* OR AB bactericid*) OR (TI biocid* OR AB biocid*) OR (TI microbicid* OR AB microbicid*)) N6 ((TI cutaneous* OR AB cutaneous*) OR (TI dermal* OR AB dermal*) OR (TI skin OR AB skin) OR (TI skins OR AB skins) OR (TI topical* OR AB topical*) OR (TI transdermal* OR AB transdermal*)) 2,986

S37 (((TI bacteria* OR AB bacteria*) OR (TI microb* OR AB microb*) OR (TI mycobacteria* OR AB mycobacteria*)) N3 (TI bind* OR AB bind*) N6 ((TI cutaneous* OR AB cutaneous*) OR (TI dermal* OR AB dermal*) OR (TI skin OR AB skin) OR (TI skins OR AB skins) OR (TI topical* OR AB topical*) OR (TI transdermal* OR AB transdermal*))) 0

S38 S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 16,353

S39 (MH "Chlorhexidine") 3,776

S40 (TI chlorhex* OR AB chlorhex*) 3,643

S41 ((TI chlorohex* OR AB chlorohex*) OR (TI clohex* OR AB clohex*) OR (TI clorhex* OR AB clorhex*) OR (TI "mk 412a" OR AB "mk 412a") OR (TI mk412a OR AB mk412a)) 79

S42 ((TI chg OR AB chg) OR (TI chx OR AB chx)) 934

S43 ((TI 18472-51-0 OR AB 18472-51-0) OR (TI 200-238-7 OR AB 200-238-7) OR (TI 242-354-0 OR AB 242-354-0) OR (TI 36466-50-9 OR AB 36466-50-9) OR (TI 3697-42-5 OR AB 3697-42-5) OR (TI 55-56-1 OR AB 55-56-1) OR (TI 56-95-1 OR AB 56-95-1) OR (TI 5908zuf22y OR AB 5908zuf22y) OR (TI 74194-72-2 OR AB 74194-72-2) OR (TI e64xl9u38k OR AB e64xl9u38k) OR (TI mor84mud8e OR AB mor84mud8e) OR (TI r4ko0dy52l OR AB r4ko0dy52l)) 0

S44 S39 OR S40 OR S41 OR S42 OR S43 5,044

S45 (MH "Copper")2,682

S46 (TI copper* OR AB copper*) 4,649

S47 ((TI "cuprum metallicum" OR AB "cuprum metallicum") OR (TI nanocopper* OR AB nanocopper*)) 18

S48 ((TI cu OR AB cu) OR (TI cuo OR AB cuo) OR (TI cuonp OR AB cuonp) OR (TI cuonps OR AB cuonps) OR (TI nanocuo OR AB nanocuo) OR (TI nanocuos OR AB nanocuos)) 2,613

S49 ((TI 1344-70-3 OR AB 1344-70-3) OR (TI 15158-11-9 OR AB 15158-11-9) OR (TI 231-159-6 OR AB 231-159-6) OR (TI 7440-50-8 OR AB 7440-50-8) OR (TI 789u1901c5 OR AB 789u1901c5)) 0

S50 (TI medcu* OR AB medcu*) 5

S51 S45 OR S46 OR S47 OR S48 OR S49 OR S50 7,279

S52 ((TI dialkylcarb* OR AB dialkylcarb*) OR (TI "dialkyl carb*" OR AB "dialkyl carb*")) 32

S53 (TI dacc OR AB dacc)206

S54 (TI sorbact* OR AB sorbact*) 43

S55 S52 OR S53 OR S54 249

S56 (MH "Honey") 1,944

- S57 ((TI honey OR AB honey) OR (TI honeys OR AB honeys)) 2,167
- S58 ((TI hy1 OR AB hy1) OR (TI "hy 1" OR AB "hy 1")) 7
- S59 ((TI y9h1v576fh OR AB y9h1v576fh) OR (TI 8028-66-8 OR AB 8028-66-8)) 0
- S60 (MH "Apitherapy") 164
- S61 (TI apitherap* OR AB apitherap*) 42
- S62 ((TI actibalm* OR AB actibalm*) OR (TI actilite* OR AB actilite*) OR (TI activon* OR AB activon*) OR (TI algivon* OR AB algivon*) OR (TI "l-mesitran*" OR AB "l-mesitran*") OR (TI lmesitran* OR AB lmesitran*) OR (TI manuka* OR AB manuka*) OR (TI medihoney* OR AB medihoney*) OR (TI melladerm* OR AB melladerm*) OR (TI melloxy* OR AB melloxy*) OR (TI revamil* OR AB revamil*) OR (TI surgihoney* OR AB surgihoney*)) 380
- S63 S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62 3,147
- S64 (MH "Iodine") OR (MH "Iodine Compounds+") OR (MH "Iodine Isotopes+") 6,637
- S65 (TI iodin* OR AB iodin*) 7,938
- S66 ((TI cadexomeriodine* OR AB cadexomeriodine*) OR (TI iodate* OR AB iodate*) OR (TI iodide* OR AB iodide*) OR (TI iodium* OR AB iodium*) OR (TI iodophor* OR AB iodophor*) OR (TI iodopovidone* OR AB iodopovidone*) OR (TI iosal* OR AB iosal*) OR (TI jodium* OR AB jodium*) OR (TI povidoneiodine* OR AB povidoneiodine*) OR (TI "pvp-i" OR AB "pvp-i") OR (TI pvpi OR AB pvpi)) 1,827
- S67 ((TI 25655-41-8 OR AB 25655-41-8) OR (TI 85h0hzu99m OR AB 85h0hzu99m) OR (TI 9679tc07x4 OR AB 9679tc07x4) OR (TI 7553-56-2 OR AB 7553-56-2) OR (TI 94820-09-4 OR AB 94820-09-4)) 0
- S68 ((TI inadine* OR AB inadine*) OR (TI iodoflex* OR AB iodoflex*) OR (TI iodisorb* OR AB iodisorb*) OR (TI povitulle* OR AB povitulle*)) 23
- S69 S64 OR S65 OR S66 OR S67 OR S68 12,207
- S70 (TI polyhexamethylene* OR AB polyhexamethylene*) 146
- S71 (TI "poly hexamethylene*" OR AB "poly hexamethylene*") 1

S72 ((TI polihexamethylene* OR AB polihexamethylene*) OR (TI "poli hexamethylene*" OR AB "poli hexamethylene*")) 0

S73 ((TI polyhexanide* OR AB polyhexanide*) OR (TI "poly hexanide*" OR AB "poly hexanide*") OR (TI polihexanide* OR AB polihexanide*) OR (TI "poli hexanide*" OR AB "poli hexanide*")) 110

S74 (TI phmb* OR AB phmb*) 144

S75 ((TI 28757-47-3 OR AB 28757-47-3) OR (TI 32289-58-0 OR AB 32289-58-0) OR (TI 322u039gmf OR AB 322u039gmf) OR (TI 4xi6112496 OR AB 4xi6112496)) 0

S76 ((TI activheal* OR AB activheal*) OR (TI celludress* OR AB celludress*) OR (TI "kendall* amd*" OR AB "kendall* amd*") OR (TI prontosan* OR AB prontosan*) OR (TI suprasorb* OR AB suprasorb*)) 77

S77 S70 OR S71 OR S72 OR S73 OR S74 OR S75 OR S76 332

S78 (MH "Ionic Silver Dressings") OR MH "Silver") OR (MH "Silver Compounds+") OR MH "Silver Sulfadiazine") 2,843

S79 (TI silver* OR AB silver*) 6,346

S80 (TI ag OR AB ag) 5,808

S81 ((TI agnp OR AB agnp) OR (TI agnps OR AB agnps) OR (TI argenti OR AB argenti) OR (TI argentum OR AB argentum) OR (TI nanosilver* OR AB nanosilver*) OR (TI ssd OR AB ssd) OR (TI ssds OR AB ssds)) 1,599

S82 ((TI 22199-08-2 OR AB 22199-08-2) OR (TI 231-131-3 OR AB 231-131-3) OR (TI 24342-30-1 OR AB 24342-30-1) OR (TI 3m4g523w1g OR AB 3m4g523w1g) OR (TI 41034-18-8 OR AB 41034-18-8) OR (TI 7440-22-4 OR AB 7440-22-4) OR (TI 7761-88-8 OR AB 7761-88-8) OR (TI 7783-90-6 OR AB 7783-90-6) OR (TI 95it3w8jze OR AB 95it3w8jze) OR (TI w46jy43ejr OR AB w46jy43ejr)) 0

S83 ((TI acticoat* OR AB acticoat*) OR (TI actisorb* OR AB actisorb*) OR (TI algicell* OR AB algicell*) OR (TI algisite* OR AB algisite*) OR (TI allevyn* OR AB allevyn*) OR (TI aquacel* OR AB aquacel*) OR (TI "askina* calgitrol*" OR AB "askina* calgitrol*") OR (TI atrauman* OR AB atrauman*) OR (TI biatain* OR AB biatain*) OR (TI durafiber* OR AB durafiber*) OR (TI exufiber* OR AB exufiber*) OR (TI granufoam* OR AB granufoam*) OR (TI kerracel* OR AB kerracel*) OR (TI kerracontact* OR AB kerracontact*) OR (TI melgisorb* OR AB melgisorb*) OR (TI mepilex* OR AB mepilex*) OR (TI polymem* OR AB polymem*) OR (TI sorbsan* OR AB

sorbsan*) OR (TI "tegaderm* alginate*" OR AB "tegaderm* alginate*") OR (TI urgoclean* OR AB urgoclean*) OR (TI urgosorb* OR AB urgosorb*) OR (TI urgotul* OR AB urgotul*)) 610

S84 S78 OR S79 OR S80 OR S81 OR S82 OR S83 14,324

S85 (MH "Alginates") AND (MH "Hydrogel Dressings") 118

S86 (MH "Alginates") AND ((MH "Peroxidases") OR (MH "Oxidoreductases")) 7

S87 ((TI alginogel* OR AB alginogel*) OR (TI "algino gel*" OR AB "algino gel*")) 18

S88 (((TI biocatalyst* OR AB biocatalyst*) OR (TI catalyst* OR AB catalyst*) OR (TI enzym* OR AB enzym*)) AND ((TI algin OR AB algin) OR (TI alginic OR AB alginic) OR (TI alginat* OR AB alginat*) OR (TI polymannur* OR AB polymannur*) OR (TI "poly mannur*" OR AB "poly mannur*")))) 64

S89 (((((TI glucose OR AB glucose) N2 (TI oxidase* OR AB oxidase*)) OR (TI "glucose aerodehydrogenase" OR AB "glucose aerodehydrogenase") OR (TI "glucose oxygen oxidoreductase" OR AB "glucose oxygen oxidoreductase") OR (TI "glucose oxyhydrase" OR AB "glucose oxyhydrase") OR (TI glucosoxidase OR AB glucosoxidase) OR (TI god OR AB god) OR (TI gox OR AB gox) OR (TI microcid OR AB microcid) OR (TI notatin* OR AB notatin*)) AND (TI alginat* OR AB alginat*)) 1

S90 (((TI lactoperoxidase* OR AB lactoperoxidase*) OR (TI lactoperoxydase* OR AB lactoperoxydase*)) AND (TI alginat* OR AB alginat*)) 1

S91 (((TI algin OR AB algin) OR (TI alginic OR AB alginic) OR (TI alginat* OR AB alginat*) OR (TI polymannur* OR AB polymannur*) OR (TI "poly mannur*" OR AB "poly mannur*")) AND ((TI gel* OR AB gel*) OR (TI hydrogel* OR AB hydrogel*))) 297

S92 (TI flaminol* OR AB flaminol*) 23

S93 S85 OR S86 OR S87 OR S88 OR S89 OR S90 OR S91 OR S92 470

S94 (TI chitosan* OR AB chitosan*) 1,073

S95 (TI deacetylchitin* OR AB deacetylchitin*) 0

S96 ((TI "deacetylated chitin*" OR AB "deacetylated chitin*") OR (TI nanochitosan* OR AB nanochitosan*) OR (TI poliglucan* OR AB poliglucan*)) 5

S97 ((TI 9012-76-4 OR AB 9012-76-4) OR (TI 42617-20-9 OR AB 42617-20-9) OR (TI 87582-10-3 OR AB 87582-10-3) OR (TI 82lks4qv2y OR AB 82lks4qv2y)) 0

S98 (TI maxiocel* OR AB maxiocel*) 4

S99 S94 OR S95 OR S96 OR S97 OR S98 1,075

S100 (TI octenidine* OR AB octenidine*) 113

S101 ((TI las189962 OR AB las189962) OR (TI "las-189962" OR AB "las-189962")) 0

S102 ((TI 71251-02-0 OR AB 71251-02-0) OR (TI 70775-75-6 OR AB 70775-75-6) OR (TI 274-861-8 OR AB 274-861-8) OR (TI 86767-75-1 OR AB 86767-75-1) OR (TI oze0372s5a OR AB oze0372s5a) OR (TI u84956nu4b OR AB u84956nu4b) OR (TI r337868tdw OR AB r337868tdw)) 0

S103 (TI octenilin* OR AB octenilin*) 17

S104 S100 OR S101 OR S102 OR S103 125

S105 S44 OR S51 OR S55 OR S63 OR S69 OR S77 OR S84 OR S93 OR S99 OR S104 42,443

S106 S28 AND S38 349

S107 S28 AND S105 513

S108 S106 OR S107 723

S109 PT editorial 284,916

S110 TI "case report" 73,172

S111 S108 NOT (S109 OR S110) 700

S112 S111 Limiters - Language: English 653

A.4: Source: Econlit

Interface / URL: OvidSP

Database coverage dates: 1886 to July 18, 2024

Search date: 01/08/2024

Retrieved records: 6

External assessment group report: Topical antimicrobial dressings for infected leg ulcers in people aged 16 and over

Date: August 2024

285 of 643

Search strategy:

- 1 ((leg or legs) adj10 (ulcer* or ulcerus)).af. (4)
- 2 ((leg or legs) adj10 (bedsore* or decubital or decubitus or sore or sores)).af. (0)
- 3 ((leg or legs) adj10 ((chronic* or longterm or long term or longlasting or long lasting) adj6 (lesion or lesions or wound or wounds))).af. (0)
- 4 ((acurris or crural or cruris) adj10 (ulcer* or ulcerus)).af. (0)
- 5 ((acurris or crural or cruris) adj10 (bedsore* or decubital or decubitus or sore or sores)).af. (0)
- 6 ((acurris or crural or cruris) adj10 ((chronic* or longterm or long term or longlasting or long lasting) adj6 (lesion or lesions or wound or wounds))).af. (0)
- 7 ((ankle* or calf or calves or gaiter* or knee or knees or shin or shins) adj10 (ulcer* or ulcerus)).af. (0)
- 8 ((ankle* or calf or calves or gaiter* or knee or knees or shin or shins) adj10 (bedsore* or decubital or decubitus or sore or sores)).af. (0)
- 9 ((ankle* or calf or calves or gaiter* or knee or knees or shin or shins) adj10 ((chronic* or longterm or long term or longlasting or long lasting) adj6 (lesion or lesions or wound or wounds))).af. (0)
- 10 (lower adj3 (extremity* or limb or limbs) adj10 (ulcer* or ulcerus)).af. (1)
- 11 (lower adj3 (extremity* or limb or limbs) adj10 (bedsore* or decubital or decubitus or sore or sores)).af. (0)
- 12 (lower adj3 (extremity* or limb or limbs) adj10 ((chronic* or longterm or long term or longlasting or long lasting) adj6 (lesion or lesions or wound or wounds))).af. (0)
- 13 or/1-12 (5)
- 14 ((stasis or varicos* or varix or vein* or venous) adj10 (ulcer* or ulcerus)).af. (3)
- 15 ((stasis or varicos* or varix or vein* or venous) adj10 (bedsore* or decubital or decubitus or sore or sores)).af. (0)
- 16 ((stasis or varicos* or varix or vein* or venous) adj10 ((chronic* or longterm or long term or longlasting or long lasting) adj6 (lesion or lesions or wound or wounds))).af. (0)
- 17 (vascul* adj10 (ulcer* or ulcerus)).af. (0)
- 18 (vascul* adj10 (bedsore* or decubital or decubitus or sore or sores)).af. (0)
- 19 (vascul* adj10 ((chronic* or longterm or long term or longlasting or long lasting) adj6 (lesion or lesions or wound or wounds))).af. (0)
- 20 ((lymphedem* or lymphoedem* or phlebolymp*) adj10 (ulcer* or ulcerus)).af. (0)
- 21 ((lymphedem* or lymphoedem* or phlebolymp*) adj10 (bedsore* or decubital or decubitus or sore or sores)).af. (0)
- 22 ((lymphedem* or lymphoedem* or phlebolymp*) adj10 ((chronic* or longterm or long term or longlasting or long lasting) adj6 (lesion or lesions or wound or wounds))).af. (0)
- 23 or/14-22 (3)
- 24 13 or 23 (6)
- 25 limit 24 to english (6)

A.5: Source: Cochrane Database of Systematic Reviews (CDSR)

Interface / URL: Cochrane Library / Wiley

Database coverage dates: Information not found. Issue searched: Issue 8 of 12, August 2024

Search date: 01/08/2024

Retrieved records: 14

Search strategy:

- #1 [mh ^"Leg Ulcer"] 628
- #2 ([mh ^"lower extremity"] OR [mh ^leg]) AND ([mh ^ulcer] OR [mh ^"skin ulcer"] OR [mh ^"buruli ulcer"] OR [mh ^"pressure ulcer"] OR [mh ^"pyoderma gangrenosum"])
- #3 ([mh ^ankle] OR [mh ^knee]) AND ([mh ^ulcer] OR [mh ^"skin ulcer"] OR [mh ^"buruli ulcer"] OR [mh ^"pressure ulcer"] OR [mh ^"pyoderma gangrenosum"])
- #4 ((leg or legs) near/10 (ulcer* or ulcus)):ti,ab,kw 2299
- #5 ((leg or legs) near/10 (bedsore* or decubital or decubitus or sore or sores)):ti,ab,kw 77
- #6 ((leg or legs) near/10 ((chronic* or longterm or "long term" or longlasting or "long lasting") near/6 (lesion or lesions or wound or wounds))):ti,ab,kw 131
- #7 ((acuris or crural or cruris) near/10 (ulcer* or ulcus)):ti,ab,kw 49
- #8 ((acuris or crural or cruris) near/10 (bedsore* or decubital or decubitus or sore or sores)):ti,ab,kw 2
- #9 ((acuris or crural or cruris) near/10 ((chronic* or longterm or "long term" or longlasting or "long lasting") near/6 (lesion or lesions or wound or wounds))):ti,ab,kw 6
- #10 ((ankle* or calf or calves or gaiter* or knee or knees or shin or shins) near/10 (ulcer* or ulcus)):ti,ab,kw 337
- #11 ((ankle* or calf or calves or gaiter* or knee or knees or shin or shins) near/10 (bedsore* or decubital or decubitus or sore or sores)):ti,ab,kw 73
- #12 ((ankle* or calf or calves or gaiter* or knee or knees or shin or shins) near/10 ((chronic* or longterm or "long term" or longlasting or "long lasting") near/6 (lesion or lesions or wound or wounds))):ti,ab,kw 24
- #13 (lower near/3 (extremity* or limb or limbs) near/10 (ulcer* or ulcus)):ti,ab,kw 578
- #14 (lower near/3 (extremity* or limb or limbs) near/10 (bedsore* or decubital or decubitus or sore or sores)):ti,ab,kw 53
- #15 (lower near/3 (extremity* or limb or limbs) near/10 ((chronic* or longterm or "long term" or longlasting or "long lasting") near/6 (lesion or lesions or wound or wounds))):ti,ab,kw 70
- #16 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 3101
- #17 [mh ^"Varicose Ulcer"] 846
- #18 ((stasis or varicos* or varix or vein* or venous) near/10 (ulcer* or ulcus)):ti,ab,kw 2340
- #19 ((stasis or varicos* or varix or vein* or venous) near/10 (bedsore* or decubital or decubitus or sore or sores)):ti,ab,kw 113

- #20 ((stasis or varicos* or varix or vein* or venous) near/10 ((chronic* or longterm or "long term" or longlasting or "long lasting") near/6 (lesion or lesions or wound or wounds))):ti,ab,kw 147
- #21 (vascul* near/10 (ulcer* or ulcus)):ti,ab,kw 385
- #22 (vascul* near/10 (bedsore* or decubital or decubitus or sore or sores)):ti,ab,kw 10
- #23 (vascul* near/10 ((chronic* or longterm or "long term" or longlasting or "long lasting") near/6 (lesion or lesions or wound or wounds))):ti,ab,kw 38
- #24 ((lymphedem* or lymphoedem* or phlebolymph*) near/10 (ulcer* or ulcus)):ti,ab,kw 23
- #25 ((lymphedem* or lymphoedem* or phlebolymph*) near/10 (bedsore* or decubital or decubitus or sore or sores)):ti,ab,kw 2
- #26 ((lymphedem* or lymphoedem* or phlebolymph*) near/10 ((chronic* or longterm or "long term" or longlasting or "long lasting"))):ti,ab,kw 209
- #27 #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 2971
- #28 #16 OR #27 4414
- #29 ([mh ^"anti-infective agents"] OR [mh ^"anti-bacterial agents"] OR [mh ^disinfectants] OR [mh ^antisepsis]) AND [mh Bandages] 143
- #30 ((antibacter* or anti next bacter* or antibiofilm* or anti next biofilm* or antibiotic* or anti next biotic* or antiinfect* or anti next infect* or antimicrob* or anti next microb* or antimycobacter* or anti next mycobacter* or antisept* or anti next sept* or bacteriocid* or bactericid* or biocid* or microbicid*) near/6 (dressing or dressings)):ti,ab,kw 432
- #31 ((bacteria* or microb* or mycobacteria*) near/3 bind* near/6 (dressing or dressings)):ti,ab,kw 6
- #32 ((antibacter* or anti next bacter* or antibiofilm* or anti next biofilm* or antibiotic* or anti next biotic* or antiinfect* or anti next infect* or antimicrob* or anti next microb* or antimycobacter* or anti next mycobacter* or antisept* or anti next sept* or bacteriocid* or bactericid* or biocid* or microbicid*) near/6 (alginat* or balm or balms or bandage* or bead or beads or bioactive or biomaterial* or biosynthetic* or cellulose* or cloth or cloths or collagen* or cotton* or cream or creams or disc or discs or disk or disks or elastin* or fabric or fabrics or fiber or fibers or fibre or fibres or fibrous or film or films or fluid or fluids or foam or foams or gauze* or gel or gels or gelling or gelatin* or hyaluronic or hydrocellular* or hydro next cellular* or hydrocolloid* or hydro next colloid* or hydrofiber* or hydrofibre* or hydrogel* or hydropolymer* or irrigat* or lint or lints or liquid or liquids or matrice* or matrix* or membrane* or mesh* or ointment or ointments or packing* or pad or pads or paste or pastes or patch or patches or plaster or plasters or polyamide* or polyester* or polymer* or polysaccharid* or polyurethane* or powder* or rayon* or ribbon* or rope or ropes or sachet or sachets or seaweed* or sea next weed* or sheet or sheets or silicon* or sleeve or sleeves or solution or solutions or sponge or sponges or strip or strips or swab or swabs or tape or tapes or tulle or tulles or wash or washes or wrap or wraps or wrapping)):ti,ab,kw 3448
- #33 ((bacteria* or microb* or mycobacteria*) near/3 bind* near/6 (alginat* or balm or balms or bandage* or bead or beads or bioactive or biomaterial* or biosynthetic* or cellulose* or cloth or cloths or collagen* or cotton* or cream or creams or disc or discs or disk or disks or elastin* or

fabric or fabrics or fiber or fibers or fibre or fibres or fibrous or film or films or fluid or fluids or foam or foams or gauze* or gel or gels or gelling or gelatin* or hyaluronic or hydrocellular* or hydro next cellular* or hydrocolloid* or hydro next colloid* or hydrofiber* or hydrofibre* or hydrogel* or hydropolymer* or irrigat* or lint or lints or liquid or liquids or matrice* or matrix* or membrane* or mesh* or ointment or ointments or packing* or pad or pads or paste or pastes or patch or patches or plaster or plasters or polyamide* or polyester* or polymer* or polysaccharid* or polyurethane* or powder* or rayon* or ribbon* or rope or ropes or sachet or sachets or seaweed* or sea next weed* or sheet or sheets or silicon* or sleeve or sleeves or solution or solutions or sponge or sponges or strip or strips or swab or swabs or tape or tapes or tulle or tulles or wash or washes or wrap or wraps or wrapping*)):ti,ab,kw 11

#34 [mh ^"anti-Infective agents, local"] 2665

#35 ([mh ^"anti-infective agents"] OR [mh ^"anti-bacterial agents"] OR [mh ^disinfectants] OR [mh ^antiseptis]) AND ([mh ^"administration, topical"] OR [mh ^"administration, cutaneous"]) 729

#36 ((antibacter* or anti next bacter* or antibiofilm* or anti next biofilm* or antibiotic* or anti next biotic* or antiinfect* or anti next infect* or antimicrob* or anti next microb* or antimycobacter* or anti next mycobacter* or antisept* or anti next sept* or bacteriocid* or bactericid* or biocid* or microbicid*) near/6 (cutaneous* or dermal* or skin or skins or topical* or transdermal*)):ti,ab,kw 2546

#37 ((bacteria* or microb* or mycobacteria*) near/3 bind* near/6 (cutaneous* or dermal* or skin or skins or topical* or transdermal*)):ti,ab,kw 1

#38 #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 8365

#39 [mh ^Chlorhexidine] 2858

#40 chlorhex*:ti,ab,kw 6350

#41 (chlorohex* or clohex* or clorhex* or "mk 412a" or mk412a):ti,ab,kw 131

#42 (chg or chx):ti,ab,kw 1275

#43 ("18472 51 0" or "200 238 7" or "242 354 0" or "36466 50 9" or "3697 42 5" or "55 56 1" or "56 95 1" or 5908zuf22y or "74194 72 2" or e64xl9u38k or mor84mud8e or r4ko0dy52l):ti,ab,kw 22

#44 #39 OR #40 OR #41 OR #42 OR #43 6524

#45 [mh ^Copper] 630

#46 copper*:ti,ab,kw 2689

#47 ("cuprum metallicum" or nanocopper*):ti,ab,kw 2

#48 (cu or cuo or cuonp or cuonps or nanocuo or nanocuos):ti,ab,kw 1442

#49 ("1344 70 3" or "15158 11 9" or "231 159 6" or "7440 50 8" or 789u1901c5):ti,ab,kw 0

#50 medcu*:ti,ab,kw 1

#51 #45 OR #46 OR #47 OR #48 OR #49 OR #50 3695

#52 (dialkylcarb* or dialkyl next carb*):ti,ab,kw 21

#53 dacc:ti,ab,kw 171

#54 sorbact*:ti,ab,kw 22

#55 #52 OR #53 OR #54 186

#56 [mh ^Honey] 246
 #57 (honey or honeys):ti,ab,kw 1493
 #58 (hy1 or "hy 1"):ti,ab,kw 23
 #59 (y9h1v576fh or "8028 66 8"):ti,ab,kw 1
 #60 [mh ^Apitherapy] 35
 #61 apitherap*:ti,ab,kw 66
 #62 (actibalm* or actilite* or activon* or algivon* or l next mesitran* or lmesitran* or manuka* or medihoney* or melladerm* or melloxy* or revamil* or surgihoney*):ti,ab,kw 218
 #63 #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 1592
 #64 [mh Iodine] OR [mh "Iodine Compounds"] 2712
 #65 iodin*:ti,ab,kw 6522
 #66 (cadexomeriodine* or iodate* or iodide* or iodium* or iodophor* or iodopovidone* or iosal* or jodium* or povidoneiodine* or "pvp i" or pvpi):ti,ab,kw 2284
 #67 ("25655 41 8" or 85h0hzu99m or 9679tc07x4 or "7553 56 2" or "94820 09 4"):ti,ab,kw 10
 #68 (inadine* or iodoflex* or iodosorb* or povitulle*):ti,ab,kw 22
 #69 #64 OR #65 OR #66 OR #67 OR #68 7035
 #70 [mh ^Biguanides] 228
 #71 (polyhexamethylene* or poly next hexamethylene*):ti,ab,kw 105
 #72 (polihexamethylene* or poli next hexamethylene*):ti,ab,kw 0
 #73 (polyhexanide* or poly next hexanide* or polihexanide* or poli next hexanide*):ti,ab,kw 116
 #74 phmb*:ti,ab,kw 103
 #75 ("28757 47 3" or "32289 58 0" or 322u039gmf or 4xi6112496):ti,ab,kw 3
 #76 (activheal* or celludress* or kendall* next amd* or prontosan* or suprasorb*):ti,ab,kw 34
 #77 #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 409
 #78 [mh ^Silver] OR [mh "Silver Compounds"] OR [mh ^"Silver Sulfadiazine"] OR [mh ^"Silver Proteins"] 784
 #79 silver*:ti,ab,kw 3092
 #80 ag:ti,ab,kw 8587
 #81 (agnp or agnps or argenti or argentum or nanosilver* or ssd or ssds):ti,ab,kw 639
 #82 ("22199 08 2" or "231 131 3" or "24342 30 1" or 3m4g523w1g or "41034 18 8" or "7440 22 4" or "7761 88 8" or "7783 90 6" or 95it3w8jze or w46jy43ejr):ti,ab,kw 5
 #83 (acticoat* or actisorb* or algicell* or algisite* or allevyn* or aquacel* or askina* next calgitrol* or atrauman* or biatain* or durafiber* or exufiber* or granufoam* or kerracel* or kerracontact* or melgisorb* or mepilex* or polymem* or sorbsan* or tegaderm* next alginate* or urgoclean* or urgisorb* or urgotul*):ti,ab,kw 423
 #84 #78 OR #79 OR #80 OR #81 OR #82 OR #83 12158
 #85 [mh ^Alginates] AND [mh ^Hydrogels] 11
 #86 [mh ^Alginates] AND ([mh ^Lactoperoxidase] OR [mh ^"Glucose Oxidase"])] 6
 #87 (alginogel* or algino next gel*):ti,ab,kw 5

#88 ((biocatalyst* or catalyst* or enzym*) and (algin or alginic or alginat* or polymannur* or poly next mannur*)):ti,ab,kw 24

#89 (((glucose near/2 oxidase*) or "glucose aerodehydrogenase" or "glucose oxygen oxidoreductase" or "glucose oxyhydrase" or "glucosoxidase" or god or gox or microcid or notatin*) and alginat*):ti,ab,kw 6

#90 ((lactoperoxidase* or lactoperoxydase*) and alginat*):ti,ab,kw 6

#91 ((algin or alginic or alginat* or polymannur* or poly next mannur*) and (gel* or hydrogel*)):ti,ab,kw 144

#92 flaminat*:ti,ab,kw 12

#93 #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 178

#94 [mh ^Chitosan] 292

#95 chitosan*:ti,ab,kw 713

#96 (deacetylchitin* or deacetylated next chitin* or nanochitosan* or poliglusam*):ti,ab,kw 12

#97 ("9012 76 4" or "42617 20 9" or "87582 10 3" or 82lks4qv2y):ti,ab,kw 0

#98 maxioce*:ti,ab,kw 2

#99 #94 OR #95 OR #96 OR #97 OR #98 713

#100 octenidine*:ti,ab,kw 127

#101 (las189962 or "las 189962"):ti,ab,kw 3

#102 ("71251 02 0" or "70775 75 6" or "274 861 8" or "86767 75 1" or oze0372s5a or u84956nu4b or r337868tdw):ti,ab,kw 12

#103 octenilin*:ti,ab,kw 8

#104 #100 OR #101 OR #102 OR #103 132

#105 #44 OR #51 OR #55 OR #63 OR #69 OR #77 OR #84 OR #93 OR #99 OR #104 31017

#106 #28 AND #38 142

#107 #28 AND #105 335

#108 #106 OR #107414

#109 #108 in Cochrane Reviews, Cochrane Protocols 14

A.6: Source: Cochrane Central Register of Controlled Trials

Interface / URL: Cochrane Library / Wiley

Database coverage dates: Information not found. Issue searched: Issue 7 of 12, July 2024

Search date: 02/08/2024

Retrieved records: 416

Search strategy:

#1 [mh ^"Leg Ulcer"] 628

#2 ([mh ^"lower extremity"] OR [mh ^leg]) AND ([mh ^ulcer] OR [mh ^"skin ulcer"] OR [mh ^"buruli ulcer"] OR [mh ^"pressure ulcer"] OR [mh ^"pyoderma gangrenosum"])

#3 ([mh ^ankle] OR [mh ^knee]) AND ([mh ^ulcer] OR [mh ^"skin ulcer"] OR [mh ^"buruli ulcer"] OR [mh ^"pressure ulcer"] OR [mh ^"pyoderma gangrenosum"])

#4 ((leg or legs) near/10 (ulcer* or ulcus)) 2416

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#5 ((leg or legs) near/10 (bedsore* or decubital or decubitus or sore or sores)) 86

#6 ((leg or legs) near/10 ((chronic* or longterm or "long term" or longlasting or "long lasting") near/6 (lesion or lesions or wound or wounds))) 152

#7 ((acuris or crural or cruris) near/10 (ulcer* or ulcus)) 99

#8 ((acuris or crural or cruris) near/10 (bedsore* or decubital or decubitus or sore or sores)) 3

#9 ((acuris or crural or cruris) near/10 ((chronic* or longterm or "long term" or longlasting or "long lasting") near/6 (lesion or lesions or wound or wounds))) 6

#10 ((ankle* or calf or calves or gaiter* or knee or knees or shin or shins) near/10 (ulcer* or ulcus)) 402

#11 ((ankle* or calf or calves or gaiter* or knee or knees or shin or shins) near/10 (bedsore* or decubital or decubitus or sore or sores)) 81

#12 ((ankle* or calf or calves or gaiter* or knee or knees or shin or shins) near/10 ((chronic* or longterm or "long term" or longlasting or "long lasting") near/6 (lesion or lesions or wound or wounds))) 29

#13 (lower near/3 (extremit* or limb or limbs) near/10 (ulcer* or ulcus)) 679

#14 (lower near/3 (extremit* or limb or limbs) near/10 (bedsore* or decubital or decubitus or sore or sores)) 54

#15 (lower near/3 (extremit* or limb or limbs) near/10 ((chronic* or longterm or "long term" or longlasting or "long lasting") near/6 (lesion or lesions or wound or wounds))) 78

#16 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 3285

#17 [mh ^"Varicose Ulcer"] 846

#18 ((stasis or varicos* or varix or vein* or venous) near/10 (ulcer* or ulcus)) 2443

#19 ((stasis or varicos* or varix or vein* or venous) near/10 (bedsore* or decubital or decubitus or sore or sores)) 137

#20 ((stasis or varicos* or varix or vein* or venous) near/10 ((chronic* or longterm or "long term" or longlasting or "long lasting") near/6 (lesion or lesions or wound or wounds))) 176

#21 (vascul* near/10 (ulcer* or ulcus)) 524

#22 (vascul* near/10 (bedsore* or decubital or decubitus or sore or sores)) 10

#23 (vascul* near/10 ((chronic* or longterm or "long term" or longlasting or "long lasting") near/6 (lesion or lesions or wound or wounds))) 39

#24 ((lymphedem* or lymphoedem* or phlebolymph*) near/10 (ulcer* or ulcus)) 30

#25 ((lymphedem* or lymphoedem* or phlebolymph*) near/10 (bedsore* or decubital or decubitus or sore or sores)) 3

#26 ((lymphedem* or lymphoedem* or phlebolymph*) near/10 ((chronic* or longterm or "long term" or longlasting or "long lasting"))) 241

#27 #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 3196

#28 #16 OR #27 4723

#29 ([mh ^"anti-infective agents"] OR [mh ^"anti-bacterial agents"] OR [mh ^disinfectants] OR [mh ^antisepsis]) AND [mh Bandages] 143

#30 ((antibacter* or anti next bacter* or antibiofilm* or anti next biofilm* or antibiotic* or anti next biotic* or antiinfect* or anti next infect* or antimicrob* or anti next microb* or antimycobacter* or anti next mycobacter* or antisept* or anti next sept* or bacteriocid* or bactericid* or biocid* or microbicid*) near/6 (dressing or dressings)) 513

#31 ((bacteria* or microb* or mycobacteria*) near/3 bind* near/6 (dressing or dressings)) 6

#32 ((antibacter* or anti next bacter* or antibiofilm* or anti next biofilm* or antibiotic* or anti next biotic* or antiinfect* or anti next infect* or antimicrob* or anti next microb* or antimycobacter* or anti next mycobacter* or antisept* or anti next sept* or bacteriocid* or bactericid* or biocid* or microbicid*) near/6 (alginat* or balm or balms or bandage* or bead or beads or bioactive or biomaterial* or biosynthetic* or cellulose* or cloth or cloths or collagen* or cotton* or cream or creams or disc or discs or disk or disks or elastin* or fabric or fabrics or fiber or fibers or fibre or fibres or fibrous or film or films or fluid or fluids or foam or foams or gauze* or gel or gels or gelling or gelatin* or hyaluronic or hydrocellular* or hydro next cellular* or hydrocolloid* or hydro next colloid* or hydrofiber* or hydrofibre* or hydrogel* or hydropolymer* or irrigat* or lint or lints or liquid or liquids or matrice* or matrix* or membrane* or mesh* or ointment or ointments or packing* or pad or pads or paste or pastes or patch or patches or plaster or plasters or polyamide* or polyester* or polymer* or polysaccharid* or polyurethane* or powder* or rayon* or ribbon* or rope or ropes or sachet or sachets or seaweed* or sea next weed* or sheet or sheets or silicon* or sleeve or sleeves or solution or solutions or sponge or sponges or strip or strips or swab or swabs or tape or tapes or tulle or tulles or wash or washes or wrap or wraps or wrapping*)) 4517

#33 ((bacteria* or microb* or mycobacteria*) near/3 bind* near/6 (alginat* or balm or balms or bandage* or bead or beads or bioactive or biomaterial* or biosynthetic* or cellulose* or cloth or cloths or collagen* or cotton* or cream or creams or disc or discs or disk or disks or elastin* or fabric or fabrics or fiber or fibers or fibre or fibres or fibrous or film or films or fluid or fluids or foam or foams or gauze* or gel or gels or gelling or gelatin* or hyaluronic or hydrocellular* or hydro next cellular* or hydrocolloid* or hydro next colloid* or hydrofiber* or hydrofibre* or hydrogel* or hydropolymer* or irrigat* or lint or lints or liquid or liquids or matrice* or matrix* or membrane* or mesh* or ointment or ointments or packing* or pad or pads or paste or pastes or patch or patches or plaster or plasters or polyamide* or polyester* or polymer* or polysaccharid* or polyurethane* or powder* or rayon* or ribbon* or rope or ropes or sachet or sachets or seaweed* or sea next weed* or sheet or sheets or silicon* or sleeve or sleeves or solution or solutions or sponge or sponges or strip or strips or swab or swabs or tape or tapes or tulle or tulles or wash or washes or wrap or wraps or wrapping*)) 17

#34 [mh ^"anti-Infective agents, local"] 2665

#35 ([mh ^"anti-infective agents"] OR [mh ^"anti-bacterial agents"] OR [mh ^disinfectants] OR [mh ^antisepsis]) AND ([mh ^"administration, topical"] OR [mh ^"administration, cutaneous"]) 729

#36 ((antibacter* or anti next bacter* or antibiofilm* or anti next biofilm* or antibiotic* or anti next biotic* or antiinfect* or anti next infect* or antimicrob* or anti next microb* or antimycobacter*

or anti next mycobacter* or antisept* or anti next sepi* or bacteriocid* or bactericid* or biocid* or microbicid*) near/6 (cutaneous* or dermal* or skin or skins or topical* or transdermal*)) 3560

#37 ((bacteria* or microb* or mycobacteria*) near/3 bind* near/6 (cutaneous* or dermal* or skin or skins or topical* or transdermal*)) 1

#38 #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 9331

#39 [mh ^Chlorhexidine] 2858

#40 chlorhex* 6531

#41 (chlorohex* or clohex* or clorhex* or "mk 412a" or mk412a)173

#42 (chg or chx) 1353

#43 ("18472 51 0" or "200 238 7" or "242 354 0" or "36466 50 9" or "3697 42 5" or "55 56 1" or "56 95 1" or 5908zuf22y or "74194 72 2" or e64xl9u38k or mor84mud8e or r4ko0dy52l) 28

#44 #39 OR #40 OR #41 OR #42 OR #43 6757

#45 [mh ^Copper] 630

#46 copper* 2910

#47 ("cuprum metallicum" or nanocopper*) 2

#48 cu:ti,ab,kw or (cuo or cuonp or cuonps or nanocuo or nanocuos) 1447

#49 ("1344 70 3" or "15158 11 9" or "231 159 6" or "7440 50 8" or 789u1901c5) 0

#50 medcu* 1

#51 #45 OR #46 OR #47 OR #48 OR #49 OR #50 3920

#52 (dialkylcarb* or dialkyl next carb*) 28

#53 dacc 191

#54 sorbact* 33

#55 #52 OR #53 OR #54 218

#56 [mh ^Honey] 246

#57 (honey or honeys) 1667

#58 (hy1 or "hy 1") 23

#59 (y9h1v576fh or "8028 66 8") 1

#60 [mh ^Apitherapy] 35

#61 apitherap* 67

#62 (actibalm* or actilite* or activon* or algivon* or I next mesitran* or lmesitran* or manuka* or medihoney* or melladerm* or melloxyl* or revamil* or surgihoney*) 282

#63 #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 1810

#64 [mh Iodine] OR [mh "Iodine Compounds"] 2712

#65 iodine* 6801

#66 (cadexomeriodine* or iodate* or iodide* or iodine* or iodophor* or iodopovidone* or iosal* or jodium* or povidoneiodine* or "pvp i" or pvp) 2402

#67 ("25655 41 8" or 85h0hzu99m or 9679tc07x4 or "7553 56 2" or "94820 09 4") 10

#68 (inadine* or iodoflex* or iodisorb* or povitulle*) 40

#69 #64 OR #65 OR #66 OR #67 OR #68 7322

#70 [mh ^Biguanides] 228

#71 (polyhexamethylene* or poly next hexamethylene*) 114

#72 (polihexamethylene* or poli next hexamethylene*) 0
 #73 (polyhexanide* or poly next hexanide* or polihexanide* or poli next hexanide*) 127
 #74 phmb* 112
 #75 ("28757 47 3" or "32289 58 0" or 322u039gmf or 4xi6112496) 3
 #76 (activheal* or celludress* or kendall* next amd* or prontosan* or suprasorb*) 46
 #77 #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 430
 #78 [mh ^Silver] OR [mh "Silver Compounds"] OR [mh ^"Silver Sulfadiazine"] OR [mh ^"Silver Proteins"] 784
 #79 silver* 8915
 #80 ag:ti,ab,kw 8587
 #81 (agnp or agnps or argenti or argentum or nanosilver* or ssd or ssds) 749
 #82 ("22199 08 2" or "231 131 3" or "24342 30 1" or 3m4g523w1g or "41034 18 8" or "7440 22 4" or "7761 88 8" or "7783 90 6" or 95it3w8jze or w46jy43ejr) 5
 #83 (acticoat* or actisorb* or algicell* or algisite* or allevyn* or aquacel* or askina* next calgitrol* or atrauman* or biatain* or durafiber* or exufiber* or granufoam* or kerracel* or kerracontact* or melgisorb* or mepilex* or polymem* or sorbsan* or tegaderm* next alginate* or urgoclean* or urgisorb* or urgotul*) 463
 #84 #78 OR #79 OR #80 OR #81 OR #82 OR #83 18056
 #85 [mh ^Alginates] AND [mh ^Hydrogels] 11
 #86 [mh ^Alginates] AND ([mh ^Lactoperoxidase] OR [mh ^"Glucose Oxidase"])] 6
 #87 (alginogel* or algino next gel*) 5
 #88 ((biocatalyst* or catalyst* or enzym*) and (algin or alginic or alginat* or polymannur* or poly next mannur*)) 60
 #89 (((glucose near/2 oxidase*) or "glucose aerodehydrogenase" or "glucose oxygen oxidoreductase" or "glucose oxyhydrase" or "glucosoxidase" or god or gox or microcid or notatin*) and alginat*) 9
 #90 ((lactoperoxidase* or lactoperoxydase*) and alginat*) 6
 #91 ((algin or alginic or alginat* or polymannur* or poly next mannur*) and (gel* or hydrogel*)) 199
 #92 flaminial* 13
 #93 #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 241
 #94 [mh ^Chitosan] 292
 #95 chitosan* 737
 #96 (deacetylchitin* or deacetylated next chitin* or nanochitosan* or poliglusam*) 17
 #97 ("9012 76 4" or "42617 20 9" or "87582 10 3" or 82lks4qv2y) 0
 #98 maxiocel* 2
 #99 #94 OR #95 OR #96 OR #97 OR #98 737
 #100 octenidine* 135
 #101 (las189962 or "las 189962") 3
 #102 ("71251 02 0" or "70775 75 6" or "274 861 8" or "86767 75 1" or oze0372s5a or u84956nu4b or r337868tdw) 12
 #103 octenilin* 8

#104 #100 OR #101 OR #102 OR #103 140
 #105 #44 OR #51 OR #55 OR #63 OR #69 OR #77 OR #84 OR #93 OR #99 OR #104 37619
 #106 #28 AND #38 203
 #107 #28 AND #105 411
 #108 #106 OR #107516
 #109 #108 in Trials 416

A.7: Source: HTA Database

Interface / URL: <https://database.inahta.org/>

Database coverage dates: Information not found. The former database was produced by the CRD until March 2018, at which time the addition of records was stopped as INAHTA was in the process of rebuilding the new database platform. In July 2019, the database records were exported from the CRD platform and imported into the new platform that was developed by INAHTA. The rebuild of the new platform was launched in June 2020

Search date: 02/08/2024

Retrieved records: 24

Search strategy:

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1      "Leg Ulcer"[mh]          37
2      ("Lower Extremity"[mh] OR "Leg"[mh]) AND ("Ulcer"[mh] OR "Skin Ulcer"[mh] OR "Buruli
Ulcer"[mh] OR "Pressure Ulcer"[mh] OR "Pyoderma Gangrenosum"[mh]) 39
3      ("Ankle"[mh] OR "Knee"[mh]) AND ("Ulcer"[mh] OR "Skin Ulcer"[mh] OR "Buruli
Ulcer"[mh] OR "Pressure Ulcer"[mh] OR "Pyoderma Gangrenosum"[mh]) 1
4      "Varicose Ulcer"[mh] 22
5      (leg OR legs OR acurris OR crural OR cruris OR ankle* OR calf OR calves OR gaiter*
OR knee OR knees OR shin OR shins OR extremi* OR limb OR limbs OR stasis OR varicos*
OR varix OR vein* OR venous OR vascul* OR lymphedem* OR lymphoedem* OR phlebolymph*)
AND (ulcer* OR ulcus OR bed sore* OR decubital OR decubitus OR sore OR sores OR lesion
OR lesions OR wound OR wounds) 182
6      #5 OR #4 OR #3 OR #2 OR #1 188
7      ("Anti-Infective Agents"[mh] OR "Anti-Bacterial Agents"[mh] OR "Disinfectants"[mh] OR
"Antisepsis"[mh]) AND "Bandages"[mhe] 8
8      "Anti-Infective Agents, Local"[mh] 28
9      ("Anti-Infective Agents"[mh] OR "Anti-Bacterial Agents"[mh] OR "Disinfectants"[mh] OR
"Antisepsis"[mh]) AND ("Administration, Topical"[mh] OR "Administration, Cutaneous"[mh])
2
10     (anti* OR bacteriocid* OR bactericid* OR bioocid* OR microbicid* OR bind*) 1880
11     #10 OR #9 OR #8 OR #7 1894
12     "Chlorhexidine"[mh] 20
13     (chlorhex* OR chlorohex* OR clohex* OR clorhex* OR 412a OR mk412a OR chg OR chx
OR "18472" OR "200-238" OR "242-354" OR "36466" OR "3697" OR "55-56-1" OR "56-95-1" OR
5908zuf22y OR "74194" OR e64xl9u38k OR mor84mud8e OR r4ko0dy52l) 30

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14 "Copper"[mh] 7

15 (copper* OR "cuprum metallicum" OR nanocopper* OR cuo OR cuonp OR cuonps OR nanocuo OR nanocuos OR "1344" OR "15158" OR "231-159" OR "7440" OR 789u1901c5 OR medcu*) 10

16 (dialkyl* OR dacc OR sorbact*) 1

17 "Honey"[mh] 0

18 "Apitherapy"[mh] 0

19 (honey OR honeys OR hy1 OR y9h1v576fh OR "8028" OR apitherap* OR actibalm* OR actilite* OR activon* OR algivon* OR mesitran* OR lmesitran* OR manuka* OR medihoney* OR melladerm* OR melloxy* OR revamil* OR surgihoney*) 3

20 "Iodine"[mhe] 14

21 "Iodine Compounds"[mhe] 3

22 (iodin* OR cadexomeriodine* OR iodate* OR iodide* OR iodium* OR iodophor* OR iodopovidone* OR iosal* OR jodium* OR povidoneiodine* OR pvp OR pvpi OR "25655" OR 85h0hzu99m OR 9679tc07x4 OR "7553" OR "94820" OR inadine* OR iodoflex* OR iodisorb* OR povitulle*) 54

23 "Biguanides"[mh] 0

24 (polyhex* OR polihex* OR hexamethylene* OR hexanide* OR phmb* OR "28757" OR "32289" OR 322u039gmf OR 4xi6112496 OR activheal* OR celludress* OR kendall* OR prontosan* OR suprasorb*) 6

25 "Silver"[mh] 11

26 "Silver Compounds"[mhe] 3

27 "Silver Sulfadiazine"[mh] 0

28 "Silver Proteins"[mh] 0

29 (silver* OR agnp OR agnps OR argenti OR argentum OR nanosilver* OR ssd OR ssds OR "22199" OR "231-131" OR "24342" OR 3m4g523w1g OR "41034" OR "7440" OR "7761" OR "7783" OR 95it3w8jze OR w46jy43ejr OR acticoat* OR actisorb* OR algicell* OR algisite* OR allevyn* OR aquacel* OR askina* OR atrauman* OR biatain* OR durafiber* OR exufiber* OR granufoam* OR kerracel* OR kerracontact* OR melgisorb* OR mepilex* OR polymem* OR sorbsan* OR tegaderm* OR urgoclean* OR urgisorb* OR urgotul*) 43

30 "Alginate"[mh] 1

31 (alginogel* OR algino OR algin OR alginic OR alginat* OR polymannur* OR mannur* OR flaminol*) 5

32 "Chitosan"[mh] 0

33 (chitosan* OR deacetyl* OR nanochitosan* OR poliglusal* OR "9012" OR "42617" OR "87582" OR 82lks4qv2y OR maxicel*) 0

34 (octenidine* OR las189962 OR "las-189962" OR "71251" OR "70775" OR "274-861" OR "86767" OR oze0372s5a OR u84956nu4b OR r337868tdw OR octenilin*) 1

35 #34 OR #33 OR #32 OR #31 OR #30 OR #29 OR #28 OR #27 OR #26 OR #25 OR #24 OR #23 OR #22 OR #21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 153

36 #11 AND #6 21

37 #35 AND #6 6
38 #37 OR #36 24

Search note:

- It is not possible to search on terms of less than 3 characters in the HTA Database (attempting to do so just results in the message "Sorry please make your search terms a minimum of 3 characters"). The following terms from the MEDLINE search strategy were therefore not included in the HTA Database translation: cu, ag, hy 1.
- The following search terms were retained in the strategy: "55-56-1" OR "56-95-1" (search line 13). Both terms return zero records and retaining or removing the terms had no impact on the number of returned records for line 13.

A.8: Source: NHS Economic Evaluation Database (NHS EED)

Interface / URL: <https://www.crd.york.ac.uk/CRDWeb>

Database coverage dates: Information not found. Bibliographic records were published on NHS EED until 31st March 2015. Searches of MEDLINE, Embase, CINAHL, PsycINFO and PubMed were continued until the end of the 2014.

Search date: 02/08/2024

Retrieved records: 23

Search strategy:

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1 (MeSH DESCRIPTOR Leg Ulcer) 86
2 (MeSH DESCRIPTOR Lower Extremity) 116
3 (MeSH DESCRIPTOR Leg) 139
4 (MeSH DESCRIPTOR ankle) 34
5 (MeSH DESCRIPTOR knee) 36
6 (MeSH DESCRIPTOR Varicose Ulcer) 61
7 (((leg OR legs OR acuris OR crural OR cruris OR ankle* OR calf OR calves OR gaiter*
OR knee OR knees OR shin OR shins OR extremit* OR limb OR limbs OR stasis OR varicos*
OR varix OR vein* OR venous OR vascul* OR lymphedem* OR lymphoedem* OR phlebolymph*)
ADJ10 (ulcer* OR ulcus OR bed sore* OR decubital OR decubitus OR sore OR sores))) 261
8 (((ulcer* OR ulcus OR bed sore* OR decubital OR decubitus OR sore OR sores) ADJ10
(leg OR legs OR acuris OR crural OR cruris OR ankle* OR calf OR calves OR gaiter* OR knee
OR knees OR shin OR shins OR extremit* OR limb OR limbs OR stasis OR varicos* OR varix
OR vein* OR venous OR vascul* OR lymphedem* OR lymphoedem* OR phlebolymph*)))
142
9 ((leg OR legs OR acuris OR crural OR cruris OR ankle* OR calf OR calves OR gaiter*
OR knee OR knees OR shin OR shins OR extremit* OR limb OR limbs OR stasis OR varicos*
OR varix OR vein* OR venous OR vascul* OR lymphedem* OR lymphoedem* OR phlebolymph*)
AND ((chronic* OR long term OR long lasting OR long lasting) ADJ6 (lesion OR
lesions OR wound OR wounds))) 73
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10 ((leg OR legs OR acuris OR crural OR cruris OR ankle* OR calf OR calves OR gaiter* OR knee OR knees OR shin OR shins OR extremity* OR limb OR limbs OR stasis OR varicos* OR varix OR vein* OR venous OR vascul* OR lymphedem* OR lymphoedem* OR phlebolymph*) AND ((lesion OR lesions OR wound OR wounds) ADJ6 (chronic* OR longterm OR long term OR longstanding OR long lasting))) 27

11 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 600

12 (MeSH DESCRIPTOR anti-infective agents) 254

13 (MeSH DESCRIPTOR anti-bacterial agents) 1331

14 (MeSH DESCRIPTOR disinfectants) 28

15 (MeSH DESCRIPTOR antiseptics) 13

16 (MeSH DESCRIPTOR anti-Infective agents, local) 145

17 ((antibacter* OR anti bacter* OR antibiofilm* OR anti biofilm* OR antibiotic* OR anti biotic* OR antiinfect* OR anti infect* OR antimicrob* OR anti microb* OR antimycobacter* OR anti mycobacter* OR antisept* OR anti sep* OR bacteriocid* OR bactericid* OR biocid* OR microbicid*)) 3416

18 (((bacteria* OR microb* OR mycobacteria*) ADJ3 bind*)) 0

19 ((bind* ADJ3 (bacteria* OR microb* OR mycobacteria*))) 0

20 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 3435

21 (MeSH DESCRIPTOR Chlorhexidine) 96

22 (((chlorhex* OR chlorohex* OR clohex* OR clorhex* OR mk 412a OR mk412a OR chg OR chx OR 18472-51-0 OR 200-238-7 OR 242-354-0 OR 36466-50-9 OR 3697-42-5 OR 55-56-1 OR 56-95-1 OR 5908zuf22y OR 74194-72-2 OR e64xl9u38k OR mor84mud8e OR r4ko0dy52l))) 183

23 (MeSH DESCRIPTOR Copper) 4

24 (((copper* OR cuprum metallicum OR nanocopper* OR cu OR cuo OR cuonp OR cuonps OR nanocuo OR nanocuos OR 1344-70-3 OR 15158-11-9 OR 231-159-6 OR 7440-50-8 OR 789u1901c5 OR medcu*))) 103

25 (((dialkyl* OR dacc OR sorbact*))) 0

26 (MeSH DESCRIPTOR Honey) 10

27 (MeSH DESCRIPTOR Apitherapy) 0

28 (((honey OR honeys OR hy1 OR hy 1 OR y9h1v576fh OR 8028-66-8 OR apitherap* OR actibalm* OR actilite* OR activon* OR algivon* OR mesitran* OR lmesitran* OR manuka* OR medihoney* OR melladerm* OR melloxy* OR revamil* OR surgihoney*))) 34

29 (MeSH DESCRIPTOR Iodine EXPLODE ALL TREES) 85

30 (MeSH DESCRIPTOR Iodine Compounds EXPLODE ALL TREES) 32

31 (((iodin* OR cadexomeriodine* OR iodate* OR iodide* OR iodium* OR iodophor* OR iodopovidone* OR iosal* OR jodium* OR povidoneiodine* OR pvp-i OR pvpi OR 25655-41-8 OR 85h0hzu99m OR 9679tc07x4 OR 7553-56-2 OR 94820-09-4 OR inadine* OR iodoflex* OR iodosorb* OR povitulle*))) 240

32 (MeSH DESCRIPTOR Biguanides) 4

33 ((polyhexamethylene* or poly hexamethylene* or polihexamethylene* OR poly hexamethylene* OR polyhexanide* OR poly hexanide* OR polihexanide* or poly hexanide* OR

phmb* OR 28757-47-3 OR 32289-58-0 OR 322u039gmf OR 4xi6112496 OR activheal* OR celludress* OR kendall* amd* OR prontosan* OR suprasorb*)) 4

34 (MeSH DESCRIPTOR Silver)25

35 (MeSH DESCRIPTOR Silver Compounds EXPLODE ALL TREES)24

36 (MeSH DESCRIPTOR Silver Sulfadiazine) 23

37 (MeSH DESCRIPTOR Silver Proteins) 0

38 (((silver* OR ag OR agnp OR agnps OR argenti OR argentum OR nanosilver* OR ssd OR ssds OR 22199-08-2 OR 231-131-3 OR 24342-30-1 OR 3m4g523w1g OR 41034-18-8 OR 7440-22-4 OR 7761-88-8 OR 7783-90-6 OR 95it3w8jze OR w46jy43ejr OR acticoat* OR actisorb* OR algicell* OR algisite* OR allevyn* OR aquacel* OR askina* OR atrauman* OR biatain* OR durafiber* OR exufiber* OR granufoam* OR kerracel* OR kerracontact* OR melgisorb* OR mepilex* OR polymem* OR sorbsan* OR tegaderm* OR urgoclean* OR urgorsorb* OR urgotul*)) 760

39 (MeSH DESCRIPTOR Alginates) 9

40 (((alginogel* OR alginogel OR algin OR alginic OR alginat* OR polymannur* OR mannur* OR flaminol*)) 49

41 (MeSH DESCRIPTOR Chitosan) 2

42 (((chitosan* OR deacetyl* OR nanochitosan* OR poliglucan* OR 9012-76-4 OR 42617-20-9 OR 87582-10-3 OR 82lks4qv2y OR maxioceal*)) 12

43 (((octenidine* OR las189962 OR las-189962 OR 71251-02-0 OR 70775-75-6 OR 274-861-8 OR 86767-75-1 OR oze0372s5a OR u84956nu4b OR r337868tdw OR octenilol*))3

44 #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 1268

45 #11 AND #20 51

46 #11 AND #44 39

47 #45 OR #46 67

48 (#47) IN NHSEED 23

A.9: Source: Conference Proceedings Citation Index – Science (CPCI-S)

Interface / URL: Web of Science

Database coverage dates: 1990 to present

Search date: 03/08/2024

Retrieved records: 66

Search strategy:

The 'Advanced Search Query Builder' interface was used.

'Exact search' was selected for all searches

- 1 TS=(lower NEAR/3 (extremity* OR limb OR limbs) NEAR/10 ((chronic* OR longterm OR "long term" OR longlasting OR "long lasting") NEAR/6 (lesion OR lesions OR wound OR wounds))) Editions: WOS.ISTP Web of Science Core Collection 14
- 2 TS=(lower NEAR/3 (extremity* OR limb OR limbs) NEAR/10 (bedsore* OR decubital OR decubitus OR sore OR sores)) Editions: WOS.ISTP Web of Science Core Collection 3
- 3 TS=(lower NEAR/3 (extremity* OR limb OR limbs) NEAR/10 (ulcer* OR ulcer*)) Editions: WOS.ISTP Web of Science Core Collection 143
- 4 TS=((ankle* OR calf OR calves OR gaiter* OR knee OR knees OR shin OR shins) NEAR/10 ((chronic* OR longterm OR "long term" OR longlasting OR "long lasting") NEAR/6 (lesion OR lesions OR wound OR wounds))) Editions: WOS.ISTP Web of Science Core Collection 6
- 5 TS=((ankle* OR calf OR calves OR gaiter* OR knee OR knees OR shin OR shins) NEAR/10 (bedsore* OR decubital OR decubitus OR sore OR sores)) Editions: WOS.ISTP Web of Science Core Collection 5
- 6 TS=((ankle* OR calf OR calves OR gaiter* OR knee OR knees OR shin OR shins) NEAR/10 (ulcer* OR ulcer*)) Editions: WOS.ISTP Web of Science Core Collection 71
- 7 TS=((acuris OR crural OR cruris) NEAR/10 ((chronic* OR longterm OR "long term" OR longlasting OR "long lasting") NEAR/6 (lesion OR lesions OR wound OR wounds))) Editions: WOS.ISTP Web of Science Core Collection 1
- 8 TS=((acuris OR crural OR cruris) NEAR/10 (bedsore* OR decubital OR decubitus OR sore OR sores)) Editions: WOS.ISTP Web of Science Core Collection 0
- 9 TS=((acuris OR crural OR cruris) NEAR/10 (ulcer* OR ulcer*)) Editions: WOS.ISTP Web of Science Core Collection 20
- 10 TS=((leg OR legs) NEAR/10 ((chronic* OR longterm OR "long term" OR longlasting OR "long lasting") NEAR/6 (lesion OR lesions OR wound OR wounds))) Editions: WOS.ISTP Web of Science Core Collection 28
- 11 TS=((leg OR legs) NEAR/10 (bedsore* OR decubital OR decubitus OR sore OR sores)) Editions: WOS.ISTP Web of Science Core Collection 7
- 12 TS=((leg OR legs) NEAR/10 (ulcer* OR ulcer*)) Editions: WOS.ISTP Web of Science Core Collection 565
- 13 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 Editions: WOS.ISTP Web of Science Core Collection 787
- 14 TS=((lymphedema* OR lymphoedema* OR phlebolymp*) NEAR/10 ((chronic* OR longterm OR "long term" OR longlasting OR "long lasting") NEAR/6 (lesion OR lesions OR wound OR wounds))) Editions: WOS.ISTP Web of Science Core Collection 3
- 15 TS=((lymphedema* OR lymphoedema* OR phlebolymp*) NEAR/10 (bedsore* OR decubital OR decubitus OR sore OR sores)) Editions: WOS.ISTP Web of Science Core Collection 0
- 16 TS=((lymphedema* OR lymphoedema* OR phlebolymp*) NEAR/10 (ulcer* OR ulcer*)) Editions: WOS.ISTP Web of Science Core Collection 6

- 17 TS=(vascul* NEAR/10 ((chronic* OR longterm OR "long term" OR longlasting OR "long lasting") NEAR/6 (lesion OR lesions OR wound OR wounds))) Editions: WOS.ISTP Web of Science Core Collection 57
- 18 TS=(vascul* NEAR/10 (bedsore* OR decubital OR decubitus OR sore OR sores)) Editions: WOS.ISTP Web of Science Core Collection 1
- 19 TS=(vascul* NEAR/10 (ulcer* OR ulcus)) Editions: WOS.ISTP Web of Science Core Collection 189
- 20 TS=((stasis OR varicos* OR varix OR vein* OR venous) NEAR/10 ((chronic* OR longterm OR "long term" OR longlasting OR "long lasting") NEAR/6 (lesion OR lesions OR wound OR wounds))) Editions: WOS.ISTP Web of Science Core Collection 60
- 21 TS=((stasis OR varicos* OR varix OR vein* OR venous) NEAR/10 (bedsore* OR decubital OR decubitus OR sore OR sores)) Editions: WOS.ISTP Web of Science Core Collection 9
- 22 TS=((stasis OR varicos* OR varix OR vein* OR venous) NEAR/10 (ulcer* OR ulcus)) Editions: WOS.ISTP Web of Science Core Collection 700
- 23 #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 Editions: WOS.ISTP Web of Science Core Collection 949
- 24 #13 OR #23 Editions: WOS.ISTP Web of Science Core Collection 1372
- 25 TS=(chlorhex* OR chlorohex* OR clohex* OR clorhex* OR "mk 412a" OR mk412a OR chg OR chx OR 18472-51-0 OR 200-238-7 OR 242-354-0 OR 36466-50-9 OR 3697-42-5 OR 55-56-1 OR 56-95-1 OR 5908zuf22y OR 74194-72-2 OR e64xl9u38k OR mor84mud8e OR r4ko0dy52l) Editions: WOS.ISTP Web of Science Core Collection 988
- 26 TS=(copper* OR "cuprum metallicum" OR nanocopper* OR cu OR cuo OR cuonp OR cuonps OR nanocuo OR nanocuos OR 1344-70-3 OR 15158-11-9 OR 231-159-6 OR 7440-50-8 OR 789u1901c5 OR medcu*) Editions: WOS.ISTP Web of Science Core Collection 131459
- 27 TS=(dialkyl* OR dacc OR sorbact*) Editions: WOS.ISTP Web of Science Core Collection 1298
- 28 TS=(honey OR honeys OR hy1 OR "hy 1" OR y9h1v576fh OR 8028-66-8 OR apitherap* OR actibalm* OR actilite* OR activon* OR algivon* OR l-mesitran* OR lmesitran* OR manuka* OR medihoney* OR melladerm* OR melloxy* OR revamil* OR surgihoney*) Editions: WOS.ISTP Web of Science Core Collection 2699
- 29 TS=(iodin* OR cadexomeriodine* OR iodate* OR iodide* OR iodium* OR iodophor* OR iodopovidone* OR iosal* OR jodium* OR povidoneiodine* OR pvp-i OR pvpi OR 25655-41-8 OR 85h0hzu99m OR 9679tc07x4 OR 7553-56-2 OR 94820-09-4 OR inadine* OR iodoflex* OR iodosorb* OR povitulle*) Editions: WOS.ISTP Web of Science Core Collection 13530
- 30 TS=(polyhexamethylene* OR "poly hexamethylene*" OR polihexamethylene* OR "poli hexamethylene*" OR polyhexanide* OR "poly hexanide*" OR polihexanide* OR "poli hexanide*" OR phmb* OR 28757-47-3 OR 32289-58-0 OR 322u039gmf OR 4xi6112496 OR activheal* OR celludress* OR "kendall* amd*" OR prontosan* OR suprasorb*) Editions: WOS.ISTP Web of Science Core Collection 113

- 31 TS=(silver* OR ag OR agnp OR agnps OR argenti OR argentum OR nanosilver* OR ssd OR ssds OR 22199-08-2 OR 231-131-3 OR 24342-30-1 OR 3m4g523w1g OR 41034-18-8 OR 7440-22-4 OR 7761-88-8 OR 7783-90-6 OR 95it3w8jze OR w46jy43ejr OR acticoat* OR actisorb* OR algicell* OR algisite* OR allevyn* OR aquacel* OR askina* OR atrauman* OR biatain* OR durafiber* OR exufiber* OR granufoam* OR kerracel* OR kerracontact* OR melgisorb* OR mepilex* OR polymem* OR sorbsan* OR tegaderm* OR urgoclean* OR urgisorb* OR urgotul*) Editions: WOS.ISTP Web of Science Core Collection 63519
- 32 TS=(alginogel* OR alginol OR algin OR alginic OR alginat* OR polymannur* OR mannur* OR flaminal*) Editions: WOS.ISTP Web of Science Core Collection 3403
- 33 TS=(chitosan* OR deacetyl* OR nanochitosan* OR poliglusam* OR 9012-76-4 OR 42617-20-9 OR 87582-10-3 OR 82lks4qv2y OR maxicel*) Editions: WOS.ISTP Web of Science Core Collection 9536
- 34 TS=(octenidine* OR las189962 OR las-189962 OR 71251-02-0 OR 70775-75-6 OR 274-861-8 OR 86767-75-1 OR oze0372s5a OR u84956nu4b OR r337868tdw OR octenilin*) Editions: WOS.ISTP Web of Science Core Collection 11
- 35 #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 Editions: WOS.ISTP Web of Science Core Collection 213573
- 36 #24 AND #35 Editions: WOS.ISTP Web of Science Core Collection 33
- 37 TS=((antibacter* OR "anti bacter*" OR antibiofilm* OR "anti biofilm*" OR antibiotic* OR "anti biotic*" OR antiinfect* OR "anti infect*" OR antimicrob* OR "anti microb*" OR antimycobacter* OR "anti mycobacter*" OR antisept* OR "anti sept*" OR bacteriocid* OR bactericid* OR biocid* OR microbicid*)) Editions: WOS.ISTP Web of Science Core Collection 40762
- 38 TS=((bacteria* OR microb* OR mycobacteria*) NEAR/3 bind*) Editions: WOS.ISTP Web of Science Core Collection 419
- 39 #37 OR #38 Editions: WOS.ISTP Web of Science Core Collection 41122
- 40 #24 AND #39 Editions: WOS.ISTP Web of Science Core Collection 47
- 41 #36 OR #40 and English (Languages) Editions: WOS.ISTP Web of Science Core Collection 66

A.10: Source: ClinicalTrials.gov

Interface / URL: <https://clinicaltrials.gov/>

Database coverage dates: Information not found. ClinicalTrials.gov was created as a result of the Food and Drug Administration Modernization Act of 1997 (FDAMA). The site was made available to the public in February 2000.

Search date: 01/08/2024

Retrieved records: 227

Search strategy:

The following 10 searches were conducted separately.

The home page interface at the above URL was used. For each search, the population terms were entered into the 'Condition/disease' search box and the intervention terms were entered into the 'Intervention/treatment' search box.

The results from each search were downloaded as an individual set. The total number of retrieved records (above) represents the sum of all searches, and includes duplicates caused by the same record being retrieved in different searches.

Search 1:

(leg OR legs OR acuris OR crural OR cruris OR ankle OR ankles OR calf OR calves OR gaiter OR gaiters OR knee OR knees OR shin OR shins OR extremity OR extremities OR limb OR limbs OR stasis OR varicosis OR varicoses OR varix OR vein OR veins OR venous OR vascular OR vasculitic OR lymphedema OR lymphedemas OR lymphedemic OR lymphoedema OR lymphoedemas OR lymphoedemic OR phlebolymphe¹edema OR phlebolymphe¹edemas OR phlebolymphe¹edemic OR phlebolymphe¹oedema OR phlebolymphe¹oedemas OR phlebolymphe¹oedemic) AND (ulcer OR ulcers OR ulcerate OR ulcerating OR ulceration OR ulcerations OR ulcer OR bed²sore OR bed²sores OR decubital OR decubitus OR sore OR sores OR lesion OR lesions OR wound OR wounds)

(chlorhexidine OR chlorhexidin OR chlorohexidine OR chlorohexy¹dine OR clohexidine OR clorhexidine OR chlorhexidin¹ium OR "mk 412a" OR mk412a OR chg OR chx OR "18472-51-0" OR "200-238-7" OR "242-354-0" OR "36466-50-9" OR "3697-42-5" OR "55-56-1" OR "56-95-1" OR 5908zuf22y OR "74194-72-2" OR e64xl9u38k OR mor84mud8e OR r4ko0dy52l)

= 23 results

Search 2:

(leg OR legs OR acuris OR crural OR cruris OR ankle OR ankles OR calf OR calves OR gaiter OR gaiters OR knee OR knees OR shin OR shins OR extremity OR extremities OR limb OR limbs OR stasis OR varicosis OR varicoses OR varix OR vein OR veins OR venous OR vascular OR vasculitic OR lymphedema OR lymphedemas OR lymphedemic OR lymphoedema OR lymphoedemas OR lymphoedemic OR phlebolymphe¹edema OR phlebolymphe¹edemas OR phlebolymphe¹edemic OR phlebolymphe¹oedema OR phlebolymphe¹oedemas OR phlebolymphe¹oedemic) AND (ulcer OR ulcers OR ulcerate OR ulcerating OR ulceration OR ulcerations OR ulcer OR bed²sore OR bed²sores OR decubital OR decubitus OR sore OR sores OR lesion OR lesions OR wound OR wounds)

(copper OR coppers OR "cuprum metallicum" OR nanocopper OR nanocoppers OR cu OR cuo OR cuonp OR cuonps OR nanocuo OR nanocu¹os OR "1344-70-3" OR "15158-11-9" OR "231-159-6" OR "7440-50-8" OR 789u1901c5 OR medcu OR medcuR OR medcuTM)

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= 5 results

Search 3:

(leg OR legs OR acuris OR crural OR cruris OR ankle OR ankles OR calf OR calves OR gaiter OR gaiters OR knee OR knees OR shin OR shins OR extremity OR extremities OR limb OR limbs OR stasis OR varicosis OR varicoses OR varix OR vein OR veins OR venous OR vascular OR vasculitic OR lymphedema OR lymphedemas OR lymphedemic OR lymphoedema OR lymphoedemas OR lymphoedemic OR phlebolymphedema OR phlebolymphedemas OR phlebolymphedemic OR phlebolymphoedema OR phlebolymphoedemas OR phlebolymphoedemic) AND (ulcer OR ulcers OR ulcerate OR ulcerating OR ulceration OR ulcerations OR ulcer OR bedsore OR bedsores OR decubital OR decubitus OR sore OR sores OR lesion OR lesions OR wound OR wounds)

(dialkyl OR dialkylcarb OR dialkylcarbamoyl OR dialkylcarbamoylchloride OR dialkylcarbamoylchlorides OR dacc OR sorbact OR sorbactR OR sorbactTM)

= 6 results

Search 4:

(leg OR legs OR acuris OR crural OR cruris OR ankle OR ankles OR calf OR calves OR gaiter OR gaiters OR knee OR knees OR shin OR shins OR extremity OR extremities OR limb OR limbs OR stasis OR varicosis OR varicoses OR varix OR vein OR veins OR venous OR vascular OR vasculitic OR lymphedema OR lymphedemas OR lymphedemic OR lymphoedema OR lymphoedemas OR lymphoedemic OR phlebolymphedema OR phlebolymphedemas OR phlebolymphedemic OR phlebolymphoedema OR phlebolymphoedemas OR phlebolymphoedemic) AND (ulcer OR ulcers OR ulcerate OR ulcerating OR ulceration OR ulcerations OR ulcer OR bedsore OR bedsores OR decubital OR decubitus OR sore OR sores OR lesion OR lesions OR wound OR wounds)

(honey OR honeys OR hy1 OR "hy 1" OR y9h1v576fh OR "8028-66-8" OR apitherapy OR apitherapies OR actibalm OR actilite OR activon OR algivon OR "I-mesitran" OR Imesitran OR manuka OR manukapli OR medihoney OR melladerm OR melloxy OR revamil OR surgihoney OR surgihoneyro OR actibalmR OR actiliteR OR activonR OR algivonR OR "I-mesitranR" OR ImesitranR OR manukaR OR manukapliR OR medihoneyR OR melladermR OR melloxyR OR revamilR OR surgihoneyR OR surgihoneyroR OR actibalmTM OR actiliteTM OR activonTM OR algivonTM OR "I-mesitranTM" OR ImesitranTM OR manukaTM OR manukapliTM OR medihoneyTM OR melladermTM OR melloxyTM OR revamilTM OR surgihoneyTM OR surgihoneyroTM)

= 7 results

Search 5:

(leg OR legs OR acuris OR crural OR cruris OR ankle OR ankles OR calf OR calves OR gaiter OR gaiters OR knee OR knees OR shin OR shins OR extremity OR extremities OR limb OR limbs OR stasis OR varicosis OR varicoses OR varix OR vein OR veins OR venous OR vascular OR vasculitic OR lymphedema OR lymphedemas OR lymphedemic OR lymphoedema OR lymphoedemas OR lymphoedemic OR phlebolymphedema OR phlebolymphedemas OR phlebolymphedemic OR phlebolymphoedema OR phlebolymphoedemas OR phlebolymphoedemic) AND (ulcer OR ulcers OR ulcerate OR ulcerating OR ulceration OR ulcerations OR ulcer OR bed sore OR bedsores OR decubital OR decubitus OR sore OR sores OR lesion OR lesions OR wound OR wounds)

(iodin OR iodine OR iodines OR cadexomeriodine OR cadexomeriodines OR iodate OR iodates OR iodide OR iodides OR iodium OR iodiums OR iodophor OR iodophors OR iodopovidone OR iodopovidones OR iosal OR jodium OR jodiums OR povidoneiodine OR povidoneiodines OR "pvp-i" OR pvpi OR "25655-41-8" OR 85h0hzu99m OR 9679tc07x4 OR "7553-56-2" OR "94820-09-4" OR inadine OR iodoflex OR iodisorb OR povitulle OR inadineR OR iodoflexR OR iodisorbR OR povitulleR OR inadineTM OR iodoflexTM OR iodisorbTM OR povitulleTM)

= 30 results

Search 6:

(leg OR legs OR acuris OR crural OR cruris OR ankle OR ankles OR calf OR calves OR gaiter OR gaiters OR knee OR knees OR shin OR shins OR extremity OR extremities OR limb OR limbs OR stasis OR varicosis OR varicoses OR varix OR vein OR veins OR venous OR vascular OR vasculitic OR lymphedema OR lymphedemas OR lymphedemic OR lymphoedema OR lymphoedemas OR lymphoedemic OR phlebolymphedema OR phlebolymphedemas OR phlebolymphedemic OR phlebolymphoedema OR phlebolymphoedemas OR phlebolymphoedemic) AND (ulcer OR ulcers OR ulcerate OR ulcerating OR ulceration OR ulcerations OR ulcer OR bed sore OR bedsores OR decubital OR decubitus OR sore OR sores OR lesion OR lesions OR wound OR wounds)

(polyhexamethylene OR polyhexamethylenes OR "poly hexamethylene" OR "poly hexamethylenes" OR polyhexamethylenebiguanide OR "poly hexamethylenebiguanide" OR polyhexamethylenebiguanides OR "poly hexamethylenebiguanides" OR polihexamethylene OR polihexamethylenes OR "poli hexamethylene" OR "poli hexamethylenes" OR polihexamethylenebiguanide OR "poli hexamethylenebiguanide" OR polihexamethylenebiguanides OR "poli hexamethylenebiguanides" OR polyhexanide OR

polyhexanides OR "poly hexanide" OR "poly hexanides" OR polihexanide OR polihexanides OR "poli hexanide" OR "poli hexanides" OR phmb OR phmbS OR "28757-47-3" OR "32289-58-0" OR 322u039gmf OR 4xi6112496 OR activheal OR celludress OR kendall OR prontosan OR suprasorb OR activhealR OR celludressR OR kendallR OR prontosanR OR suprasorbR OR activhealTM OR celludressTM OR kendallTM OR prontosanTM OR suprasorbTM)

= 22 results

Search 7.

(leg OR legs OR acuris OR crural OR cruris OR ankle OR ankles OR calf OR calves OR gaiter OR gaiters OR knee OR knees OR shin OR shins OR extremity OR extremities OR limb OR limbs OR stasis OR varicosis OR varicoses OR varix OR vein OR veins OR venous OR vascular OR vasculitic OR lymphedema OR lymphedemas OR lymphedemic OR lymphoedema OR lymphoedemas OR lymphoedemic OR phlebolymphe'dema OR phlebolymphe'demas OR phlebolymphe'demic OR phlebolymphe'dema OR phlebolymphe'demas OR phlebolymphe'demic) AND (ulcer OR ulcers OR ulcerate OR ulcerating OR ulceration OR ulcerations OR ulcer OR bed sore OR bed sores OR decubital OR decubitus OR sore OR sores OR lesion OR lesions OR wound OR wounds)

(silver OR silvers OR ag OR agnp OR agnps OR argenti OR argentum OR nanosilver OR nanosilvers OR ssd OR ssds OR "22199-08-2" OR "231-131-3" OR "24342-30-1" OR 3m4g523w1g OR "41034-18-8" OR "7440-22-4" OR "7761-88-8" OR "7783-90-6" OR 95it3w8jze OR w46jy43ejr OR acticoat OR actisorb OR algicell OR algisite OR allevyn OR aquacel OR askina OR atrauman OR biatain OR durafiber OR exufiber OR granufoam OR kerracel OR kerracontact OR melgisorb OR mepilex OR polymem OR silvercel OR silverlon OR sorbsan OR "tegaderm alginate" OR urgoclean OR urgisorb OR urgotul OR acticoatR OR actisorbR OR algicellR OR algisiteR OR allevynR OR aquacelR OR askinaR OR atraumanR OR biatainR OR durafiberR OR exufiberR OR granufoamR OR kerracelR OR kerracontactR OR melgisorbR OR mepilexR OR polymemR OR silvercelR OR silverlonR OR sorbsanR OR "tegaderm alginateR" OR "tegadermR alginate" OR "tegadermR alginateR" OR urgocleanR OR urgisorbR OR urgotulR OR acticoatTM OR actisorbTM OR algicellTM OR algisiteTM OR allevynTM OR aquacelTM OR askinaTM OR atraumanTM OR biatainTM OR durafiberTM OR exufiberTM OR granufoamTM OR kerracelTM OR kerracontactTM OR melgisorbTM OR mepilexTM OR polymemTM OR silvercelTM OR silverlonTM OR sorbsanTM OR "tegaderm alginateTM" OR "tegadermTM alginate" OR "tegadermTM alginateTM" OR urgocleanTM OR urgisorbTM OR urgotulTM)

= 109 results

Search 8:

External assessment group report: Topical antimicrobial dressings for infected leg ulcers in people aged 16 and over

Date: August 2024

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(leg OR legs OR acuris OR crural OR cruris OR ankle OR ankles OR calf OR calves OR gaiter OR gaiters OR knee OR knees OR shin OR shins OR extremity OR extremities OR limb OR limbs OR stasis OR varicosis OR varicoses OR varix OR vein OR veins OR venous OR vascular OR vasculitic OR lymphedema OR lymphedemas OR lymphedemic OR lymphoedema OR lymphoedemas OR lymphoedemic OR phlebolymphe¹dema OR phlebolymphe¹demas OR phlebolymphe¹demic OR phlebolymphe¹oedema OR phlebolymphe¹oedemas OR phlebolymphe¹oedemic) AND (ulcer OR ulcers OR ulcerate OR ulcerating OR ulceration OR ulcerations OR ulcer OR ulcers OR bedsore OR bedsores OR decubital OR decubitus OR sore OR sores OR lesion OR lesions OR wound OR wounds)

((alginogel OR alginogels OR "algino gel" OR "algino gels" OR ((biocatalyst OR biocatalysts OR catalyst OR catalysts OR enzyme OR enzymes) AND (algin OR alginic OR alginate OR alginates OR polymannuronate OR polymannuronates OR polymannuronic OR "poly mannuronate" OR "poly mannuronates" OR "poly mannuronic")) OR (glucose AND oxidase) OR (glucose AND oxidases) OR "glucose aerodehydrogenase" OR "glucose oxygen oxidoreductase" OR "glucose oxyhydrase" OR glucosoxidase OR god OR gox OR microcid OR notatin OR lactoperoxidase OR lactoperoxydase OR lactoperoxidases OR lactoperoxydases OR ((algin OR alginic OR alginate OR alginates OR polymannuronate OR polymannuronates OR polymannuronic OR "poly mannuronate" OR "poly mannuronates" OR "poly mannuronic") AND (gel OR gels OR hydrogel OR hydrogels)) OR flaminol OR flaminolR OR flaminolTM))

= 14 results

Search 9:

(leg OR legs OR acuris OR crural OR cruris OR ankle OR ankles OR calf OR calves OR gaiter OR gaiters OR knee OR knees OR shin OR shins OR extremity OR extremities OR limb OR limbs OR stasis OR varicosis OR varicoses OR varix OR vein OR veins OR venous OR vascular OR vasculitic OR lymphedema OR lymphedemas OR lymphedemic OR lymphoedema OR lymphoedemas OR lymphoedemic OR phlebolymphe¹dema OR phlebolymphe¹demas OR phlebolymphe¹demic OR phlebolymphe¹oedema OR phlebolymphe¹oedemas OR phlebolymphe¹oedemic) AND (ulcer OR ulcers OR ulcerate OR ulcerating OR ulceration OR ulcerations OR ulcer OR ulcers OR bedsore OR bedsores OR decubital OR decubitus OR sore OR sores OR lesion OR lesions OR wound OR wounds)

(chitosan OR chitosans OR deacetylchitin OR deacetylchitins OR "deacetylated chitin" OR "deacetylated chitins" OR nanochitosan OR nanochitosans OR poliglucosam OR poliglucosams OR "9012-76-4" OR "42617-20-9" OR "87582-10-3" OR 82lks4qv2y OR maxicel OR maxicelR OR maxicelTM)

= 9 results

Search 10:

(leg OR legs OR acuris OR crural OR cruris OR ankle OR ankles OR calf OR calves OR gaiter OR gaiters OR knee OR knees OR shin OR shins OR extremity OR extremities OR limb OR limbs OR stasis OR varicosis OR varicoses OR varix OR vein OR veins OR venous OR vascular OR vasculitic OR lymphedema OR lymphedemas OR lymphedemic OR lymphoedema OR lymphoedemas OR lymphoedemic OR phlebolymphe¹edema OR phlebolymphe¹edemas OR phlebolymphe¹edemic OR phlebolymphe¹oedema OR phlebolymphe¹oedemas OR phlebolymphe¹oedemic) AND (ulcer OR ulcers OR ulcerate OR ulcerating OR ulceration OR ulcerations OR ulcer OR bed sore OR bed sores OR decubital OR decubitus OR sore OR sores OR lesion OR lesions OR wound OR wounds)

(octenidine OR octenidines OR las189962 OR "las-189962" OR "71251-02-0" OR "70775-75-6" OR "274-861-8" OR "86767-75-1" OR oze0372s5a OR u84956nu4b OR r337868tdw OR octenilin OR octeniline OR octenilinR OR octenilineR OR octenilinTM OR octenilineTM)

= 2 results

Search note:

Reflecting the LSA methods context and review protocol, a pragmatic approach was taken to some elements of strategy translation for ClinicalTrials.gov. This was designed to focus the search on records that were most likely to be relevant, and to reduce the number of irrelevant records for screening. The pragmatic approach included the following:

- The condition concept terms were searched on using the 'Condition/disease' search box.
- The intervention concept terms were searched on using the 'Intervention/treatment' search box.
- The search was designed to retrieve records that referred to the specific eligible agents. It was not designed to retrieve records that only referred to non-specific antimicrobial/bacterial-binding dressings.

The approach was discussed and agreed within the EAG team. Any risk of missing relevant studies was mitigated by additional search activities conducted by the EAG. These included:

- The search of Cochrane Central Register of Controlled Trials (which includes records from ClinicalTrials.gov and WHO ICTRP).
- The check of company submitted evidence.
- The check of the included studies lists of any retrieved relevant systematic reviews published in the last 5 years.

A.11: Source: WHO International Clinical Trials Registry Portal (ICTRP)

Interface / URL: <https://trialsearch.who.int/>

Database coverage dates: Information not found. On the date of search, files had been imported from data providers between 26 June 2024 and 29 July 2024.

Search date: 03/08/2024

Retrieved records: 95

Search strategy:

The following search was conducted using the search interface at the above URL. 'Without Synonyms' was selected for all searches.

(leg OR legs OR acuris OR crural OR cruris OR ankle* OR calf OR calves OR gaiter* OR knee OR knees OR shin OR shins OR extremity* OR limb OR limbs OR stasis OR varicos* OR varix OR vein* OR venous OR vascul* OR lymphedem* OR lymphoedem* OR phlebolymph*) AND (ulcer* OR ulcus OR bedsore* OR decubital OR decubitus OR sore OR sores OR ((chronic* or longterm or "long term" or longlasting or "long lasting")) AND (lesion OR lesions OR wound OR wounds))) AND (chlorhex* OR chlorohex* OR clohex* OR clorhex* OR "mk 412a" OR mk412a OR chg OR chx OR "18472 51 0" OR "200 238 7" OR "242 354 0" OR "36466 50 9" OR "3697 42 5" OR "55 56 1" OR "56 95 1" OR 5908zuf22y OR "74194 72 2" OR e64xl9u38k OR mor84mud8e OR r4ko0dy52l OR copper* OR "cuprum metallicum" OR nanocopper* OR cu OR cuo OR cuonp OR cuonps OR nanocuo OR nanocuos OR "1344 70 3" OR "15158 11 9" OR "231 159 6" OR "7440 50 8" OR 789u1901c5 OR medcu* OR dialkyl* OR dacc OR sorbact* OR honey OR honeys OR hy1 OR "hy 1" OR y9h1v576fh OR "8028 66 8" OR apitherap* OR actibalm* OR actilite* OR activon* OR algivon* OR "l mesitran*" OR lmesitran* OR manuka* OR medihoney* OR melladerm* OR melloxy* OR revamil* OR surgihoney* OR iodine* OR cadexomeriodine* OR iodate* OR iodide* OR iodium* OR iodophor* OR iodopovidone* OR iosal* OR jodium* OR povidoneiodine* OR "pvp i" OR pvpi OR "25655 41 8" OR 85h0hzu99m OR 9679tc07x4 OR "7553 56 2" OR 94820 09 4 OR inadine* OR iodoflex* OR iodosorb* OR povitulle* OR polyhexamethylene* OR "poly hexamethylene*" OR polihexamethylene* OR "poli hexamethylene*" OR polyhexanide* OR "poly hexanide*" OR polihexanide* OR "poli hexanide*" OR phmb* OR "28757 47 3" OR "32289 58 0" OR 322u039gmf OR 4xi6112496 OR activheal* OR celludress* OR "kendall* amd*" OR prontosan* OR suprasorb* OR silver* OR ag OR agnp OR agnps OR argenti OR argentum OR nanosilver* OR ssd OR ssds OR "22199 08 2" OR "231 131 3" OR "24342 30 1" OR 3m4g523w1g OR "41034 18 8" OR "7440 22 4" OR "7761 88 8" OR "7783 90 6" OR 95it3w8jze OR w46jy43ejr OR acticoat* OR actisorb* OR algicell* OR algisite* OR allevyn* OR aquacel* OR askina* OR atrauman* OR biatain* OR durafiber* OR exufiber* OR granufoam* OR kerracel* OR kerracontact* OR melgisorb* OR mepilex* OR polymem* OR sorbsan* OR tegaderm* OR urgoclean* OR urgisorb* OR urgotul* OR alginogel* OR algino OR algin OR alginic OR alginat* OR polymannur* OR mannur* OR flaminol* OR chitosan* OR deacetyl* OR nanochitosan* OR poliglusal* OR "9012 76 4" OR "42617 20 9" OR "87582 10 3" OR 82lks4qv2y OR maxicel* OR octenidine* OR las189962 OR "las 189962" OR "71251 02 0" OR "70775 75 6" OR "274 861 8" OR "86767 75 1" OR oze0372s5a OR u84956nu4b OR r337868tdw OR octenilin*) = 95 (99 records for 95 trials found)

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Search note:

Reflecting the LSA methods context and review protocol, a pragmatic approach was taken to some elements of strategy translation for WHO ICTRP. This was designed to focus the search on records that were most likely to be relevant, and to reduce the number of irrelevant records for screening. The pragmatic approach included the following:

- The search was designed to retrieve records that referred to the specific eligible agents. It was not designed to retrieve records that only referred to non-specific antimicrobial/bacterial-binding dressings.

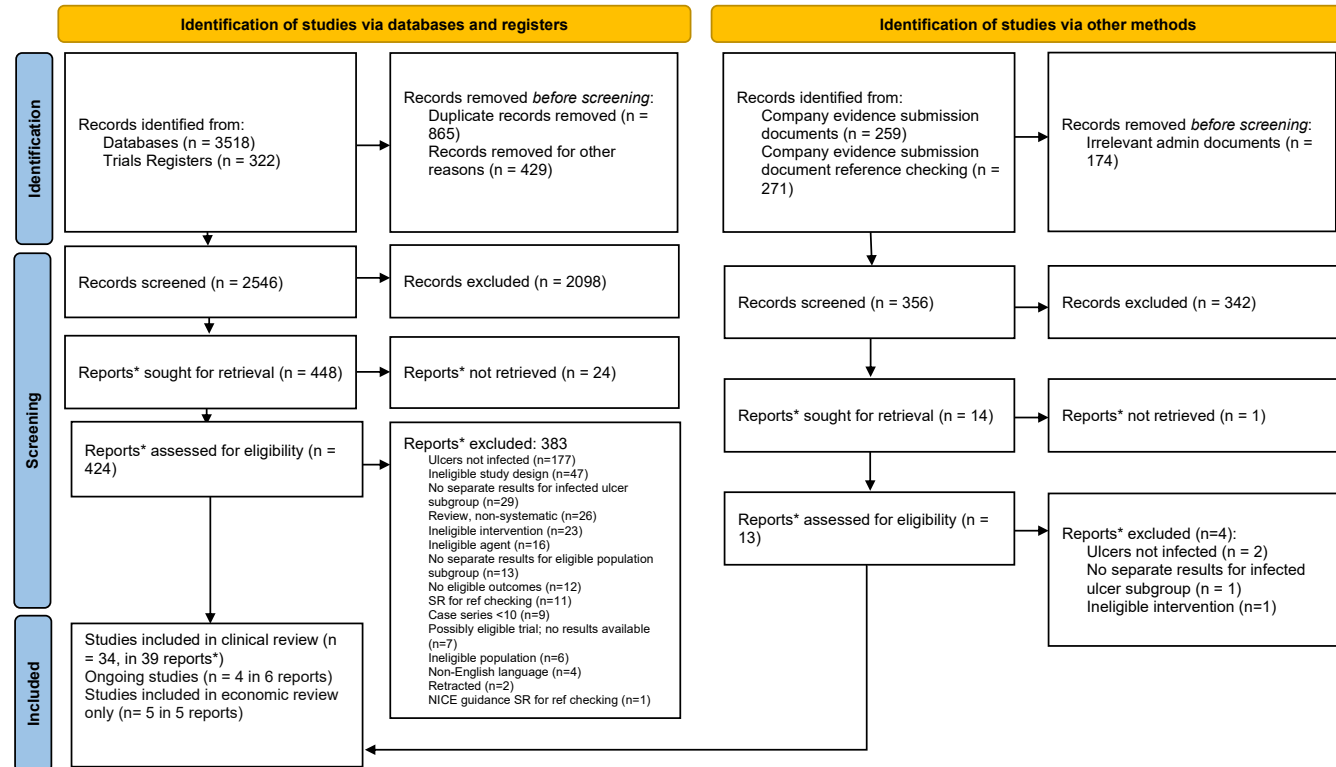
The approach was discussed and agreed within the EAG team. Any risk of missing relevant studies was mitigated by additional search activities conducted by the EAG. These included:

- The search of Cochrane Central Register of Controlled Trials (which includes records from ClinicalTrials.gov and WHO ICTRP).
- The check of company submitted evidence.

The check of the included studies lists of any retrieved relevant systematic reviews published in the last 5 years.

Figure 11.1: PRISMA study selection diagram

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources



*"Note that a "report" could be a journal article, preprint, conference abstract, study register entry, clinical study report, dissertation, unpublished manuscript, government report or any other document providing relevant information": <https://www.bmj.com/content/372/bmj.n71>.

Adapted from: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: <http://www.prisma-statement.org/>

11.2 Appendix B: Excluded studies

Table 10.3: Studies excluded following assessment of a full text (n=412)

Reference	Exclusion reason
Abdollahimajd F, Pourani MR, Mahdavi H, Mirzadeh H, Younespour S, Moravvej H. Efficacy and safety of chitosan-based bio-compatible dressing versus nanosilver (Acticoat(TM)) dressing in treatment of recalcitrant diabetic wounds: a randomized clinical trial. <i>Dermatol Ther.</i> 2022.35(9):e15682. doi: 10.1111/dth.15682	Ineligible intervention
ABIGO Medical AB. Clinical investigation of sorbact® dressings. Identifier: NCT05089890. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2021. Available from https://clinicaltrials.gov/study/NCT05089890 .	Ulcers not infected
Adderley U. The latest evidence for practice. Are silver dressings under compression effective for treating venous leg ulcers? <i>Nursing in Practice: The Journal for Today's Primary Care Nurse.</i> 2011.(58):58-58.	Review, non-systematic
Ahmed N, Khanzada AA, Joyo MR, Afzal T, Keerio NH, Shah GA, et al. The outcome of natural honey used in chronic ulcers. <i>IJPSR.</i> 2021.12(3):1984-89. doi: https://dx.doi.org/10.26452/ijrps.v12i3.4804	Ulcers not infected
Almazan T, Jung J. Treatment of recalcitrant chronic GVHD ulcers using combined silver collagen matrix and silver foam dressings may impact antibiotic resistance and hospitalizations in patients with chronic GVHD. <i>J Am Acad Dermatol.</i> 2016.74(5 SUPPL. 1):AB296.	Case series <10
Alvarez OM, Phillips TJ, Menzoian JO, Patel M, Andriessen A. An RCT to compare a bio-cellulose wound dressing with a non-adherent dressing in VLU. <i>J Wound Care.</i> 2012.21(9):448-53. doi: https://dx.doi.org/10.12968/jowc.2012.21.9.448	Ulcers not infected
Alves M, Chapelon B, Senet P, Cartier H, Bohbot S. Leg ulcers presenting major risk of secondary infection, as seen in outpatient care. Advantages of an absorbent dressing impregnated with silver salts. <i>Journal of Wound, Ostomy and Continence Nursing.</i> 2008.35:S8-S8. doi: 10.1097/01.won.0000319269.38219.e7	Ineligible study design
Andriessen A, Polignano R, Abel M. Monitoring the microcirculation to evaluate dressing performance in patients with venous leg ulcers. <i>J Wound Care.</i> 2009.18(4):145-50. doi: https://dx.doi.org/10.12968/jowc.2009.18.4.41606	Ulcers not infected
Andriessen AE, Eberlein T. Assessment of a wound cleansing solution in the treatment of problem wounds. <i>Wounds: A Compendium of Clinical Research and Practice.</i> 2008.20(6):171-5.	Ulcers not infected
Anonymous. Dressing choice unimportant for leg ulcers. <i>J Natl Med Assoc.</i> 2007.99(12):1422.	Review, non-systematic

Reference	Exclusion reason
Anonymous. Flamazine is nurse prescribable. N2N: Nurse2Nurse. 2002.2(8):39-39.	Ineligible study design
Anonymous. Leg ulcers: topical antibacterial eliminates associated odor. Geriatrics. 1992.47(9):25.	Ineligible agent
Anonymous. Ontario health technology assessment series skin substitutes for adults with diabetic foot ulcers and venous leg ulcers: a health technology assessment. Ont Health Technol Assess Ser. 2021.21(7)	SR for ref checking
Anonymous. Relative clinical and cost effectiveness of superabsorbents for the management of venous leg ulcers in the UK. Wounds UK. 2013.9(2):58-62.	Ineligible study design
Apollonio A, Antignani PL, Di Salvo M, Failla G, Guarnera G, Mosti G, et al. A large Italian observational multicentre study on vascular ulcers of the lower limbs (studio ulcere vascolari). Int Wound J. 2016.13(1):27-34. doi: https://dx.doi.org/10.1111/iwj.12216	No separate results for infected ulcer subgroup
Arendsen LP, Vig S, Thakar R, Sultan AH. Impact of copper compression stockings on venous insufficiency and lipodermatosclerosis: a randomised controlled trial. Journal of Vascular Surgery: Venous and Lymphatic Disorders. 2019.7(2):282. doi: https://dx.doi.org/10.1016/j.jvsv.2018.12.002	Ulcers not infected
Armstrong SH, Ruckley CV. Use of a fibrous dressing in exuding leg ulcers. J Wound Care. 1997.6(7):322-24.	Ulcers not infected
Atkinson K, Orig R, Vernon T. The coloplast 3-step approach: simplifying wound healing. Wounds UK. 2024.20(2):50-56.	No separate results for infected ulcer subgroup
Atri SC, Misra J, Bisht D, Misra K. Use of homologous platelet factors in achieving total healing of recalcitrant skin ulcers. Surgery. 1990.108(3):508-12.	Ulcers not infected
B. Braun Ltd. Centre of Excellence Infection Control. Trial on the efficacy of prontosan wound irrigation solution and prontosan wound gel. Identifier: NCT01153633. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2009. Available from https://clinicaltrials.gov/study/NCT01153633 .	Ulcers not infected
B. Braun Medical Inc. Prontosan quality of life study in patients with chronic leg wound(s). Identifier: NCT03369756. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2018. Available from https://clinicaltrials.gov/study/NCT03369756 .	Ulcers not infected
B. Braun Medical Inc. Prontosan versus saline in the cleansing of chronic leg ulcers in diabetic patients. Identifier: NCT01554644. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2012. Available from https://clinicaltrials.gov/study/NCT01554644 .	Ulcers not infected

Reference	Exclusion reason
Bain MA, Koullias GJ, Morse K, Wendling S, Sabolinski ML. Type I collagen matrix plus polyhexamethylene biguanide antimicrobial for the treatment of cutaneous wounds. J. 2020.9(10):691-703. doi: https://dx.doi.org/10.2217/cer-2020-0058	Ulcers not infected
Barrett S, Rippon MG, Rogers AA. Effectiveness of wound contact layers in enabling undisturbed wound management: a case series. J Wound Care. 2023.32(3):134-44. doi: https://dx.doi.org/10.12968/jowc.2023.32.3.134	Ulcers not infected
Barrigah-Benissan K, Ory J, Sotto A, Salipante F, Lavigne JP, Loubet P. Antiseptic agents for chronic wounds: a systematic review. Antibiotics (Basel). 2022.11(3):350. doi: https://dx.doi.org/10.3390/antibiotics11030350	SR for ref checking
Barros N, Nakano LCU, Nunes RP, Ito I, Nunes M, Lima HG, et al. Treatment with silver sulfadiazine 1% in varicose ulcer. In: International Congress of Phlebology, 1996. 339-41	Unobtainable
Barrows C. Enhancing patient outcomes--reducing the bottom line: the use of antimicrobial soft silicone foam dressing in home health. Home Healthc Nurse. 2009.27(5):279-84.	Ineligible study design
Bartoszewicz M, Smutnicka D, Secewicz A, Feliks Junka A, Maczynska B, Krasowski G. Effectiveness of octenidine-based dressing in eradication of persistent bacteria colonizing venous ulcers. EWMA journal. 2013; (1 Suppl): 79, abstract no. 119. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00872795/full	Unobtainable
Beele H, Meuleneire F, Nahuys M, Percival SL. A prospective randomised open label study to evaluate the potential of a new silver alginate/carboxymethylcellulose antimicrobial wound dressing to promote wound healing. Int Wound J. 2010.7(4):262-70. doi: https://dx.doi.org/10.1111/j.1742-481X.2010.00669.x	Ulcers not infected
Belcaro G, Cesarone MR, Errichi BM, Ricci A, Antelman P, Dugall M, et al. Silver oxide ointment wound dressing in venous ulcerations: home, self-management. Panminerva Med. 2011.53(3 Suppl 1):29-33.	Unobtainable
Beldon P, Gray D, Cooper P, Barrett S. An evaluation of versiva xc gelling foam dressing and its effect on wound-related quality of life. Wounds UK. 2010.6(1):76-84.	Ulcers not infected
Bellingeri A, Falciani F, Traspardini P, Moscatelli A, Russo A, Tino G, et al. Effect of a wound cleansing solution on wound bed preparation and inflammation in chronic wounds: a single-blind RCT. J Wound Care. 2016.25(3):160, 62-6, 68. doi: https://dx.doi.org/10.12968/jowc.2016.25.3.160	Ulcers not infected
Benbow M. Product focus. Acticoat: Smith+Nephew. N2N: Nurse2Nurse. 2003.3(9):28-30.	Ineligible study design

Reference	Exclusion reason
Bergemann R, Lauterbach KW, Vanscheidt W, Neander KD, Engst R. Economic evaluation of the treatment of chronic wounds: hydroactive wound dressings in combination with enzymatic ointment versus gauze dressings in patients with pressure ulcer and venous leg ulcer in Germany. <i>Pharmacoeconomics</i> . 1999.16(4):367-77. doi: https://dx.doi.org/10.2165/00019053-199916040-00005	No eligible outcomes
Bhatt P. Quality of life case series review: wound bed preparation from a UK perspective. <i>Br J Community Nurs</i> . 2024.29(Sup6):S8-S14. doi: https://dx.doi.org/10.12968/bjcn.2024.29.Sup6.S8	No separate results for infected ulcer subgroup
Bilyayeva OO, Neshta VV, Golub AA, Sams-Dodd F. Comparative clinical study of the wound healing effects of a novel micropore particle technology: effects on wounds, venous leg ulcers, and diabetic foot ulcers. <i>Wounds: A Compendium of Clinical Research AND Practice</i> . 2017.29(8):247-54.	No separate results for eligible population subgroup
Binic I, Jankovic A, Jankovic D, Jankovic I, Vrucinic Z. Evaluation of healing and antimicrobiological effects of herbal therapy on venous leg ulcer: pilot study. <i>Phytother Res</i> . 2010.24(2):277-82. doi: https://dx.doi.org/10.1002/ptr.2931	Ulcers not infected
Bishop JB, Phillips LG, Mustoe TA, VanderZee AJ, Wiersema L, Roach DE, et al. A prospective randomized evaluator-blinded trial of two potential wound healing agents for the treatment of venous stasis ulcers. <i>J Vasc Surg</i> . 1992.16(2):251-7. doi: https://dx.doi.org/10.1067/mva.1992.37086	No separate results for infected ulcer subgroup
Bolton L. Are silver products safe and effective for chronic wound management? <i>Journal of Wound, Ostomy, and Continence Nursing</i> . 2006.33(5):469-77. doi: https://dx.doi.org/10.1097/00152192-200609000-00003	Review, non-systematic
Bongiovanni CM, Hughes MD, Bomengen RW. Accelerated wound healing: multidisciplinary advances in the care of venous leg ulcers. <i>Angiology</i> . 2006.57(2):139-44. doi: https://dx.doi.org/10.1177/000331970605700202	Ineligible study design
Borges EL, Frison SS, Honorato-Sampaio K, Guedes ACM, Lima VLDAN, Oliveira OMMD, et al. Effect of polyhexamethylene biguanide solution on bacterial load and biofilm in venous leg ulcers: a randomized controlled trial. <i>Journal of Wound, Ostomy, and Continence Nursing</i> . 2018.45(5):425-31. doi: https://dx.doi.org/10.1097/WON.0000000000000455	Ineligible intervention
Bradbury S, Ivins N, Harding K. Case series evaluation of a silver non-adherent dressing. <i>Wounds UK</i> . 2011.7(2):12-19.	Ulcers not infected
Brett Crist. VeraFlo with prontosan® and wound and fracture healing. Identifier: NCT02621073. In: <i>ClinicalTrials.gov</i> [internet]. Bethesda: US National Library of Medicine; 2015. Available from https://clinicaltrials.gov/study/NCT02621073 .	No eligible outcomes
Briggs M, Closs SJ. Patients' perceptions of the impact of treatments and products on their experience of leg ulcer pain. <i>J Wound Care</i> . 2006.15(8):333-7. doi: https://dx.doi.org/10.12968/jowc.2006.15.8.26941	No separate results for infected ulcer subgroup

Reference	Exclusion reason
Brigham and Women's Hospital. Clinical trial of a silver eluting dressing system (SILVER). Identifier: NCT01229358. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2010. Available from https://clinicaltrials.gov/study/NCT01229358 .	Ulcers not infected
Butcher M. Catch or kill? How DACC technology redefines antimicrobial management...dialkylcarbamoylchloride (DACC) technology. Br J Community Nurs. 2011.4-22.	Review, non-systematic
Cabrera CA, Ramos AN, Loandos MDH, Valdez JC, Sesto Cabral ME. Novel topical formulation for ischemic chronic wounds. Technological design, quality control and safety evaluation. Pharmaceutical Development and Technology. 2016.21(4):399-404. doi: https://dx.doi.org/10.3109/10837450.2015.1011661	Ineligible intervention
Calvary Hospital Bronx NY. Effect of prontosan wound irrigation solution on venous ulcers. Identifier: NCT01048307. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2009. Available from https://clinicaltrials.gov/study/NCT01048307 .	Ulcers not infected
Caras J. Silver polymeric membrane dressing for management of chronic left lateral and medial malleolus wounds/venous insufficiency. Journal of Wound, Ostomy and Continence Nursing. 2006.33:S18-9.	Ineligible study design
CareNow Medical Pvt Ltd. To determine effectiveness of theruptor sterile barrier wound dressing In chronic infected wounds. Identifier: CTRI/2022/03/041044. In: Chinese Clinical Trial Register [internet]. Chengdu: Chinese University of Hong Kong: 2022. Available from http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=59330 .	Ineligible intervention
Carson SN, Pankovich A, Travis E, To D, Rodriguez A. Healing chronic infected foot wounds with human fibroblast-derived dermal substitute and silver dressings. Wounds: A Compendium of Clinical Research and Practice. 2005.17(10):282-89.	Ineligible population
Carville K, Kapp S, Newall N, Saflekas S, Lewin G, Gliddon T. Predicting covert and overt infection in leg ulcers: a randomised controlled trial. In: 3rd Congress of the World Union of Wound Healing Societies Meeting; 2008, 4-8 June; Toronto, Canada 2008; Abstract no. OR124. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00645333/full	Unobtainable
Carville K, Smith J. A report on the effectiveness of comprehensive wound assessment and documentation in the community. Primary Intention: The Australian Journal of Wound Management. 2004.12(1):41-49.	Ulcers not infected
Casey G, van Rij A. Manuka honey and leg ulcers. N Z Med J. 1997.110(1045):216.	Ineligible study design
Catanzano O, Docking R, Schofield P, Boateng J. Advanced multi-targeted composite biomaterial dressing for pain and infection control in chronic leg ulcers. Carbohydr. 2017.172:40-48. doi: https://dx.doi.org/10.1016/j.carbpol.2017.05.040	No eligible outcomes

Reference	Exclusion reason
Chadwick P, Ivins N, Pilcher M, Stephen-Haynes J. Case studies: octenilin wound irrigation solution and octenilin wound gel in practice. Wounds UK. 2016.46-53.	Ineligible study design
Chaloner D. A comparative study of two silver containing dressings, acticoat 7 and avance in the treatment of chronic venous ulcers. 2nd World Union of Wound Healing Societies Meeting; 8-13 July, 2004; Paris. 2004: 134. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00499740/full	Unobtainable
Chang Gung Memorial Hospital. Efficacy of wound care and reduction of wound complications by use of aquacel® ag surgical dressing in MIS TKA. Identifier: NCT02445300. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2013. Available from https://clinicaltrials.gov/study/NCT02445300 .	Ulcers not infected
Chen Y, Xiang Y, Zhu T, Chen S, Du J, Luo J, et al. A dZnONPs enhanced hybrid injectable photocrosslinked hydrogel for infected wounds treatment. Gels. 2022.8(8):24. doi: https://dx.doi.org/10.3390/gels8080463	Ineligible study design
Cherry G, Hofman D, Poore S, Wilson J, Hill D. Tissue repair in patients with chronic venous leg ulcers treated with prezatide copper acetate gell and standard compression therapy: re-analysed after 24 weeks follow up. 14th Annual Symposium on Advances in Wound Care and Medical Research Forum on Wound Repair; 2001 30 april - 3 may; Las Vegas, Nevada. 2001: Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00407595/full	Unobtainable
Cherry GW, Hofman D, Poore S. Tissue repair in patients with chronic venous leg ulcers treated with prezatide copper acetate gel or standard compression therapy. Wound Repair Regen. 1998.(3):A243.	Ulcers not infected
Chrisman CA. Care of chronic wounds in palliative care and end-of-life patients. Int Wound J. 2010.7(4):214-35. doi: 10.1111/j.1742-481X.2010.00682.x	Review, non-systematic
Coelho S, Amarelo M, Ryan S, Reddy M, Sibbald RG. Rheumatoid arthritis-associated inflammatory leg ulcers: a new treatment for recalcitrant wounds. Int Wound J. 2004.1(1):81-4. doi: https://dx.doi.org/10.1111/j.1742-481x.2004.0002.x	Ulcers not infected
Cole W, Krumbeck J, Schattinger C. A single-center pilot study investigating the effects of a native cross-linked extracellular matrix with polyhexamethylene biguanide to manage chronic lower extremity wounds exhibiting bacterial contamination. Wound Management and Prevention. 2023.69(2):5-13.	Ulcers not infected
Coloplast A/S. A clinical investigation comparing the clinical performance and cost effectiveness of biatain® silicone compared with SOC (BISIL). Identifier: NCT05786612. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2023. Available from https://clinicaltrials.gov/study/NCT05786612 .	Ulcers not infected

Reference	Exclusion reason
Coloplast A/S. A RCT Evaluating the Clinical Benefit of a Silver Dressing in the Treatment of Venous Leg Ulcers. Identifier: NCT05923749. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2023. Available from https://clinicaltrials.gov/study/NCT05923749 .	Possibly eligible trial; no results available
Coloplast A/S. Biatain ag vs biatain in the treatment of leg ulcers. Identifier: NCT00807664. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2008. Available from https://clinicaltrials.gov/study/NCT00807664 .	Ulcers not infected
ConvaTec Inc. Aquacel® ag dressing and urgotul® silver dressing on healing of chronic venous leg ulcers. Identifier: NCT01084577. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2010. Available from https://clinicaltrials.gov/study/NCT01084577 .	Ulcers not infected
ConvaTec Inc. Aquacel® ag+ extra™ and cutimed™ sorbact® dressing in the management of venous leg ulcers over a 12-week period. Identifier: NCT05892341. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2022. Available from https://clinicaltrials.gov/study/NCT05892341 . * ConvaTec submitted a clinical study report with results during the RFI process, but this was not added to the review as the trial population did not meet the decision problem and evidence for the sub-agents assessed was already included in the review.	Ulcers not infected
ConvaTec Inc. Compare aquacel® ag versus mepilex® border ag to manage bioburden in leg ulcers. Identifier: NCT01427491. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2011. Available from https://clinicaltrials.gov/study/NCT01427491 .	Possibly eligible trial; no results available
Cooper R. A review of the evidence for the use of topical antimicrobial agents in wound care. World Wide Wounds. 2004.2004	Review, non-systematic
Cornforth A. Use of honey in the management of venous leg ulcers. Practice Nurse. 2009.38(2):12-16.	Review, non-systematic
Coutts P, Sibbald RG. The effect of a silver-containing hydrofiber dressing on superficial wound bed and bacterial balance of chronic wounds. Int Wound J. 2005.2(4):348-56. doi: https://dx.doi.org/10.1111/j.1742-4801.2005.00150.x	Ulcers not infected
Coutts PM, Ryan J, Sibbald RG. Case series of lower-extremity chronic wounds managed with an antibacterial foam dressing bound with gentian violet and methylene blue. Adv Skin Wound Care. 2014.27(3 Suppl 1):9-13. doi: https://dx.doi.org/10.1097/01.ASW.0000443270.71030.71	No separate results for eligible population subgroup

Reference	Exclusion reason
Cullen B, Gibson M, Nisbet L. Targeted use of collagen/ORC improves clinical outcomes. <i>Wound Repair Regen</i> . 2012.20(5):A93.	Ulcers not infected
Cullen BM, Serena TE, Gibson MC, Snyder RJ, Hanft JR, Yaakov RA. Randomized controlled trial comparing collagen/oxidized regenerated cellulose/silver to standard of care in the management of venous leg ulcers. <i>Adv Skin Wound Care</i> . 2017.30(10):464-68. doi: https://dx.doi.org/10.1097/01.ASW.0000524452.80170.d8	Ulcers not infected
Cwajda-Bialasik J, Moscicka P, Szewczyk MT. Antiseptics and antimicrobials for the treatment and management of chronic wounds: a systematic review of clinical trials. <i>Postep Derm Alergol</i> . 2022.39(1):141-51. doi: https://dx.doi.org/10.5114/ADA.2022.113807	SR for ref checking
Danielsen L, Cherry GW, Harding K, Rollman O. Cadexomer iodine in ulcers colonised by pseudomonas aeruginosa. <i>J Wound Care</i> . 1997.6(4):169-72. doi: https://dx.doi.org/10.12968/jowc.1997.6.4.169	Ulcers not infected
Daroczy J. Quality control in chronic wound management: the role of local povidone-iodine (Betadine) therapy. <i>Dermatology</i> . 2006.212 Suppl 1:82-7. doi: https://dx.doi.org/10.1159/000089204	Ineligible intervention
Daróczy J. Quality control in chronic wound management:: The role of local povidone-iodine (Betadine®) therapy. <i>Dermatology</i> . 2006.212(suppl 1):82-87. doi: 10.1159/000089204	Ineligible intervention
Darwin ES, Thaler ER, Lev-Tov HA. Wound odor: current methods of treatment and need for objective measures. <i>G Ital Dermatol Venereol</i> . 2019.154(2):127-36. doi: https://dx.doi.org/10.23736/S0392-0488.18.05960-6	Review, non-systematic
de la Brassinne M, Thirion L, Horvat LIL. A novel method of comparing the healing properties of two hydrogels in chronic leg ulcers. <i>J Eur Acad Dermatol Venereol</i> . 2006.20(2):131-5. doi: https://dx.doi.org/10.1111/j.1468-3083.2006.01342.x	Ulcers not infected
Demling RH, DeSanti L. The role of silver in wound healing. Part 1: effects of silver on wound management. <i>Wounds: A Compendium of Clinical Research and Practice</i> . 2001.13(1):4-15.	Ulcers not infected
Dhoonmoon L, Dyer M. Improving leg ulcer care in the community. <i>JCN</i> . 2020.34(6):40-44.	Ineligible intervention
Di Domenico G, Leonardi GM, Guerra Narducci V, Mottola M, Di Spirito F, Tartaglia N, et al. Effect of treatment with growth factors in the repair of lower limbs stumps amputation. <i>Vox Sang</i> . 2010.99(SUPPL. 1):263. doi: https://dx.doi.org/10.1111/j.1423-0410.2010.01343-2.x	Ineligible population
Di Domenico G, Leonardi GM, Mottola M, De Cristofano P, Irace R, Tartaglia T, et al. Platelet gel combined with teicoplanin in the treatment of the inferior limbs ulcers. <i>Vox Sang</i> . 2009.96(Suppl 1):249-50. doi: https://dx.doi.org/10.1111/j.1423-0410.2009.01156.x	Ineligible agent

Reference	Exclusion reason
Dissemond J, Aare K, Ozer K, Gandhi D, Ryan JL, DeKoven M. Aquacel ag advantage/ag+ extra and cutimed sorbact in the management of hard-to-heal wounds: a cohort study. J Wound Care. 2023.32(10):624-33. doi: https://dx.doi.org/10.12968/jowc.2023.32.10.624	No separate results for eligible population subgroup
Downe A. Use of Urgotul SSD® to reduce bacteria and promote healing in chronic wounds. Br J Community Nurs. 2013.S32-S38. doi: 10.12968/bjcn.2013.18.sup3.s32	Ineligible study design
Dr PDMMC Hospital. Efficacy of Superoxidised solution versus Povidone iodine in the management of lower limb ulcers. Identifier: CTRI/2021/10/037199. In: Chinese Clinical Trial Register [internet]. Chengdu: Chinese University of Hong Kong; 2021. Available from http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=60650 .	No separate results for eligible population subgroup
Dryden M, Dickinson A, Brooks J, Hudgell L, Saeed K, Cutting KF. A multi-centre clinical evaluation of reactive oxygen topical wound gel in 114 wounds. J Wound Care. 2016.25(3):140, 42-6. doi: https://dx.doi.org/10.12968/jowc.2016.25.3.140	No separate results for eligible population subgroup
Dunford C, Cooper R, Molan P. Using honey as a dressing for infected skin lesions. Nurs Times. 2000.96(Suppl 14):7-9.	Ineligible study design
Dunford CE, Hanano R. Acceptability to patients of a honey dressing for non-healing venous leg ulcers. J Wound Care. 2004.13(5):193-7. doi: https://dx.doi.org/10.12968/jowc.2004.13.5.26614	Ulcers not infected
Eberlein T, Haemmerle G, Signer M, Gruber-Moesenbacher U, Traber J, Mittlboeck M, et al. Comparison of PHMB-containing dressing and silver dressings in patients with critically colonised or locally infected wounds. J Wound Care. 2012.21(1):12-20.	No separate results for infected ulcer subgroup
Emoled. Leg ulcers standards of care enhancement (LUCE). Identifier: NCT04689009. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine; 2019. Available from https://clinicaltrials.gov/study/NCT04689009 .	Ineligible intervention
Engelhardt M, Spech E, Diener H, Faller H, Augustin M, Debus ES. Validation of the disease-specific quality of life wuerzburg wound score in patients with chronic leg ulcer. Vasa - European Journal of Vascular Medicine. 2014.43(5):372-0380.	Ulcers not infected
Failla G, Campo S, Ardita G, Finocchiaro P, Mugno F, Attanasio L, et al. Proteases and chronic leg ulcers. Minerva Cardioangiol. 2008.56(4):409-15.	Ulcers not infected
Febe B. Medical grade honey reduces protease activity while promoting wound healing. J Wound Care. 2020.29(SUPPL 7B):204.	Ulcers not infected
First Hospital of Jilin University. Effectiveness and safety of using prontosan to treat bacterial biofilm. Identifier: NCT06185465. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine; 2024. Available from https://clinicaltrials.gov/study/NCT06185465 .	Possibly eligible trial; no results available

Reference	Exclusion reason
Forbes TA, Shaw L, Millard Z, Kausman J, Walker AM, Quinlan C. Just a spoonful of sugar - medihoney for paediatric peritoneal dialysis exit-site infection, a case series. <i>Pediatr Nephrol</i> . 2014.29(9):1766. doi: https://dx.doi.org/10.1007/s00467-014-2904-6	Ineligible population
Forder R, Burns R. Post-market clinical evaluation of the safety and performance of activheal® silicone foam and activheal® silicone foam lite dressings. <i>Wounds UK</i> . 2020.16(3):68-76.	Ulcers not infected
Forder R, Rogers AA, Ousey K, Rippon MG. Activheal PHMB foam dressing range: a product evaluation. <i>Wounds UK</i> . 2024.20(1):66-75.	Review, non-systematic
Forner-Cordero I, Navarro-Monsoliu R, Munoz-Langa J, Alcober-Fuster P, Rel-Monzo P. Use of a nanocrystalline silver dressing on lymphatic ulcers in patients with chronic lymphoedema. <i>J Wound Care</i> . 2007.16(5):235-9. doi: https://dx.doi.org/10.12968/jowc.2007.16.5.27045	Ulcers not infected
Franken K, Neuman HAM, Andersen KE, Larsen AM. The preliminary results of a comparative study on performance characteristics of a new foam dressing Biatain versus Allevyn on venous leg ulcers. In: 9th European Conference on Advances in Wound Management; 1999, 9-11 November; Harrogate UK 1999; 8. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00364480/full	Unobtainable
Franks PJ, Moody M, Moffatt CJ, Hiskett G, Gatto P, Davies C, et al. Randomized trial of two foam dressings in the management of chronic venous ulceration. <i>Wound Repair Regen</i> . 2007.15(2):197-202. doi: https://dx.doi.org/10.1111/j.1524-475X.2007.00205.x	Ulcers not infected
Friman G. A new hydrophobized wound dressing (sorbact 105) in the treatment of infected wounds. <i>Curr Ther Res Clin Exp</i> . 1987.42(1):88-93.	Ineligible intervention
Fronzo C. Antimicrobial stewardship: wound treatment challenges. <i>J Wound Care</i> . 2022.31(2):118-20. doi: https://dx.doi.org/10.12968/jowc.2022.31.2.118	Ineligible study design
Gamborg Nielsen P, Munk Madsen S, Stromberg L. Treatment of chronic leg ulcers with a hydrocolloid dressing. <i>Acta Derm Venereol Suppl</i> . 1989.152:1-12.	No eligible outcomes
Garber N. Intractable postphlebotic ulceration of the leg. <i>S Afr Med J</i> . 1985.67(14):553-54.	Ineligible agent
Gardner S. Using treatment pathways to improve healing of venous leg ulceration. <i>Wounds UK</i> . 2013.9(1):67-75.	No separate results for infected ulcer subgroup
Garval E, Plee J, Lesage C, Grange-Prunier A, Bernard P, Perceau G. Frequency of contact sensitization to modern dressings used to treat chronic leg ulcer. <i>Ann Dermatol Venereol</i> . 2018.145(5):339-46. doi: https://dx.doi.org/10.1016/j.annder.2018.01.048	Non-English language

Reference	Exclusion reason
Gazzabin L, Serantoni S, Palumbo FP, Giordan N. Hyaluronic acid and metallic silver treatment of chronic wounds: healing rate and bacterial load control. J Wound Care. 2019.28(7):482-90. doi: https://dx.doi.org/10.12968/jowc.2019.28.7.482	Ineligible intervention
Gethin G, Cowman S. Bacteriological changes in sloughy venous leg ulcers treated with manuka honey or hydrogel: an RCT. J Wound Care. 2008.17(6):241-4, 46-7. doi: https://dx.doi.org/10.12968/jowc.2008.17.6.29583	Ulcers not infected
Gethin G, Cowman S. Manuka honey vs. hydrogel--a prospective, open label, multicentre, randomised controlled trial to compare desloughing efficacy and healing outcomes in venous ulcers [retraction notice in CN-02126318]. J Clin Nurs. 2009; (3): 466-74. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00683483/full	Retracted
Gethin G. Manuka honey versus hydrogel - a prospective, open label, multicentre, randomised controlled trial to compare desloughing efficacy and healing outcomes in venous ulcers. 2007.	Retracted
Ghosh P, Poopalalingam S, Vallejo A. EP234 Cost-effectiveness, budget impact & healthcare resource savings of topical antimicrobial polyhexamethylene biguanide with a surfactant betaine on wound bed preparation in venous leg ulcers: an analysis in Australia. Journal of Wound Management. 2023.24(2):157-57.	Ulcers not infected
Gibson M, Foster S, Cullen B, Nisbet L, Lanzara S, Zamboni P. Modulating inflammation in chronic wounds with collagen/orc/silver. Journal of Wound, Ostomy and Continence Nursing. 2011.38:S6-S6.	Ulcers not infected
Gilligan A, Waycaster C, Carter M, Fife C. Comparative effectiveness of clostridial collagenase ointment to medicinal honey for treatment of venous leg ulcers in the hospital outpatient department setting. J Manag Care Spec Pharm. 2015.21(10-a SUPPL.):S66.	Ulcers not infected
Giulia D, Valentina D, Agata J, Stephane F, Marco R. Fluorescence biomodulation in venous leg ulcers: a retrospective comparative study with standard of care. J Wound Care. 2020.29(SUPPL 7B):201. doi: https://dx.doi.org/10.12968/jowc.2020.29.Sup7b.1	Ulcers not infected
Glinski W, Chodyncka B, Roszkiewicz J, Bogdanowski T, Lecewicz-Torun B, Kaszuba A, et al. The beneficial augmentative effect of micronised purified flavonoid fraction (MPFF) on the healing of leg ulcers: an open, multicentre, controlled, randomised study. Phlebology. 1999.14(4):151-57.	Ineligible agent
Goedkoop R, Juliet R, You PHK, Daroczy J, De Roos KP, Lijnen R, et al. Wound stimulation by growth-arrested human keratinocytes and fibroblasts: HP802-247, a new-generation allogeneic tissue engineering product. Dermatology. 2010.220(2):114-20. doi: https://dx.doi.org/10.1159/000277380	Ineligible intervention
Goss SG, Alcantara SD, Gendics C, Yang Q, Schultz G, Lantis IJC. Medical honey may decrease pro-inflammatory cytokine production in chronically infected venous leg ulcers. Wound Repair Regen. 2014.22(5):A81. doi: https://dx.doi.org/10.1111/wrr.12218	No eligible outcomes

Reference	Exclusion reason
Graham GS. Healing outcomes of MRSA infected wounds with a protocol combining oakin dressing with elements of de-escalation theory. J Wound Care. 2014.23:S4-S9. doi: 10.12968/jowc.2014.23.Sup2a.S4	Ineligible agent
Gray TA, Rhodes S, Atkinson RA, Rothwell K, Wilson P, Dumville JC, et al. Opportunities for better value wound care: a multiservice, cross-sectional survey of complex wounds and their care in a UK community population. BMJ Open. 2018.8(3):e019440. doi: https://dx.doi.org/10.1136/bmjopen-2017-019440	Ineligible study design
Greener M. Urgoclean ag: evidence base and mode of action. Br J Nurs. 2017.26(Suppl 20a):S12-S15. doi: https://dx.doi.org/10.12968/bjon.2017.26.Sup20a.S12	Review, non-systematic
Grigoropoulos A, Zouridaki E, Sgontzou T, Vitsos A, Antoniou C, Katsarou A, et al. Clinical evaluation of wound healing capacity of isopod ceratothoa oestroides oil extract. Free Radic Biol Med. 2017.108(Supplement 1):S67. doi: https://dx.doi.org/10.1016/j.freeradbiomed.2017.04.229	Ulcers not infected
Grönberg A, Mahlapuu M, Ståhle M, Whately-Smith C, Rollman O. Treatment with LL-37 is safe and effective in enhancing healing of hard-to-heal venous leg ulcers: a randomized, placebo-controlled clinical trial. Wound Repair Regen. 2014; (5): 613-21. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01101427/full	Ineligible intervention
Grothier L. Gentle foam dressings: interim results of an evaluation of the allevyn range. Br J Nurs. 2009.18(11):S12-S16. doi: 10.12968/bjon.2009.18.sup4.42728	Ineligible agent
Guest JF, Ruiz FJ, Mihai A, Lehman A. Cost effectiveness of using carboxymethylcellulose dressing compared with gauze in the management of exuding venous leg ulcers in Germany and the USA. Curr Med Res Opin. 2005.21(1):81-92. doi: https://dx.doi.org/10.1185/030079904x15219	Ineligible agent
Guiomar AJ, Urbano AM. Polyhexanide-releasing membranes for antimicrobial wound dressings: a critical review. Membranes (Basel). 2022.12(12):18. doi: https://dx.doi.org/10.3390/membranes12121281	Review, non-systematic
Gupta S, Shinde RK, Shinde S. Comparison of the outcomes of cadexomer iodine and povidone-iodine ointments in wound management. Cureus. 2022.14(5):e24667. doi: https://dx.doi.org/10.7759/cureus.24667	No separate results for eligible population subgroup
Hall K. The effects of silver containing alginate primary dressings compared to alginate primary dressings on the healing of chronic venous leg ulcers. Clinical Nurse Specialist: The Journal for Advanced Nursing Practice. 2011.25(3):152-52. doi: 10.1097/NUR.0b013e3182195290	Ulcers not infected
Hampton S. An evaluation of the efficacy of cutimed sorbact in different types of non-healing wounds. Wounds UK. 2007.3(4):113-19.	Ulcers not infected

Reference	Exclusion reason
Hanft J, Serena T, Snyder R. Evaluation of the clinical effectiveness of a collagen-orc antimicrobial matrix in venous leg ulcers. 16th Conference of the European Wound Management Association; 2006, 18-20 may; Prague, Czech Republic. 2006: p 151. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00605639/full	Ineligible agent
Hanft JR, Serena T, Snyder R. A study to evaluate the clinical effectiveness of a collagen-ORC antimicrobial matrix in venous leg ulcers. Wound Repair Regen. 2006.(2):A64.	Ulcers not infected
Hanft JR, Smith T, Legel K. Topical active leptospermum honey in recalcitrant venous leg wounds: a preliminary case series. Ostomy Wound Manage. 2009.55(4):83-83.	Ulcers not infected
Hansson C, Persson LM, Stenquist B, Nordin P, Roed-Petersen J, Westerhof W, et al. The effects of cadexomer iodine paste in the treatment of venous leg ulcers compared with hydrocolloid dressing and paraffin gauze dressing. Int J Dermatol. 1998.37(5):390-96. doi: https://dx.doi.org/10.1046/j.1365-4362.1998.00415.x	Ulcers not infected
Hansson C. The effects of cadexomer iodine paste in the treatment of venous leg ulcers compared with hydrocolloid dressing and paraffin gauze dressing. Cadexomer iodine study group. Int J Dermatol. 1998.37(5):390-6. doi: https://dx.doi.org/10.1046/j.1365-4362.1998.00415.x	Ulcers not infected
Harding K, Cutting K, Price P. The cost-effectiveness of wound management protocols of care. Br J Nurs. 2000.9(19 Tissue Viability Supplement):S6, S8, S10-S20.	No separate results for infected ulcer subgroup
Harding K, Gottrup F, Jawien A, Mikosinski J, Twardowska-Sauchka K, Kaczmarek S, et al. A prospective, multi-centre, randomised, open label, parallel, comparative study to evaluate effects of aquacel r ag and urgotul r silver dressing on healing of chronic venous leg ulcers. Int Wound J. 2012.9(3):285-94. doi: https://dx.doi.org/10.1111/j.1742-481X.2011.00881.x	Ulcers not infected
Harding K, Gottrup F, Jawień A, Mikosiński J, Twardowska-Sauchka K, Kaczmarek S, et al. A prospective, multi-centre, randomised, open label, parallel, comparative study to evaluate effects of aquacel® ag and urgotul® silver dressing on healing of chronic venous leg ulcers. Int Wound J. 2012.(3):285-94. doi: 10.1111/j.1742-481X.2011.00881.x	Ulcers not infected
Harding K, Gray D, Timmons J, Hurd T. Evolution or revolution? Adapting to complexity in wound management. Int Wound J. 2007.4 Suppl 2:1-12. doi: https://dx.doi.org/10.1111/j.1742-481X.2007.00329.x	Ineligible study design
Harding KG, Price P, Robinson B, Thomas S, Hofman D. Cost and dressing evaluation of hydrofiber and alginate dressings in the management of community-based patients with chronic leg ulceration. Wounds. 2001.13(6):229-36.	Ulcers not infected
Harrison JE. The adjunctive use of collagen/oxidized regenerated cellulose dressing in complex wounds. Journal of Wound, Ostomy and Continence Nursing. 2017.44:S22-S22. doi: 10.1097/won.0000000000000331	Case series <10

Reference	Exclusion reason
Hayes L. Improving outcomes and quality of life for patients with chronic venous ulcers. <i>Ostomy Wound Manage.</i> 2015.61(7):8-10.	Ineligible study design
Health Research Council of New Zealand. Honey as adjuvant leg ulcer therapy: a randomised controlled trial of a honey-impregnated dressing for venous leg ulcers. Identifier: ISRCTN06161544. In: ISRCTN Registry [internet]. London: BioMed Central Limited: 2004. Available from http://isrctn.com/ISRCTN06161544 .	No separate results for infected ulcer subgroup
Heasley DD. Evaluation of a composite silver dressing and pain relief at the wound site in full thickness vascular ulcers. <i>Journal of Wound, Ostomy and Continence Nursing.</i> 2007.34:S14-5. doi: 10.1097/01.won.0000270878.32063.10	Ulcers not infected
Heasley DD. Evaluation of a silver collagen based gel and attained pain relief in arterial ulcers. <i>Journal of Wound, Ostomy and Continence Nursing.</i> 2011.38:S18-S18.	Ulcers not infected
Hendrickson MA. Utilizing active leptospermum honey dressings in the treatment of cutaneous small-vessel vasculitis. <i>Ostomy Wound Manage.</i> 2010.56(4):10-12.	Ineligible study design
Herrington MT. Antimicrobial foam dressing used in the treatment of wounds in patients with compromised vascular and arterial sufficiency. <i>Ostomy Wound Manage.</i> 2009.20-21.	Ineligible study design
Herron K. Impact of a novel synthetic nanofibre matrix to treat hard-to-heal wounds. <i>J Wound Care.</i> 2022.31(11):962-68. doi: 10.12968/jowc.2022.31.11.962	Case series <10
Herruzo R, Fondo Alvarez E, Herruzo I, Santiso Casanova E, Cerame Perez S. Synergistic effect of two formulations of hypochlorous acid in the treatment of 346 chronic ulcers. <i>Wound Repair Regen.</i> 2023.31(3):401-09. doi: https://dx.doi.org/10.1111/wrr.13079	No separate results for eligible population subgroup
Herskovitz I, MacQuhae FE, Borda LJ, Bhagwandin S, Paredes JA, Polanco T, et al. A novel topical wound therapy delivery system. <i>Wounds: A Compendium of Clinical Research and Practice.</i> 2017.29(9):269-76.	Ulcers not infected
Hillstrom L. Iodosorb compared to standard treatment in chronic venous leg ulcers - a multicenter study. <i>Acta Chir Scand.</i> 1988.154(Suppl 544):53-56.	No separate results for infected ulcer subgroup
Hollister Wound Care LLC. Restore calcium alginate dressing, silver vs aquacel ag in the treatment of critically colonized venous leg ulcers. Identifier: NCT01396304. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2011. Available from https://clinicaltrials.gov/study/NCT01396304 .	Ulcers not infected
Holloway GA, Johansen KH, Barnes RW, Pierce GE. Multicenter trial of cadexomer iodine to treat venous stasis ulcer. <i>West J Med.</i> 1989.151(1):35-8.	Ulcers not infected

Reference	Exclusion reason
Holubova A, Chlupacova L, Cetlova L, Cremers NAJ, Pokorna A. Medical-grade honey as an alternative treatment for antibiotics in non-healing wounds-a prospective case series. <i>Antibiotics (Basel)</i> . 2021.10(8):28. doi: https://dx.doi.org/10.3390/antibiotics10080918	Case series <10
Howell-Jones RS, Price PE, Howard AJ, Thomas DW. Antibiotic prescribing for chronic skin wounds in primary care. <i>Wound Repair Regen</i> . 2006.14(4):387-93. doi: 10.1111/j.1743-6109.2006.00144.x	Ineligible intervention
Hughes MA, Jones J. A large-scale evaluation of managing moderate and highly exuding wounds in the community. <i>Wounds UK</i> . 2017.13(3):78-85.	Ulcers not infected
Hull University Teaching Hospitals NHS Trust. DACC in the REduction of Surgical Site INfection (DRESSING). Identifier: NCT02992951. In: <i>ClinicalTrials.gov</i> [internet]. Bethesda: US National Library of Medicine: 2017. Available from https://clinicaltrials.gov/study/NCT02992951 .	Ulcers not infected
Humphrey D, Schurr MJ, Shillinglaw W. Ultrathin dissolvable antimicrobial wound dressing is safe and effective in patients with complex chronic wounds. <i>Wound Repair Regen</i> . 2017.25(4):A39. doi: https://dx.doi.org/10.1111/wrr.12573	Ulcers not infected
Hurd T, Gregory L, Jones A, Brown S. A multi-centre in-market evaluation of allevyn gentle border. <i>Wounds UK</i> . 2009.5(3):32-44.	Ulcers not infected
Hurd T, Woodmansey EJ, Watkins HMA. A retrospective review of the use of a nanocrystalline silver dressing in the management of open chronic wounds in the community. <i>Int Wound J</i> . 2021.18(6):753-62. doi: https://dx.doi.org/10.1111/iwj.13576	Ulcers not infected
Imbernon-Moya A, Ortiz-de Frutos FJ, Sanjuan-Alvarez M, Portero-Sanchez I, Merinero-Palomares R, Alcazar V. Topical sevoflurane for chronic venous ulcers infected by multi-drug-resistant organisms. <i>Int Wound J</i> . 2017.14(6):1388-90. doi: https://dx.doi.org/10.1111/iwj.12794	Ineligible intervention
Institute of medical sciences. Effect of platelet rich plasma and silver ion dressing on venous ulcer healing. Identifier: CTRI/2023/04/051654. In: <i>Clinical Trials Register - India (CTRI)</i> [internet]. New Delhi: National Institute of Medical Statistics: 2023. Available from http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=83570 .	Ulcers not infected
Integra LifeSciences Corporation. A multi-center, prospective, randomized study with primatrix and primatrix ag for the treatment of venous leg ulcers. Identifier: NCT01612806. In: <i>ClinicalTrials.gov</i> [internet]. Bethesda: US National Library of Medicine: 2011. Available from https://clinicaltrials.gov/study/NCT01612806 .	Ulcers not infected
Ivins N, Harding KG, Price P, Jørgensen B, Lohmann M, Gottrup F. Safety and efficacy in long-term use of a sustained silver-releasing foam dressing: a randomized, controlled trial on venous leg ulcers. Symposium on advanced wound care (SAWC) AND medical research forum on wound repair; 2006 april 30 - may 3; san antonio, texas. 2006: Poster 12. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00605572/full	Unobtainable

Reference	Exclusion reason
Ivins N, Jørgensen B, Lohmann M, Harding KG, Price P, Gottrup F. Safety and efficacy in long term use of a sustained silver-releasing foam dressing: a randomised, controlled trial on venous leg ulcers. 15th Conference of the European Wound Management Association, 2005 September 15-17, Stuttgart, Germany. 2005: Poster abstracts P180 284. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00605417/full	Unobtainable
Ivins N. Successful management of a venous leg ulcer using durafiber dressings. <i>Wounds Int.</i> 2012.3(4):26-26.	Ineligible study design
Jenwitheesuk K, Surakunprapha P, Chowchuen B. The use of nanocrystalline silver for the treatment of massive soft tissue defects with exposed bone. <i>J Med Assoc Thai.</i> 2013.96 Suppl 4:S177-84.	No separate results for infected ulcer subgroup
Jha V, Kumar A. A comprehensive prospective cross sectional study of clinical features and management of ulcers of the lower limb. <i>International Journal of Pharmaceutical and Clinical Research.</i> 2021.13(2):06-15.	Ineligible intervention
Joergensen B, Blaise S, Svensson AS. A randomised, open-label, parallel-group, multicentre, comparative study to compare the efficacy and safety of exufiber R with aquacel R Extra TM dressings in exuding venous and mixed aetiology leg ulcers. <i>Int Wound J.</i> 2022.19 Suppl 1:22-38. doi: https://dx.doi.org/10.1111/iwj.13913	Ulcers not infected
Johnson S, Forder R. Clinical evaluation of the activheal foam contact dressing. <i>Wounds UK.</i> 2012.8(4):134-43.	Ineligible agent
Johnson S, Spruce PAM. A clinical in-market evaluation of activheal foam contact dressing. <i>Wounds UK.</i> 2013.9(1):38-45.	No separate results for infected ulcer subgroup
Jones NIA, Ivins N, Ebdon V, Hagelstein S, Harding K. A case series evaluating the use of a gelling fibre dressing for moderate to highly exuding wounds. <i>Wounds UK.</i> 2017.13(3):72-78.	Ulcers not infected
Jordan-O'Brien J, Lee S, Moneley D, Donegan C. The use of adjunct therapies for chronic wound management in older adults in a teaching hospital. <i>Ir J Med Sci.</i> 2014.183(7 SUPPL. 1):S310-S11. doi: https://dx.doi.org/10.1007/s11845-014-1177-1	Ulcers not infected
Jorgensen B, Bech-Thomsen N, Grenov B, Gottrup F. Effect of a new silver dressing on chronic venous leg ulcers with signs of critical colonisation. <i>J Wound Care.</i> 2006.15(3):97-100. doi: https://dx.doi.org/10.12968/jowc.2006.15.3.26876	Ulcers not infected
Jorgensen B, Price P, Andersen KE, Gottrup F, Bech-Thomsen N, Scanlon E, et al. The silver-releasing foam dressing, contreet foam, promotes faster healing of critically colonised venous leg ulcers: a randomised, controlled trial. <i>Int Wound J.</i> 2005.2(1):64-73. doi: https://dx.doi.org/10.1111/j.1742-4801.2005.00084.x	Ulcers not infected
Judy D, Burton C, Johnson J, Yates S. Silver impregnated dressings: do they help chronic venous ulcers heal? <i>J Am Acad Dermatol.</i> 2010.62(3 SUPPL. 1):AB150. doi: https://dx.doi.org/10.1016/j.jaad.2009.11.582	Ulcers not infected

Reference	Exclusion reason
Jull A, Walker N, Parag V, Molan P, Arroll B, Waters J. Honey as adjuvant therapy for leg ulcers (HALT) trial: a randomized controlled trial (ISRCTN 06161544). 16th Conference of the European Wound Management Association, 2006 may 18-20, Prague, Czech Republic. 2006: Abstract no.029. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00605632/full	No separate results for infected ulcer subgroup
Jull A, Walker N, Parag V, Molan P, Rodgers A. Randomized clinical trial of honey-impregnated dressings for venous leg ulcers. Br J Surg. 2008.95(2):175-82. doi: https://dx.doi.org/10.1002/bjs.6059	No separate results for infected ulcer subgroup
Jull A, Walker N, Rodgers A, Bennett D, Molan P, Arroll B. Honey for leg ulcers—The HALT trial. In: 2nd world union of wound healing societies meeting, 2004 july 8-13, paris 2004; 88. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00488228/full	Unobtainable
Kaltostat: ConvaTec; Mepilex: Molnlyke Health Care AB. An open randomised comparative study to evaluate the performance of aquacel® extra* in venous leg ulcers. Identifier: NL-OMON37546. In: Overview of Medical Research in the Netherlands (OMON) [internet]. Amsterdam: The Central Committee on Research Involving Human Subjects: 2012. Available from https://trialsearch.who.int/Trial2.aspx?TrialID=NL-OMON37546 .	Ulcers not infected
Kapp H, Smola H. Reduced cellular toxicity of a new silver-containing antimicrobial dressing and its clinical performance in non-healing wounds. Primary Intention: The Australian Journal of Wound Management. 2005.13(4):S1-7.	Unobtainable
Karlsmark T, Agerslev RH, Bendz SH, Larsen JR, Roed-Petersen J, Andersen KE. Clinical performance of a new silver dressing, contreet foam, for chronic exuding venous leg ulcers. J Wound Care. 2003.12(9):351-4. doi: https://dx.doi.org/10.12968/jowc.2003.12.9.26534	Ulcers not infected
Karr JC, de Mola FL, Pham T, Tooke L. Wound healing and cost-saving benefits of combining negative-pressure wound therapy with silver. Adv Skin Wound Care. 2013.26(12):562-5. doi: https://dx.doi.org/10.1097/01.ASW.0000434518.86905.8a	Ulcers not infected
Kashan University of Medical Sciences. The effect of milk and propolis with honey on infectious wounds. Identifier: Irct20200516047462N. In: Iranian Registry of Clinical Trials (IRCT) [internet]. Tehran: Iran University of Medical Sciences (IUMS): 2024. Available from: https://trialsearch.who.int/Trial2.aspx?TrialID=IRCT20200516047462N6 .	Possibly eligible trial; no results available
Kawczyk-Krupka A, Krupka-Olek M, Bozek A, Aebisher D, Bartusik-Aebisher D, Olek M, et al. Photodynamic therapy as an alternative to antibiotic therapy for the treatment of infected leg ulcers. Photodiagnosis and Photodynamic Therapy. 2024.46:104135. doi: https://dx.doi.org/10.1016/j.pdpdt.2024.104135	No eligible outcomes
Kearsley M. Leg ulcers: adsorbing the problem... actisorb dressings. Community Outlook. 1986.19-21.	Ineligible study design

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Kerihuel JC. Effect of activated charcoal dressings on healing outcomes of chronic wounds. J Wound Care. 2010.19(5):208, 10-2, 14-5. doi: https://dx.doi.org/10.12968/jowc.2010.19.5.48047	Ulcers not infected
Kero M, Tarvainen K, Hollmen A, Pekamaki K. A comparison of cadexomer iodine with dextranomer in the treatment of venous leg ulcers. Curr Ther Res Clin Exp. 1987.42(5):761-67.	Ulcers not infected
Kerstein MD, Gemmen E, van Rijswijk L, Lyder CH, Phillips T, Xakellis G, et al. Cost and cost effectiveness of venous and pressure ulcer protocols of care. Dis Manag Health Out. 2001.9(11):651-63.	Ulcers not infected
Kingley A, Tadej M, Colbourn A, Kerr A, Aslan CB. Suprasorb x + PHMB: antimicrobial and hydrobalance action in a new wound dressing. Wounds UK. 2009.5(1):72-77.	Ineligible study design
Kirsner R, Falanga V, Fivenson D, Thibodeaux K, Cavorsi J, de la Pava D, et al. Clinical experience with a human skin equivalent for the treatment of venous leg ulcers: process and outcomes. Wounds: A Compendium of Clinical Research and Practice. 1999.11(6):137-44.	Review, non-systematic
Klebes M, Ulrich C, Kluschke F, Patzelt A, Vandersee S, Richter H, et al. Combined antibacterial effects of tissue-tolerable plasma and a modern conventional liquid antiseptic on chronic wound treatment. J Biophotonics. 2015.8(5):382-91. doi: https://dx.doi.org/10.1002/jbio.201400007	Ulcers not infected
König M, Vanscheidt W, Augustin M, Kapp H. Enzymatic versus autolytic debridement of chronic leg ulcers: a prospective randomised trial. J Wound Care. 2005.14(7):320-23.	Ulcers not infected
Kordestani S, Shahrezaee M, Tahmasebi MN, Hajimahmodi H, Haji Ghasemali D, Abyaneh MS. A randomised controlled trial on the effectiveness of an advanced wound dressing used in Iran. J Wound Care. 2008.17(7):323-7. doi: https://dx.doi.org/10.12968/jowc.2008.17.7.30525	No separate results for infected ulcer subgroup
Kotz P, Fisher J, McCluskey P, Hartwell SD, Dharma H. Use of a new silver barrier dressing, allevyn parallelogram open Ag in exuding chronic wounds. Int Wound J. 2009.6(3):186-94. doi: https://dx.doi.org/10.1111/j.1742-481X.2009.00608.x	Ulcers not infected
Krasowski G, Jawien A, Tukiendorf A, Rybak Z, Junka A, Olejniczak-Nowakowska M, et al. A comparison of an antibacterial sandwich dressing vs dressing containing silver. Wound Repair Regen. 2015.23(4):525-30. doi: https://dx.doi.org/10.1111/wrr.12301	Ulcers not infected
Kucharzewski M, Wilemska-Kucharzewska K, Kozka M, Splakowska M. Leg venous ulcer healing process after application of membranous dressing with silver ions. Phlebologie. 2013.42(6):340-46. doi: https://dx.doi.org/10.12687/phleb2141-6-2013	Unobtainable

Reference	Exclusion reason
Kuffler DP. Eliminating non-healing wounds: a review. <i>Regenerative Medicine</i> . 2021.16(4):391-404. doi: https://dx.doi.org/10.2217/rme-2020-0163	Review, non-systematic
Kumar KN, Sashikalyan G. Topical silver dressing versus conventional saline dressing in the management of non-healing ulcers: a prospective randomized interventional study. <i>International Journal of Pharmaceutical and Clinical Research</i> . 2023.15(5):795-801.	Ulcers not infected
Kuopio University Hospital. Resin salve versus honey treatment in wound care. Identifier: NCT01868412. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2013. Available from https://clinicaltrials.gov/study/NCT01868412 .	No separate results for infected ulcer subgroup
Kuznetsov NA, Barinov VE, Teleshov BV, Trepilets VE, Zheltikov AN. Surgical technologies in the treatment of varicose veins of the lower extremities complicated with trophic ulcer. <i>Khirurgiia</i> . 2005.(4):37-41.	Non-English language
Laboratoires URGO. Assessment of efficacy & safety for a new wound dressing urgo 310 3166 in the local treatment of VLU or mixed leg ulcers. Identifier: NCT02583958. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2014. Available from https://clinicaltrials.gov/study/NCT02583958 .	Ulcers not infected
Laboratoires URGO. Clinical trial to evaluate the efficacy, tolerance and acceptability of urgo dressing vs a hydrofibre in the local management of venous or predominantly venous mixed leg ulcers. Identifier: NCT01449422. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2011. Available from https://clinicaltrials.gov/study/NCT01449422 .	Ulcers not infected
Lademann J, Ulrich C, Kluschke F, Patzelt A, Czaika VA, Richter H, et al. Effects of tissue-tolerable plasma on chronic wound treatment compared to a modern conventional liquid antiseptic. <i>Skin Research and Technology</i> . 2013.19(1):e562. doi: https://dx.doi.org/10.1111/srt.12017	Ulcers not infected
Lansdown A, Williams A, Chandler S, Benfield S. Wound care. Silver dressings: absorption and antibacterial efficacy. <i>Nurs Times</i> . 2005.101(46):45-46.	Unobtainable
Lansdown AB, Jensen K, Jensen MQ. Contreet foam and contreet hydrocolloid: an insight into two new silver-containing dressings. <i>J Wound Care</i> . 2003.12(6):205-10. doi: https://dx.doi.org/10.12968/jowc.2003.12.6.26507	Review, non-systematic
Lantis J, Theoharides T, Fuller A. The evaluation of growth factors in hard to heal venous leg ulcers. <i>Wound Repair Regen</i> . 2011.19(5):A83. doi: https://dx.doi.org/10.1111/j.1524-475X.2011.00728.x	Ulcers not infected
Laudanska H, Gustavson B. In-patient treatment of chronic varicose venous ulcers. A randomized trial of cadexomer iodine versus standard dressings. <i>J Int Med Res</i> . 1988.16(6):428-35. doi: https://dx.doi.org/10.1177/030006058801600604	Ulcers not infected

Reference	Exclusion reason
Lazareth I, Meaume S, Sigal-Grinberg ML, Combemale P, Guyadec TL, Zagnoli A, et al. The role of a silver releasing lipido-colloid contact layer in venous leg ulcers presenting inflammatory signs suggesting heavy bacterial colonization: results of a randomized controlled study. Wounds: A Compendium of Clinical Research and Practice. 2008.20(6):158-66.	Ulcers not infected
Lazareth I, Meaume S, Sigal-Grinberg ML, Combemale P, Le Guyadec T, Zagnoli A. Efficacy of a silver lipidocolloid dressing on heavily colonised wounds: a republished RCT. J Wound Care. 2012.21(2):96-102. doi: https://dx.doi.org/10.12968/jowc.2012.21.2.96	Ulcers not infected
Lazareth I, Ourabah Z, Senet P, Cartier H, Sauvadet A, Bohbot S. Evaluation of a new silver foam dressing in patients with critically colonised venous leg ulcers. J Wound Care. 2007.16(3):129-32. doi: https://dx.doi.org/10.12968/jowc.2007.16.3.27015	Ulcers not infected
Leak K, Johnson SUE. Silgen ag -- an evaluation of a novel silver application. Wounds UK. 2017.13(4):127-31.	Case series <10
Leak K, Jones A, Brown S. Non-comparative in-market evaluation of allevyn gentle. Wounds UK. 2010.6(1):41-54.	Ulcers not infected
Leaper D, Munter C, Meaume S, Scalise A, Mompo NB, Jakobsen BP, et al. The use of biatain ag in hard-to-heal venous leg ulcers: meta-analysis of randomised controlled trials. PLoS ONE. 2013.8(7):e67083. doi: https://dx.doi.org/10.1371/journal.pone.0067083	SR for ref checking
Leaper DJ, Durani P. Topical antimicrobial therapy of chronic wounds healing by secondary intention using iodine products. Int Wound J. 2008.5(2):361-68. doi: https://dx.doi.org/10.1111/j.1742-481X.2007.00406.x	Review, non-systematic
Leaper DJ, Stewart AJ. A comparative trial of sherisorb gel and cadexomer iodine: problems of community-based trials involving chronic leg ulcers. Advances in Wound Management. 1986: 121-26. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00421754/full	No eligible outcomes
Lee BY, Trainor FS, Thoden WR. Topical application of povidone-iodine in the management of decubitus and stasis ulcers. J Am Geriatr Soc. 1979.27(7):302-6. doi: https://dx.doi.org/10.1111/j.1532-5415.1979.tb06044.x	No separate results for eligible population subgroup
Lee HO. A study of combined intervention: cardexomer iodine, calcium alginate and polyurethane foam for the management of chronic venous ulcers. WCET Journal. 2009.29(2):37-37.	Ineligible study design
Lee K. The experience of applying silver-containing hydrofiber dressing on refractory problem wounds. WCET Journal. 2009.29(4):29-29.	Unobtainable
Levin RF, Farren M. Silver dressings and venous leg ulcers. WCET Journal. 2010.30(3):41-42.	Unobtainable

Reference	Exclusion reason
Levin RF. Translating research evidence for WCET practice: what is the effectiveness of silver impregnated dressings and topical agents for leg ulcers? WCET Journal. 2008.28(3):21-22.	Ineligible study design
Lev-Tov H, Ajdic D, Mervis J, Kirsner R, Serena T, Reyzelman A, et al. A clinical investigation to evaluate the effect of an antimicrobial gelling fiber dressing* on exudate and bioburden in medium to highly exuding wounds. J Wound Care. 2020.29(SUPPL 7B):199.	Ulcers not infected
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Lindsay G, Latta D, Lyons KGB. A study in general practice of the efficacy of cadexomer iodine in venous leg ulcers treated on alternate days. Acta Ther. 1986.12(2):141-48.	Ulcers not infected
Linehan J, Cubeddu J. Venous disease of the lower extremity: curbing the frustration. Journal of the American Academy of Physician Assistants. 1994.7(9):611-21.	Ineligible study design
Lipman M, Udall I. Use of 10% povidone-iodine moistened gauze primary dressings in the treatment of venous stasis ulcers that have failed to heal with standard wound care. Wound Repair Regen. 2010.18(2):A52. doi: https://dx.doi.org/10.1111/j.1524-475X.2010.00581.x	Ulcers not infected
Lo SF. Antimicrobial silver dressings beneath compression for venous ulceration are not cost-effective compared with standard dressings. Evid Based Nurs. 2010.13(4):120-1. doi: https://dx.doi.org/10.1136/ebn1045	Ineligible study design
Lohmann & Rauscher GmbH & Co. KG. Post-market clinical follow-up study to evaluate the performance and safety of Suprasorb® A + Ag wound dressing and rope in the treatment of chronic wounds. Identifier: DRKS00014861. In: German Clinical Trials Register. Freiburg; Institute for Medical Biometry and Statistics - University of Freiburg: 2018. Available from: https://drks.de/search/en/trial/DRKS00014861 .	Possibly eligible trial; no results available
Lohmann & Rauscher. Suprasorb® A + Ag in the Treatment of Wounds at Risk of Infection and Infected Wounds. Identifier: NCT05646121. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2022. Available from: https://clinicaltrials.gov/study/NCT05646121?term=NCT05646121&rank=1 .	Possibly eligible trial; no results available
Lopez P, Dachs R. Effectiveness of dressings for healing venous leg ulcers. Am Fam Physician. 2007.75(5):650-51.	Review, non-systematic
Loreen Herwaldt. PVI to prevent s. aureus SSI after fixation of HELEF (POTENT Study) (POTENT). Identifier: NCT05763602. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2022. Available from https://clinicaltrials.gov/study/NCT05763602 .	Ineligible intervention

Reference	Exclusion reason
Lund University. Investigation of a novel formulation with a lactic acid bacterial microbiome on chronic ulcers. Identifier: ISRCTN22579989. In: ISRCTN Registry [internet]. London: BioMed Central Limited: 2017. Available from http://isrctn.com/ISRCTN22579989 .	Ulcers not infected
Ma H, O'Donnell TF, Rosen NA, lafrati MD. The real cost of treating venous ulcers in a contemporary vascular practice. <i>Journal of Vascular Surgery-Venous and Lymphatic Disorders</i> . 2014.2(4):355-61. doi: 10.1016/j.jvsv.2014.04.006	Ineligible intervention
Maaz Arif M, Khan SM, Gull N, Tabish TA, Zia S, Ullah Khan R, et al. Polymer-based biomaterials for chronic wound management: promises and challenges. <i>International Journal of Pharmaceutics</i> . 2021.598:120270. doi: https://dx.doi.org/10.1016/j.ijpharm.2021.120270	Review, non-systematic
Maduba CC, Nhadozie UU, Modekwe VI, Nwankwo EU. Comparing hospital stay and patient satisfaction in a resource poor setting using conventional and locally adapted negative pressure wound dressing methods in management of leg ulcers with split skin grafts: a comparative prospective study. <i>Pan Afr Med J</i> . 2020.36:105. doi: https://dx.doi.org/10.11604/pamj.2020.36.105.19961	Ineligible population
Maggio D, Graves L. Evidence-based practice: using active leptospermum honey dressings in an indigent population. <i>Ostomy Wound Manage</i> . 2010.56(11):20-22.	Ineligible study design
Mancini S, Cuomo R, Poggialini M, D'Aniello C, Botta G. Autolytic debridement and management of bacterial load with an occlusive hydroactive deressing impregnated with polyhexamethylene biguanide. <i>Acta Biomed Ateneo Parmense</i> . 2018.88(4):409-13. doi: https://dx.doi.org/10.23750/abm.v88i4.5802	Ulcers not infected
Manizate F, Fuller A, Gendics C, Lantis JC. A prospective, single-center, nonblinded, comparative, postmarket clinical evaluation of a bovine-derived collagen with ionic silver dressing versus a carboxymethylcellulose and ionic silver dressing for the reduction of bioburden in variable-etiology, bilateral lower-extremity wounds. <i>Adv Skin Wound Care</i> . 2012.25(5):220-5. doi: https://dx.doi.org/10.1097/01.ASW.0000414705.56138.65	Ulcers not infected
Mansson T, Avrach W, Hansson C, Karlsmark O, Kristensen O, Menke H, et al. Effect of iodosorb dressing, duoderm and vaseline gauze on symptomatic parameters in exuding venous leg ulcers. 5th European Conference on Advances in Wound Managment; November 21-24; Harrogate, UK. 1995: 31-32. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01932891/full	Unobtainable
Mansson T, Tenvall GR, Sundberg J. A cost analysis as part of a clinical comparative leg ulcer study of Iodosorb dressing, Duoderm E and Jelonet. European Wound Management Association Conference; 1997, 27-29 April; Milan, Italy. 1997.	Ulcers not infected

Reference	Exclusion reason
Mansson T. Effect of iodosorb dressing, duoderm e and jelonet on symptomatic parameters in exudative venous leg ulcers. Proceedings of the 5th European Conference on Advances in Wound Management; 1995, 21-24 November; Harrogate, UK. 1996: 160-62. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00249738/full	Ulcers not infected
Margraf HW, Covey Jr TH. A trial of silver zinc allantoinate in the treatment of leg ulcers. Arch Surg. 1977.112(6):699-704.	No separate results for infected ulcer subgroup
Markoishvili K, Tsitlanadze G, Katsarava R, Morris JG, Sulakvelidze A. A novel sustained-release matrix based on biodegradable poly(ester amide)s and impregnated with bacteriophages and an antibiotic shows promise in management of infected venous stasis ulcers and other poorly healing wounds. Int J Dermatol. 2002.41(7):453-8. doi: https://dx.doi.org/10.1046/j.1365-4362.2002.01451.x	Ineligible agent
Marti-Carvajal AJ, Knight-Madden JM, Martinez-Zapata MJ. Interventions for treating leg ulcers in people with sickle cell disease. Cochrane Database Syst Rev. 2021.1:CD008394. doi: https://dx.doi.org/10.1002/14651858.CD008394.pub4	SR for ref checking
Maydick D. Profiles in excellence 2008. Derma Sciences' medihoney proven to speed healing in stalled leg ulcers. Podiatry Management. 2008.27(9):206-06.	Review, non-systematic
Mayer A, Slezak V, Takac P, Olejnik J, Majtan J. Treatment of non-healing leg ulcers with honeydew honey. J Tissue Viability. 2014.23(3):94-7. doi: https://dx.doi.org/10.1016/j.jtv.2014.08.001	Ulcers not infected
McAusland S. Report on 103 cases of varicose ulceration treated with silver dinaphthylmethane disulphonate. Med Press. 1951.226(20):483-5.	Ineligible study design
McKnight AG. A clinical trial of povidone-iodine in the treatment of chronic leg ulcers. Practitioner. 1965.195:230-4.	Unobtainable
Meaume S, Dissemond J, Addala A, Vanscheidt W, Stucker M, Goerge T, et al. Evaluation of two fibrous wound dressings for the management of leg ulcers: results of a European randomised controlled trial (EARTH RCT). J Wound Care. 2014.23(3):105-6,08-11, 14-6. doi: https://dx.doi.org/10.12968/jowc.2014.23.3.105	Ulcers not infected
MedCu Technologies Ltd. Efficacy of wound dressings With copper oxide. Identifier: NCT04634838. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2021. Available from https://clinicaltrials.gov/study/NCT04634838 .	Ulcers not infected
Medline Industries. A clinical evaluation of a honey impregnated dressing at removing necrotic tissue from chronic wounds. Identifier: NCT03412929. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2018. Available from https://clinicaltrials.gov/study/NCT03412929 .	Ulcers not infected

Reference	Exclusion reason
Meissner MH. Venous ulcer care: which dressings are cost effective? <i>Phlebology</i> . 2014.29(Suppl 1):174-80. doi: https://dx.doi.org/10.1177/0268355514529699	Ulcers not infected
Metcalfe D, Parsons D, Bowler P. A next-generation antimicrobial wound dressing: a real-life clinical evaluation in the UK and Ireland. <i>J Wound Care</i> . 2016.25(3):132, 34-8. doi: https://dx.doi.org/10.12968/jowc.2016.25.3.132	No separate results for eligible population subgroup
Michaels JA, Campbell WB, King BM, Macintyre J, Palfreyman SJ, Shackley P, et al. A prospective randomised controlled trial and economic modelling of antimicrobial silver dressings versus non-adherent control dressings for venous leg ulcers: the VULCAN trial. <i>Health Technol Assess</i> . 2009.13(56):1-114, iii. doi: https://dx.doi.org/10.3310/hta13560	Ulcers not infected
Mihelic M, Rucigaj TP. The role of therapeutic dressings with silver in chronic wounds therapy. <i>Acta Med Croatica</i> . 2015.69(Suppl 1):73-75.	Ulcers not infected
Mirko T, Edoardo C, Demetrio G, Alfonso C, Lorenzo T. Comparative study of two modality of wound care treatment with antibacterial dressings in venous leg ulcers: a randomized controlled trial. <i>J Wound Care</i> . 2020.29(SUPPL 7B):199.	Ulcers not infected
Miyachi Y, Imamura S. Use of sugar and povidone-iodine in the treatment of refractory cutaneous ulcers. <i>J Dermatolog Treat</i> . 1990.1(4):191-93.	No separate results for infected ulcer subgroup
MLcoch T, Bartakova J, Chadimova K, Ornstova E, Hajickova B, Dolezal T. PMD22 Cost-effectiveness analysis of sucrose octasulfate (urgostart) dressing in the treatment of diabetic foot and venous leg ulcers. <i>Value Health</i> . 2019.22(Suppl 3):S673. doi: https://dx.doi.org/10.1016/j.jval.2019.09.1435	Ulcers not infected
Moberg S, Hoffman L, ML G. A Randomized Trial of Cadexomer Iodine in Decubitus Ulcers. <i>J Am Geriatr Soc</i> . 1983.31(8):462-65. doi: https://doi.org/10.1111/j.1532-5415.1983.tb05117.x	Ulcers not infected
Molnlycke Health Care AB. An open, non-comparative, multicenter investigation to evaluate the safety and performance of exufiber ag+, a gelling fiber silver dressing, when used in medium to high exuding chronic wounds. Identifier: NCT05494450. In: <i>ClinicalTrials.gov</i> [internet]. Bethesda: US National Library of Medicine: 2022. Available from https://clinicaltrials.gov/study/NCT05494450 .	Ulcers not infected
Monaco AS, Hylinski JH, Valins RJ. Leg ulcers and foot care in the diabetic patient. <i>Osteopathic Annals</i> . 1979.7(4):43-49.	Review, non-systematic

Reference	Exclusion reason
Moore K, Thomas A, Harding KG. Iodine released from the wound dressing iodisorb modulates the secretion of cytokines by human macrophages responding to bacterial lipopolysaccharide. <i>Int J Biochem Cell Biol.</i> 1997.29(1):163-71. doi: https://dx.doi.org/10.1016/s1357-2725(96)00128-8	Ineligible study design
Moore K. A new silver dressing for wounds with delayed healing. <i>Wounds UK.</i> 2006.2(2):70-78.	No separate results for infected ulcer subgroup
Moore RA, Liedl DA, Jenkins S, Andrews KL. Using a silver-coated polymeric substrate for the management of chronic ulcerations: the initial Mayo Clinic experience. <i>Adv Skin Wound Care.</i> 2008.21(11):517-20. doi: https://dx.doi.org/10.1097/01.ASW.0000323579.87700.ec	Ulcers not infected
Moore Z. Honey-impregnated dressings and usual care did not differ for healing venous leg ulcers. <i>Evid Based Nurs.</i> 2008.11(3):87. doi: https://dx.doi.org/10.1136/ebn.11.3.87	Ulcers not infected
Morris C, Timmons J, Sykes R. The management of chronic wound biofilm with a monofilament fibre debridement biofilm pathway: results of an audit. <i>J Wound Care.</i> 2017.26(SUPPL 6):362. doi: https://dx.doi.org/10.12968/jowc.2017.26.Sup6b.1	Ineligible study design
Morris WT. Leg ulcers. Choosing appropriate therapy. <i>Curr Ther.</i> 1987.28(4):121-33.	Ineligible study design
Moses RL, Prescott TAK, Mas-Claret E, Steadman R, Moseley R, Sloan AJ. Evidence for natural products as alternative wound-healing therapies. <i>Biomolecules.</i> 2023.13(3):444. doi: https://dx.doi.org/10.3390/biom13030444	Review, non-systematic
Moss C, Taylor AE, Shuster S. Comparison of cadexomer iodine and dextranomer for chronic venous ulcers. <i>Clin Exp Dermatol.</i> 1987.12(6):413-8. doi: https://dx.doi.org/10.1111/j.1365-2230.1987.tb01939.x	Ulcers not infected
Moss C, Taylow A, Shuster S. Comparative study of cadexomer iodine and dextranomer in chronic leg ulcers. <i>Scott Med J.</i> 1984: 54. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00346371/full	Ulcers not infected
Mthanti SMJ, Pelle G, Cremers NAJ. L-mesitran foam: evaluation of a new wound care product. <i>Case Reports in Dermatological Medicine.</i> 2022.2022:4833409. doi: https://dx.doi.org/10.1155/2022/4833409	Ineligible study design
Munoz AL, Merchan WH, Resende Pires AL, Moraes AM, Gomez LA. Biostimulation of venous chronic ulcers with platelet-rich plasma gel and biocompatible membranes of chitosan and alginate: a pilot study. <i>Wound Medicine.</i> 2019.26(1):100161. doi: https://dx.doi.org/10.1016/j.wndm.2019.100161	Case series <10
Münter KC, Beele H, Russell L, Crespi A, Gröchenig E, Basse P, et al. Effect of a sustained silver-releasing dressing on ulcers with delayed healing: the CONTOP study. <i>J Wound Care.</i> 2006.15(5):199-206.	No separate results for infected ulcer subgroup

Reference	Exclusion reason
Munter KC, Beele H. The CONTOP study: improved healing of delayed healing ulcers with sustained silver-releasing foam dressing versus other silver dressings. <i>Journal of Wound, Ostomy and Continence Nursing</i> . 2007.34:S68-S68. doi: 10.1097/01.won.0000271038.01843.5f	No separate results for infected ulcer subgroup
Mussi C, Salvioli G. Clinical evaluation of Sorbact® in the treatment of infected pressure sores. <i>Acta Vulnologica</i> . 2004.2(1):9-11.	Unobtainable
National Institute Of Unani Medicine. To see the healing property of marham-e-khal in non healing ulcer in comparison to 5% betadine ointment as local application. Identifier: CTRI/2021/04/032562. In: Clinical Trials Register - India (CTRI) [internet]. New Delhi: National Institute of Medical Statistics: 2021. Available from http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=51056 .	Ulcers not infected
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Nestjones D, Vandeputte J. Clinical evaluation of melladerm plus: a honey-based wound gel. <i>Wounds UK</i> . 2012.8(2):106-12.	Ineligible study design
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Okany CC, Atimomo CE, Akinyanju OO. Efficacy of natural honey in the healing of leg ulcers in sickle cell anaemia. <i>Niger Postgrad Med J</i> . 2004.11(3):179-81.	Ulcers not infected
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O'Meara S, Al-Kurdi D, Ologun Y, Ovington LG, Martyn-St James M, Richardson R. Antibiotics and antiseptics for venous leg ulcers. <i>Cochrane Database Syst Rev</i> . 2014; (1): Available from: http://dx.doi.org/10.1002/14651858.CD003557.pub5	NICE guidance SR for ref checking
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Reference	Exclusion reason
Ormiston MC, Seymour MT, Venn GE, Cohen RI, Fox JA. Controlled trial of iodosorb in chronic venous ulcers. Br Med J (Clin Res Ed). 1985.291(6499):902. doi: https://dx.doi.org/10.1136/bmj.291.6499.902-a	Ulcers not infected
Ormiston MC, Seymour MTJ, Venn GE, Cohen RI, Fox JA. A randomised comparison of cadexomer iodine and a standard treatment in out-patients with chronic venous ulcers. Cadexomer Iodine. 1983: 63-69. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00605499/full	Ulcers not infected
Oropallo AR. Use of native type I collagen matrix plus polyhexamethylene biguanide for chronic wound treatment. Plast. 2019.7(1):e2047. doi: https://dx.doi.org/10.1097/GOX.0000000000002047	No separate results for eligible population subgroup
Padaria SF. Epidermal growth factor in the management of venous leg ulcers. Phlebology. 2022.37(Suppl 2):264. doi: https://dx.doi.org/10.1177/02683555221110363	Ulcers not infected
Panca M, Cutting K, Guest JF. Clinical and cost-effectiveness of absorbent dressings in the treatment of highly exuding VLU. J Wound Care. 2013.22(3):109-10, 12-8. doi: https://dx.doi.org/10.12968/jowc.2013.22.3.109	Ineligible intervention
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PD Patel Ayurved Hospital Nadiad. Non healing ulcer management by apamarga kshar taila and povidone iodine. Identifier: CTRI/2018/08/015220. In: Clinical Trials Register - India (CTRI) [internet]. New Delhi: National Institute of Medical Statistics: 2018. Available from http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=27081 .	Ulcers not infected

Reference	Exclusion reason
Pecova J, Rohlikova V, Smoldasova M, Marek J. Clinical efficacy of hyaluronic acid with iodine in hard-to-heal wounds. <i>Pharmaceutics</i> . 2023.15(9):01. doi: https://dx.doi.org/10.3390/pharmaceutics15092268	No separate results for eligible population subgroup
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Pierluigi G, Luigi C, Emanuele IB, Federica M. Clorhexidine digluconate solution in skin xerosis. our experience. <i>J Wound Care</i> . 2020.29(SUPPL 7B):284.	Ulcers not infected
Planinsek Rucigaj T. Comparative effects of honey based and silver/ charcoal based dressings on the healing of venous leg ulcers: a randomized clinical study. 17th Conference of the European Wound Management Association; 2007, 2-4 May; Glasgow, Scotland. 2007: 54. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00605510/full	Ulcers not infected
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Reference	Exclusion reason
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Reese A, Willoughby D, Davis SC, Silver T, Venn T. Revisiting the use of honey for treating chronic wounds. <i>American Journal for Nurse Practitioners</i> . 2011.15(9/10):27-34.	Review, non-systematic
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Ribeiro CT, Dias FA, Fregonezi GA. Hydrogel dressings for venous leg ulcers. <i>Cochrane Database Syst Rev</i> . 2022.8:CD010738. doi: https://dx.doi.org/10.1002/14651858.CD010738.pub2	SR for ref checking
Rippon M, Davies P, White R, Bosanquet N. The economic impact of hard-to-heal leg ulcers. <i>Wounds UK</i> . 2007.3(2):58-69.	Ineligible intervention
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Reference	Exclusion reason
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Rodriguez I, Alvarez A, Massey C, Miller L, Rannou R, Croce M, et al. Novel bioengineered collagen with manuka honey and hydroxyapatite sheet for the treatment of lower extremity chronic wounds in an urban hospital wound care setting. Wounds: A Compendium of Clinical Research and Practice. 2023.35(1):E35-E38. doi: https://dx.doi.org/10.25270/wnds/22034	Ulcers not infected
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Rucigaj TP, Mihelic M. Comparative effects of honey based and silver/charcoal based dressings on the healing of venous leg ulcers. Acta Med Croatica. 2015.69(Supplement 1):67-72.	Ulcers not infected
Russell D, Atkin L, Betts A, Dowsett C, Fatoye F, Gardner S, et al. Using a modified delphi methodology to gain consensus on the use of dressings in chronic wounds management. J Wound Care. 2018.27(3):156-65. doi: https://dx.doi.org/10.12968/jowc.2018.27.3.156	Ineligible study design
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Sáez-Martín LC, García-Martínez L, Román-Curto C, Sánchez-Hernández MV, Suárez-Fernández RM. Negative pressure and nanocrystalline silver dressings for nonhealing ulcer: A randomized pilot study. Wound Repair Regen. 2015.23(6):948-52. doi: 10.1111/wrr.12358	Ulcers not infected
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Reference	Exclusion reason
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Scanlon E, Karlsmark T, Leaper DJ, Carter K, Poulsen PB, Hart-Hansen K, et al. Cost-effective faster wound healing with a sustained silver-releasing foam dressing in delayed healing leg ulcers--a health-economic analysis. <i>Int Wound J</i> . 2005.2(2):150-60. doi: https://dx.doi.org/10.1111/j.1742-4801.2005.00083.x	Ulcers not infected
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Seckam AM, Twardowska-Sauchka K, Heggemann J, Sus-Burghart A, Augustin M. Clinical performance and quality of life impact of an absorbent bacteria-binding foam dressing. <i>Br J Nurs</i> . 2021.30(5):S21-S30. doi: https://dx.doi.org/10.12968/bjon.2021.30.5.S21	No separate results for infected ulcer subgroup
Senet P, Petersen B. Hard-to-heal venous leg ulcers: results from a double-blind RCT of a silver foam dressing. <i>EWMA Journal</i> . 2012.(2):188.	Ulcers not infected
Sharpe A, Tickle J, Hampton S, Gray D. A multicentre evaluation of a new chitosan FHO2™ spray-on dressing patients with chronic wounds in the UK. <i>JCN</i> . 2018.32(3):30-38.	Ulcers not infected

Reference	Exclusion reason
Shirgill S, Poologasundarampillai G, Kuehne S, Jabbari S, Ward J. Investigating the antimicrobial effects of metal-doped bioactive glass fibres on chronic wound biofilms. <i>Tissue Engineering - Part A</i> . 2023.29(13-14)doi: https://dx.doi.org/10.1089/ten.tea.2023.29043.abstracts	Ineligible study design
Shuttleworth GJ, Mayho GV. Controlled trial of iodosorb in chronic venous ulcers. <i>Br Med J (Clin Res Ed)</i> . 1985.291(6495):605-6. doi: https://dx.doi.org/10.1136/bmj.291.6495.605-c	Ineligible study design
Sibbald RG, Browne AC, Coutts P, Queen D. Screening evaluation of an ionized nanocrystalline silver dressing in chronic wound care. <i>Ostomy Wound Manage</i> . 2001.47(10):38-43.	No separate results for infected ulcer subgroup
Sibbald RG, Contreras-Ruiz J, Coutts P, Fierheller M, Rothman A, Woo K. Bacteriology, inflammation, and healing: a study of nanocrystalline silver dressings in chronic venous leg ulcers. <i>Adv Skin Wound Care</i> . 2007.20(10):549-58. doi: https://dx.doi.org/10.1097/01.ASW.0000294757.05049.85	Ulcers not infected
Sibbald RG, Coutts P, Woo KY. Reduction of bacterial burden and pain in chronic wounds using a new polyhexamethylene biguanide antimicrobial foam dressing-clinical trial results. <i>Adv Skin Wound Care</i> . 2011.24(2):78-84. doi: https://dx.doi.org/10.1097/01.ASW.0000394027.82702.16	Ulcers not infected
Sigal M, Dalac S, Le Guyadec T, Jegou J, Bohbot S. Clinical evaluation of a new dressing with polyabsorbent fibres and antimicrobial silver matrix* in the local management of chronic wounds with inflammatory signs from debridement stage. <i>J Wound Care</i> . 2017.26(SUPPL 6):217. doi: https://dx.doi.org/10.12968/jowc.2017.26.Sup6b.1	Ulcers not infected
Sigal-Grinberg M, Senet P, Lazareth I, Sauvadet A, Bohbot S. Evaluation of a new contact layer impregnated with silver salts in the management of critically colonized venous leg ulcers. Results of a randomized clinical trial. 17th Conference of the European Wound Management Association, 2007 May 2-4, Glasgow, Scotland. 2007: 31. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00605506/full	Ulcers not infected
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Smith J, Hill J, Barrett S, Hayes W, Kirby P, Walsh S, et al. Evaluation of urgotol plus k-four compression for venous leg ulcers. <i>Br J Nurs</i> . 2004.13(6 Suppl):S20-8. doi: https://dx.doi.org/10.12968/bjon.2004.13.Sup1.12536	Ineligible agent
Smith LA. Clinical experience using silver antimicrobial dressings on venous stasis ulcers. <i>Ostomy/wound management</i> . 2003.Suppl:10-12.	Unobtainable

Reference	Exclusion reason
Smith S. Successful management of infected wounds using a solution and gel containing betaine and PHMB. Wound Pract Res. 2013.21(4):183-85.	Case series <10
Smith T, Legel K, Hanft JR. Topical leptospermum honey (medihoney) in recalcitrant venous leg wounds: a preliminary case series. Adv Skin Wound Care. 2009.22(2):68-71. doi: https://dx.doi.org/10.1097/01.ASW.0000345283.05532.9a	Ulcers not infected
Snyder R, Richter D, Hill ME. A retrospective study of sequential therapy with advanced wound care products versus saline gauze dressings: comparing healing and cost. Ostomy Wound Manage. 2010.56(11A):9-15.	No separate results for infected ulcer subgroup
Sobotka L, Adamkova V, Borkovcova J. Combined self-adherent antimicrobial wound dressing in treatment of leg ulcers-observation study. J Wound Care. 2017.26(SUPPL 6):343. doi: https://dx.doi.org/10.12968/jowc.2017.26.Sup6b.1	Ulcers not infected
Sopata M, Kucharzewski M, Tomaszewska E. Antiseptic with modern wound dressings in the treatment of venous leg ulcers: clinical and microbiological aspects. J Wound Care. 2016.25(8):419-26. doi: https://dx.doi.org/10.12968/jowc.2016.25.8.419	Ulcers not infected
Sopata M, Tomaszewska E, Muszynski Z, Ciupinska M. Can antiseptics with modern wound dressings have beneficial effect on venous leg ulcers treatment? Clinical and microbiological aspects. Wound Repair Regen. 2014.22(2):A60. doi: https://dx.doi.org/10.1111/wrr.12155	Ulcers not infected
Spira JAO, Borges EL, Junior JFP, Monteiro DS, Kitagawa KY. Estimated costs in treating sickle cell disease leg ulcer. Rev Esc Enferm USP. 2020.54:e03582. doi: https://dx.doi.org/10.1590/S1980-220X2018053603582	Ineligible study design
Sridhar S, Nanjappa N. Microbiological and clinical response of superoxidized solution versus povidone iodine in the management of lower limb ulcers. Natl J Physiol Pharm Pharmacol. 2017.7(10):1074-80. doi: https://dx.doi.org/10.5455/njppp.2017.7.0307117052017	No separate results for eligible population subgroup
Stephen-Haynes J. Evaluation of a honey-impregnated tulle dressing in primary care. Br J Community Nurs. 2004.(Suppl):S21-27.	No separate results for infected ulcer subgroup
Stewart AJ, Leaper DJ. Treatment of chronic leg ulcers in the community: a comparative trial of scherisorb and iodisorb. Phlebology / Venous Forum of the Royal Society of Medicine. 1987.115-21.	Ulcers not infected
Strilko BL, Barkauskas C, McIntosh A. Addressing exudate in patients with refractory leg ulcers: novel bilayered polymeric silver dressing. Journal of Wound, Ostomy and Continence Nursing. 2009.36:S29-30.	Ulcers not infected
Strohal R, Mittlböck M, Müller W, Hammerle G. Management of hard-to-heal leg ulcers with an acid-oxidising solution versus standard of care: the MACAN study. J Wound Care. 2021.30(9):694-704. doi: https://dx.doi.org/10.12968/jowc.2021.30.9.694	Ineligible intervention

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Sundberg J, Meller R. A retrospective review of the use of cadexomer iodine in the treatment of chronic wounds. Wounds: A Compendium of Clinical Research and Practice. 1997.9(3):68-86.	Review, non-systematic
Tadej M, Colbourn C, Kerr A, Bree-Aslan C. Reducing bacterial loading using suprasorb x + PHMB. JCN. 2009.23(9):34-37.	Review, non-systematic
Tarvainen K. Cadexomer iodine (iodosorb) compared with dextranomer (debrisan) in the treatment of chronic leg ulcers. Acta Chir Scand Suppl. 1988.544:57-9.	Ulcers not infected
Tellechea O, Tellechea A, Teixeira V, Ribeiro F. Efficacy of honey gel in the treatment of chronic lower leg ulcers: a prospective study. EWMA Journal. 2013.13(2):35-39.	No separate results for infected ulcer subgroup
The Swedish Council on Health Technology A. Chronic ulcers in the elderly – prevention and treatment. Sweden: 2014. Available from: http://www.sbu.se/en/publications/sbu-assesses/chronic-ulcers-in-the-elderly--prevention-and-treatment/ .	Ulcers not infected
Thomas S. Sorbsan in the management of leg ulcers. Pharm J. 1989.706-09.	Ineligible agent
Thomason H, Beasley A. A new innovation in treating infected wounds and disrupting biofilms. Wounds UK. 2016.12(1):78-84.	Ineligible study design
Tiwary SK, Choubey KK, Nath G, Kumar P, Khanna AK. Effect of four-layer dressing on the microbiological profile of venous leg ulcer. J Wound Care. 2023.32(Sup3):S22-S30. doi: 10.12968/jowc.2023.32.Sup3.S22	Ineligible intervention
Tolentino AC, Turkos M, Dick S. Cost-analysis of medihoney calcium alginate versus aquacel ag dressing for chronic leg ulcers treatment under the Brazilian public payer perspective. Value Health. 2015.18(3):A45.	Ineligible study design
Tonda-Turo C, Bofto M, Ruini F, Calzone S, Robino P, Nebbia P, et al. Nanotechnology-based strategies to treat chronic wounds. Journal of Applied Biomaterials and Functional Materials. 2016.14(3):e391. doi: https://dx.doi.org/10.5301/jabfm.5000321	Ineligible study design
Tonello C, Scomparin MA, Scarpazza O, Camporese G, Nalin F, Salmistraro G, et al. Aquacel ag+extra: antimicrobial dressing with debriding action. J Wound Care. 2017.26(SUPPL 6):345. doi: https://dx.doi.org/10.12968/jowc.2017.26.Sup6b.1	No separate results for infected ulcer subgroup
Torkington-Stokes R, Moran K, Martinez DS, Granara DC, Metcalf DG. Improving outcomes for patients with hard-to-heal wounds following adoption of the wound hygiene protocol: real-world evidence. J Wound Care. 2024.33(5):304-10. doi: https://dx.doi.org/10.12968/jowc.2024.33.5.304	Ineligible population
* Convatec submitted a document reporting eligible subgroup data for the infected, non-arterial leg ulcers (98 of 693 wounds). However, the EAG considered that this document did not provide sufficient information to allow an adequate	

Reference	Exclusion reason
assessment of the reliability of evidence (specifically lacking in details on the baseline data for this subgroup, descriptions of the study's design and outcome event numerators as key outcomes reported as proportions only). This study was therefore not included.	
Trial C, Darbas H, Lavigne JP, Sotto A, Simoneau G, Tillet Y, et al. Assessment of the antimicrobial effectiveness of a new silver alginate wound dressing: a RCT. J Wound Care. 2010.19(1):20-6. doi: https://dx.doi.org/10.12968/jowc.2010.19.1.46095	No separate results for eligible population subgroup
Trudigan J, Law P, Tarbox B. Evaluation of urgoclean for the treatment of sloughy, exuding wounds. Wounds UK. 2014.10(1):56-62.	Ineligible agent
Udwadia TE. Ghee and honey dressing for infected wounds. Indian J Surg. 2011.73(4):278-83. doi: https://dx.doi.org/10.1007/s12262-011-0240-7	No eligible outcomes
University Hospital Geneva. Evaluation of a ionic silver and honey preparation to treat chronic wounds of the lower legs. Identifier: NCT01111695. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2010. Available from https://clinicaltrials.gov/study/NCT01111695 .	Ulcers not infected
University of Miami. VLU dressing study. Identifier: NCT03621592. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2018. Available from https://clinicaltrials.gov/study/NCT03621592 .	Ulcers not infected
Urwin S, Dumville JC, Sutton M, Cullum N. Health service costs of treating venous leg ulcers in the UK: evidence from a cross-sectional survey based in the north west of England. BMJ Open. 2022.12(1):e056790. doi: https://dx.doi.org/10.1136/bmjopen-2021-056790	Ineligible study design
Valerie EJ, Virginie J. Evaluation of a silver lipido-colloid dressing (urgotul silver) in local treatment of venous leg ulcers presenting with a high risk of secondary infection. Results of a randomized clinical trial. J Wound Care. 2020.29(SUPPL 7B):278.	No eligible outcomes
Vallejo A, Wallis M, McMillan D. EP316 Use of low-frequency contact ultrasonic debridement with an without polyhexamethylene biguanide in hard-to-heal leg ulcers: an RCT. Journal of Wound Management. 2023.24(2):206-06.	Ulcers not infected
Vallipriya V, Mullaiventhan M, Kumari RRV. The evidence for the use of specific dressings for different types of chronic ulcers: a systematic review. International Journal of Academic Medicine and Pharmacy. 2023.6(1):176-80. doi: https://dx.doi.org/10.47009/jamp.2024.6.1.34	SR for ref checking
Vandenbulcke K, Horvat LIL, De Mil M, Slegers G, Beele H. Evaluation of the antibacterial activity and toxicity of 2 new hydrogels: a pilot study. International Journal of Lower Extremity Wounds. 2006.5(2):109-14. doi: https://dx.doi.org/10.1177/1534734606289507	No eligible outcomes

Reference	Exclusion reason
Vandeputte J, Van Waeyenberge PH. Clinical evaluation of I-mesitran - a honey-based wound ointment. Professional Nursing Today. 2007.11(2):26-31.	Ulcers not infected
Vanderbilt University Medical Center. Enhanced secondary intention healing vs. standard secondary intention healing in mohs surgical defects on the head and distal lower extremities. Identifier: NCT04545476. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2020. Available from https://clinicaltrials.gov/study/NCT04545476 .	Ulcers not infected
Vanscheidt W, Harding K, Téot L, Siebert J. Effectiveness and tissue compatibility of a 12-week treatment of chronic venous leg ulcers with an octenidine based antiseptic - a randomized, double-blind controlled study. Int Wound J. 2012.9(3):316-23. doi: 10.1111/j.1742-481X.2011.00886.x	Ineligible intervention
Velickovic VM, Chadwick P, Rippon MG, Ilic I, McGlone ER, Gebreslassie M, et al. Cost-effectiveness of superabsorbent wound dressing versus standard of care in patients with moderate-to-highly exuding leg ulcers. J Wound Care. 2020.29(4):235-46. doi: https://dx.doi.org/10.12968/jowc.2020.29.4.235	No separate results for infected ulcer subgroup
Verdú Soriano J, Nolasco Bonmatí A, López Casanova P, Torra i Bou JE. Auriga-04 study on the use of a range of allevyn hydro-cellular dressings in the treatment of bed sores and leg ulcers by primary health care professionals. Revista de Enfermeria (Barcelona, Spain). 2006; (4): 43-49. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00605564/full	Non-English language
Vice-Chancellor in Research Affairs Shahid Beheshti University of Medical Sciences. Evaluation of efficacy and side effects of chitosan alginate dressings in chronic wound heal. In: Iranian Registry of Clinical Trials (IRCT) [internet]. Tehran: Iran University of Medical Sciences (IUMS): 2017. Available from https://trialsearch.who.int/Trial2.aspx?TrialID=IRCT2016041927480N1 .	Ulcers not infected
Virchow Biotech Pvt Ltd. Study on dexadine (cadexomer iodine) in the treatment of chronic wounds. Identifier: CTRI/2016/03/006779. In: Clinical Trials Register - India (CTRI) [internet]. New Delhi: National Institute of Medical Sciences: 2016. Available from http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=13593 .	Ulcers not infected
Vitse J, Tchero H, Meaume S, Dompmartin A, Malloizel-Delaunay J, Geri C, et al. Silver sulfadiazine and cerium nitrate in ischemic skin necrosis of the leg and foot: results of a prospective randomized controlled study. International Journal of Lower Extremity Wounds. 2018.17(3):151-60. doi: https://dx.doi.org/10.1177/1534734618795534	Ulcers not infected
Voigt DW, Paul CN. The use of acticoat as silver impregnated telfa dressings in a regional burn and wound care center: the clinicians view. Wounds: A Compendium of Clinical Research and Practice. 2001.13(2):11-22.	Ineligible study design
Walker M, Metcalf D, Parsons D, Bowler P. A real-life clinical evaluation of a next-generation antimicrobial dressing on acute and chronic wounds. J Wound Care. 2015.24(1):11-22. doi: https://dx.doi.org/10.12968/jowc.2015.24.1.11	No separate results for infected ulcer subgroup

Reference	Exclusion reason
Weiss RA, Weiss MA, Ford RW. Randomized comparative study of cutinova foam and allevyn with jobst ulcercare stockings for the treatment of venous stasis ulcers. <i>Phlebology</i> . 1996.11(Suppl 1):14-16.	Ulcers not infected
Wendling S, Sabolinski M. PMU6 Effectiveness of a native type I collagen matrix plus polyhexamethylene biguanide antimicrobial (PHMB) for the treatment of cutaneous wounds in a real world setting. <i>Value Health</i> . 2020.23(Suppl 1):S234. doi: https://dx.doi.org/10.1016/j.jval.2020.04.784	Ulcers not infected
Wild T, Eberlein T, Andriessen A. Wound cleansing efficacy of two cellulose-based dressings. <i>Wounds UK</i> . 2010.6(3):14-21.	Ineligible agent
Williams C. The benefits of aquacel hydrofibre wound dressing. <i>Nursing and Residential Care</i> . 1999.1(8):462-65.	Ineligible study design
Witowska I, Mitura K. Is the presence of biofilm the main factor that keep us away from successful wound healing-report of a case series treated with hydrofiber silver dressings. <i>J Wound Care</i> . 2017.26(Suppl 6):347. doi: https://dx.doi.org/10.12968/jowc.2017.26.Sup6b.1	Ulcers not infected
Wolcott RD, Cook RG, Johnson E, Jones CE, Kennedy JP, Simman R, et al. A review of iodine-based compounds, with a focus on biofilms: results of an expert panel. <i>J Wound Care</i> . 2020.29(Suppl 7):S38-S43. doi: https://dx.doi.org/10.12968/jowc.2020.29.Sup7.S38	Ineligible study design
Woo K, Dowsett C, Costa B, Ebohon S, Woodmansey EJ, Malone M. Efficacy of topical cadexomer iodine treatment in chronic wounds: systematic review and meta-analysis of comparative clinical trials. <i>Int Wound J</i> . 2021.18(5):586-97. doi: https://dx.doi.org/10.1111/iwj.13560	SR for ref checking
Woo K, Hill R, LeBlanc K, Percival SL, Schultz G, Weir D, et al. Effect of a surfactant-based gel on patient quality of life. <i>J Wound Care</i> . 2018.27(10):664-78. doi: https://dx.doi.org/10.12968/jowc.2018.27.10.664	Case series <10
Woo KY, Coutts PM, Sibbald RG. A randomized controlled trial to evaluate an antimicrobial dressing with silver alginate powder for the management of chronic wounds exhibiting signs of critical colonization. <i>Adv Skin Wound Care</i> . 2012.25(11):503-8. doi: https://dx.doi.org/10.1097/01.ASW.0000422628.63148.4b	Ulcers not infected
Wound Management Innovation CRC. Compare the efficiency of two treatments used to remove unhealthy tissue from non-healing leg ulcers. Identifier: ACTRN12618000211268. In: Australian New Zealand Clinical Trials Registry [internet]. Sydney: National Health and Medical Research Council (NHMRC) Clinical Trials Centre - University of Sydney: 2018. Available from https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=374342 .	Ineligible intervention
Wunderlich U, Orfanos CE. Treatment of venous ulcera cruris with dry wound dressings. Phase overlapping use of silver impregnated activated charcoal xerodressing. <i>Der Hautarzt; Zeitschrift fur Dermatologie, Venerologie, und verwandte Gebiete</i> . 1991.(7):446-50.	Non-English language

Reference	Exclusion reason
Yan S, Colin X, Coudray-Omnes C, Guido-Morin P, Kommala DR. A budget impact analysis comparing a hydrofiber; dressing to an alginate dressing in managing exuding venous leg ulcers in France. <i>Int Wound J</i> . 2014.11(3):304-13. doi: https://dx.doi.org/10.1111/j.1742-481X.2012.01095.x	Ulcers not infected
Yang CK, Alcantara S, Goss S, Lantis JC. Cost analysis of negative-pressure wound therapy with instillation for wound bed preparation preceding split-thickness skin grafts for massive (>100 cm(2)) chronic venous leg ulcers. <i>J Vasc Surg</i> . 2015.61(4):995-9. doi: https://dx.doi.org/10.1016/j.jvs.2014.11.076	Ineligible agent
Yarwood-Ross L. Venous ulcers: assessment and wound dressing selection. <i>Nursing and Residential Care</i> . 2013.15(9):596-601.	Ineligible study design
Zarick CS, Benkert EA, Oliver NG, Steinberg JS, Evans KK, Attinger CE, et al. The potential of gelam honey in promoting the proliferative phase of corneal reepithelialization. <i>Wounds: A Compendium of Clinical Research and Practice</i> . 2017.29(12):380-86.	Ulcers not infected
Zelenikova R, Vyhldalova D. Applying honey dressings to non-healing wounds in elderly persons receiving home care. <i>J Tissue Viability</i> . 2019.28(3):139-43. doi: https://dx.doi.org/10.1016/j.jtv.2019.04.002	Ulcers not infected
Zhang L, Wang S, Tan M, Zhou H, Tang Y, Zou Y. Efficacy of oxidized regenerated cellulose/collagen dressing for management of skin wounds: a systematic review and meta-analysis. <i>Evid Based Complement Alternat Med</i> . 2021.2021:1058671. doi: https://dx.doi.org/10.1155/2021/1058671	SR for ref checking
Zhao M, Zhang D, Tan L, Huang H. Silver dressings for the healing of venous leg ulcer: a meta-analysis and systematic review. <i>Medicine</i> . 2020.99(37):e22164. doi: https://dx.doi.org/10.1097/MD.00000000000022164	SR for ref checking
Ziegler K, Gorl R, Effing J, Ellermann J, Mappes M, Otten S, et al. Reduced cellular toxicity of a new silver-containing antimicrobial dressing and clinical performance in non-healing wounds. <i>Skin Pharmacol Physiol</i> . 2006.19(3):140-46. doi: https://dx.doi.org/10.1159/000092594	Ulcers not infected
Zuccarelli F. A comparative study of the hydrocellular dressing allevyn and the hydrocolloid dressing duoderm in the local treatment of leg ulcers. <i>Phlebologie</i> . 1992; (4): 529-33. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00092986/full	Unobtainable

RFI: request for information

11.3 Appendix C: Detailed appraisal of studies

11.3.1 Full intervention characteristics of all included studies

Table 11.1: Intervention characteristics and details of wound cleansing and secondary dressing

Study	Agent	Dressing type	Secondary dressing	Pre-dressing debridement	Pre-dressing cleaning/irrigation	Intended frequency of dressing change
Chitosan						
Mo 2015 (Mo et al. 2015)	Intervention: Chitosan	Absorbent acylated chitosan fibre – (Foshan UMT Ltd, which manufactures Kytocel). Category: Alginate, gelling fibre, absorbent fibre	NR	NR	Sterile saline solution	Dressing change frequency was every 3-4 days
	Comparator: No agent	Gauze (Vaseline gauze; Shaoxing Zhende Surgical Dressing Co. Ltd, China) Category: Wound contact layers, gauze				

Study	Agent	Dressing type	Secondary dressing	Pre-dressing debridement	Pre-dressing cleaning/irrigation	Intended frequency of dressing change
Orig et al. 2016 (Orig and Singleton 2016)	Intervention: Chitosan	KytoCel gelling fibre Category: Alginate, gelling fibre, absorbent fibre	Variety of secondary dressings used, including super absorbent dressings, surgical pads and foams	NR	NR	Wear time ranged from 2 to 7 days
Copper						
Dokic 2023 (Dokic S et al. 2023)	Intervention: Copper wound dressings	Not reported within presentation, study submitted by Edge medical which manufactures MedCu and is hosted on MedCu.com, therefore considered to be MedCu. Category: Wound contact layer	NR	NR	NR	NR

Study	Agent	Dressing type	Secondary dressing	Pre-dressing debridement	Pre-dressing cleaning/irrigation	Intended frequency of dressing change
Melamed 2021 (Melamed et al. 2021)	Intervention: Cupric oxide dressing In a 2 week screening period participants received “standard of care” dressings (n=8 non-antimicrobial hydrofiber dressings, n=5 silver hydrofiber). After 4 weeks with copper dressing patients received standard-of-care dressing for a further 2 weeks (dressings NR).	External layer of polypropylene nonwoven fabric and internal layer of needle-punch polyester and hydrofibers, both impregnated with cupric oxide microparticles (study submitted by Edge medical and authors affiliated with MedCu Ltd., which manufactures MedCu) Category: Wound contact layer	NR	NR	NR	Dressing was applied twice weekly
Treadwell 2022 (Treadwell T et al. 2022)	Intervention: cupric oxide-impregnated dressing	Not reported within poster, study submitted by Edge medical which manufactures MedCu, therefore considered MedCu. Category: Wound contact layer	Secondary dressing depending on patient diagnosis	Wounds were debrided	NR	Dressing changed once a week
DACC						

Study	Agent	Dressing type	Secondary dressing	Pre-dressing debridement	Pre-dressing cleaning/irrigation	Intended frequency of dressing change
Bruce 2012 (Bruce 2012)	Intervention: DACC	Cutimed Sorbact, (Cutimed). Category: Wound contact layer	Clinicians were able to choose the most appropriate fixation for the dressing including retention, tubular and compression bandages	NR	NR	Dressings changed every 2 to 3 days
Enzyme Alginogel						

Study	Agent	Dressing type	Secondary dressing	Pre-dressing debridement	Pre-dressing cleaning/irrigation	Intended frequency of dressing change
Durante 2012 (Durante 2012)	Intervention: Enzyme Alginogel	Flaminal Gel. The attending physician selected Flaminal Hydro (3% alginate) or Flaminal Forte (5.5% alginate), according to exudate levels. Category: Ointments, gels, hydrogels	Secured by secondary bandages (polyurethane foam or non-adherent dressing gauze, depending on exudate level). Wounds also received standard complementary treatment of care, such as off-loading shoes for DFUs, pressure-redistributing mattresses for pressure ulcers and compression bandaging for mixed aetiology leg ulcers.	NR	Wounds were pre-cleaned with polyhexanide solution.	The enzyme alginogel was left on the wound for 1 to 4 days, as long as the gel remained intact. For necrotic and sloughy wounds, dressings were changed daily; for granulating wounds, dressings were changed every 2 to 4 days.
Jones et al. 2018 (Jones)	Intervention: Enzyme Alginogel	Flaminal Hydro/Forte gel. The dressing used was Flaminal Forte in	NR	NR	NR	NR

Study	Agent	Dressing type	Secondary dressing	Pre-dressing debridement	Pre-dressing cleaning/irrigation	Intended frequency of dressing change
and Oates 2018)		70% of patients and Flaminal Hydro in 30% of patients.				
	Comparator: No comparator, single-arm study.	Category: Ointments, gels, hydrogels				
King et al. 2023 (King and Rolland 2023)	Intervention: Enzyme Alginogel	Flaminal Hydro/Forte Gel. The dressing used was Flaminal Forte in 66% of patients and Flaminal Hydro in 31% of patients. 3% used a combination of both formulations	NR	NR	NR	NR
	Comparator: No comparator, single-arm study	Category: Ointments, gels, hydrogels				
Honey						

Study	Agent	Dressing type	Secondary dressing	Pre-dressing debridement	Pre-dressing cleaning/irrigation	Intended frequency of dressing change
Biglari et al 2013 (Biglari et al. 2013)	Intervention: Honey (various Medihoney™ dressing products, sub-agent manuka honey)	Topical Medihoney or Medihoney wound gel (sub-agent manuka honey). In 66% of all treatments, antibacterial honey (Medihoney™) was applied, in 22%, antibacterial wound gel (Medihoney™), in 6%, a combination of both, and in 6%, the product was not specified Category: Ointments, gels, hydrogels.	Different centres applied secondary dressings preferred by the physician involved (including calcium alginate, hydrofiber dressings and sterile gauzes moistened with sterile isotonic sodium chloride solution)	NR	Physicians were advised to clean wounds with sterile isotonic sodium chloride solution; to protect wound margins where necessary with Cavilon and to avoid additional use of antiseptics after 24 hours of treatment with honey	Physicians were advised to change dressings every 1 to 3 days
Yang et al 2015 (Yang K et al. 2015)	Intervention: Honey (manuka, topical medical grade honey)	Topical medical honey dressing – submitted by ManukaMed which produces a Manuka honey dressing) Category: Ointments, gels, hydrogels	Multi-layer compression wrap	Weekly wound debridement	NR	NR

Study	Agent	Dressing type	Secondary dressing	Pre-dressing debridement	Pre-dressing cleaning/irrigation	Intended frequency of dressing change
Moghazy et al. 2010 (Moghazy et al. 2010)	Intervention: Honey (monofloral)	Gauze (Medium-pored non-sterile gauze submerged and saturated with honey; described as clover honey so considered monofloral). Category: Wound contact layers, gauze	“Fluffy” (as described by authors) dressing was applied over the gauze and kept in place by bandage.	The wound was meticulously debrided (sometimes under anaesthesia).	Wounds were thoroughly washed using normal saline (no antiseptic). Heavily infected wounds were rinsed with warm tap water after debridement.	Frequency of dressing depended upon the amount of exudates; whenever the dressing is soaked, it should be changed by the same technique. Once single daily dressing was reached, the patient was discharged and followed up in the outpatient clinic.
Iodine						
Skog 1983 (Skog et al. 1983)	Intervention: Cadexomer iodine	Iodosorb powder (Perstorp AB) Category: Ointments, gels, hydrogels	Dry dressing with compression bandage	NR	Gently washed in running water	During the first few days of the trial the dressing could be changed twice daily, but this was seldom necessary. For the remainder of the trial dressings were changed daily.
	Comparator: Standard treatment	Paraffin-impregnated dressings, saline dressings and bland ointments. Additional agents (not specifically antimicrobials) employed included merbromine, Salvstrumpa	Compression bandage			

Study	Agent	Dressing type	Secondary dressing	Pre-dressing debridement	Pre-dressing cleaning/irrigation	Intended frequency of dressing change
		and systemic antibiotics.				
Octenidine						
Hammerle and Strohal, 2016 (Hammerle and Strohal 2016)	Intervention: Octenidine	Octenilin wound gel (Schuelke and Mayr) Category: Ointments, gels, hydrogels	Secondary foam or alginate dressing	NR	All wounds, excluding those with local infection, were cleaned with sodium chloride using wound gauze	NR
	Comparator: Octenidine	Octenilin wound gel (Schuelke and Mayr) Category: Ointments, gels, hydrogels	Non-adhering wound contact layer, suction gauze		Infected wounds were cleaned with octenidine dihydrochloride (Octenisept).	
PHMB						
Vallejo et al. 2022 (Vallejo et al. 2022)	Intervention: PHMB	Various forms of PHMB dressing (AMD foam, or gel with PHMB, or Kerlix AMD gauze, H&R Healthcare, UK) Category: Mixed “Ointments, gels, hydrogels”, “foams, absorbent pads” and “Wound contact layers, gauze”	Absorbent pad if required	All participants received low-frequency contact ultrasonic debridement treatment with 0.9% saline medium weekly for the first 6 weeks	Topical PHMB as a soak in plain gauze for 15 minutes at each dressing change	NR

Study	Agent	Dressing type	Secondary dressing	Pre-dressing debridement	Pre-dressing cleaning/irrigation	Intended frequency of dressing change
	Comparator: Non-antimicrobial products with cleansing	Non-medicated dressing product similar to those used in intervention group (e.g. Kendall foam or plain gel) Category: Mixed "Ointments, gels, hydrogels", "foams, absorbent pads" and "Wound contact layers, gauze"			The control group received cleansing of the wound after and between treatments with reliably clean water or 0.9% saline	
Koullias 2022 (Koullias et al. 2022)	Intervention: PHMB	PuraPly AM Type 1 collagen PHMB matrix barrier (Organogenesis) Category: Wound contact layers, gauze	NR	NR	NR	NR
Silver						
Dimakakos et al. 2009 (Dimakakos et al. 2009)	Intervention: ionic silver complex silver releasing dressing	Contreet Ag (now marketed as Biatain Ag) foam dressing Category: Foams, absorbent pads	Compression bandage	NR	Wound pre-cleansed with sterile water and 10% iodine solution	Wound dressings were changed twice a week
	Comparator: No agent	Biatain non-adhesive foam				

Study	Agent	Dressing type	Secondary dressing	Pre-dressing debridement	Pre-dressing cleaning/irrigation	Intended frequency of dressing change
		Category: Foams, absorbent pads				
Degreef et al. 1984 (Degreef and Michiels 1984)	Intervention: Silver sulphadiazine	1% silver sulfadiazine cream, (Flammazine cream, Duphar) Category: Ointments, gels, hydrogels	Sterile bandage	NR	NR	Applied once a day in a thin layer of 2 to 3 mm
Forlee 2014 (Forlee et al. 2014)	Intervention: Ionic silver dressing	DURAFIBER™ Ag Gelling fibre Category: Alginate, gelling fibre, absorbent fibre	Compression therapy, pressure relief and wound debridement were carried out as appropriate	Wound debridement (mechanical debridement with sterile gauze hydrated with sterile water) carried out if deemed appropriate.	Wound cleansing was carried out at 105 (97.2%) assessments. Ulcers were cleaned with saline and 1% lignocaine	Changed as necessary
Humbert 2006 (Humbert et al. 2006)	Intervention: Ionic silver complex	Biatain Ag, silver foam dressing Category: Foams, absorbent pads	Secondary and/or cover dressings were applied, followed by compression at	NR	Wounds were cleaned with saline prior to dressing	Frequency of dressing replacements (mean, SD): 2.7 (1.3)

Study	Agent	Dressing type	Secondary dressing	Pre-dressing debridement	Pre-dressing cleaning/irrigation	Intended frequency of dressing change
			discretion of the investigator.			Total n of dressing changes (n=40 patients): 206
	Comparator: No agent	Calcium alginate fibre dressing (Algosteril, Brothier Laboratories) Category: Alginate, gelling fibre, absorbent fibre	34/40 (85%) patients in the silver arm and 37/40 (92.5%) in the no agent arm used compression bandaging		Wounds were cleaned with saline prior to dressing If required, the no agent dressing could be moistened with saline or Ringer's solution	Frequency of dressing replacements (mean, SD): 2.8 (1.4) Total n of dressing changes (n= 40 patients): 184
Manning 2020 (Manning et al. 2020)	Intervention: Ionic and metallic silver	Bioabsorbable polymeric matrix containing ionic and metallic silver (Imbed Biosciences Inc) Category: Wound contact layers, gauze	The matrix was covered with a secondary dressing	If clinically indicated, debridement was performed to remove excessive necrotic tissue	Wounds briefly cleaned and irrigated with sterile saline	NR
Meaume et al, 2005 (Meaume et al. 2005)	Intervention: Metallic silver	Silvercel metallic silver-releasing hydro-alginate Category: Alginate, gelling fibre, absorbent fibre	Sterile pads (Topper, Johnson & Johnson) were used as secondary dressings	Necrotic plaque was removed on study entry, either by surgical or mechanical debridement	Wounds were cleansed with sterile saline (CDM, Lavoisier, France)	At least 5 changes each week in weeks 1 to 2; thereafter every 2 to 3 days as needed
	Comparator: No agent	Algosteril calcium alginate (Brothier Laboratories)				

Study	Agent	Dressing type	Secondary dressing	Pre-dressing debridement	Pre-dressing cleaning/irrigation	Intended frequency of dressing change
		Category: Alginate, gelling fibre, absorbent fibre				
Melotte 1985 (Melotte et al. 1985)	Intervention: Silver sulfadiazine	1% silver sulfadiazine cream (Flammazine, Duphar) Category: Ointments, gels, hydrogels	Cream covered by a sterile bandage	NR	NR	NR
Mölnlycke Health Care AB 2014 (NCT01036438) (NCT01036438 2009)	Intervention: Silver sulphate	Mepilex Ag absorbent foam (Mölnlycke Health Care) Category: Foams, absorbent pads	NR	NR	NR	NR
	Comparator: No agent	Mepilex absorbent foam (Mölnlycke Health Care) Category: Foams, absorbent pads				
Truchetet 2012 (Truchetet et al. 2012)	Intervention: Silver Sulphate	Mepilex Ag silicone-foam silver releasing dressing (Mölnlycke Health Care) Category: Foams, absorbent pads	NR	NR	NR	Planned frequency to change the dressing 2-3 times a week in 64% of patients (n=508)

Study	Agent	Dressing type	Secondary dressing	Pre-dressing debridement	Pre-dressing cleaning/irrigation	Intended frequency of dressing change
Woolstencroft 2018 (Woolstencroft 2018)	Intervention: Silver oxysalts	KerraContact Ag dressing with Ag Oxysalts, silver wound dressing with 2 non-adherent polyethene mesh contact layers and a polyester core Category: Alginate, gelling fibre, absorbent fibre	NR	NR	Sterile normal saline was used to clean wounds in 53.8% of patients (n=7)	NR
Harding 2016 (Harding et al. 2016)	Intervention: Ionic silver with anti-biofilm agents	Week 1 to 4: Aquacel Ag+ hydrofiber dressing Week 5 to 8: Aquacel Category: Alginate, gelling fibre, absorbent fibre	The primary dressing was completely covered by a moisture-retentive secondary dressing appropriate to the clinical condition of the wound and the volume of exudate. An appropriate compression system (minimum UK Class 3) was applied.	NR	NR	Weekly

Study	Agent	Dressing type	Secondary dressing	Pre-dressing debridement	Pre-dressing cleaning/irrigation	Intended frequency of dressing change
Lantis 2011 (Lantis and Gendics 2011)	Intervention: Silver sulphadiazine	Allevyn Ag non-adhesive polyurethane foam dressing Category: Foams, absorbent pads	Multilayer compression bandaging	Some level of debridement at every dressing change	NR	Weekly
Vanscheidt 2003 (Vanscheidt et al. 2003)	Intervention: Ionic silver dressing	Aquacel Ag, (precise dressing product unclear but reported to include sodium carboxymethylcellulose fibres, thus considered absorbent fibre) Category: Alginate, gelling fibre, absorbent fibre	Moisture-retentive secondary dressing (DuoDERM Extra Thin, DuoDERM CGF, or CombiDERM). Patients were treated with compression therapy where clinically indicated	NR	NR	Dressings were changed as clinically indicated but were not left in place for more than 7 days

Study	Agent	Dressing type	Secondary dressing	Pre-dressing debridement	Pre-dressing cleaning/irrigation	Intended frequency of dressing change
Jorgensen 2008 (Jorgensen et al. 2008)	Intervention: Silver sulphadiazine -releasing permeable wound contact layer (Physiotulle Ag)	Physiotulle Ag hydrocolloid silver contact dressing Category: Wound contact layer	Biatain ibuprofen foam dressing with compression therapy	Wounds were mechanically debrided if necessary	Wounds were cleansed if necessary	On days 3 and 5 and thereafter as needed
Comparative studies of eligible agents						
Miller et al. 2010 (Miller et al. 2010)	Intervention: Ionic silver dressing	Acticoat and Acticoat 7, polyester core between polyethylene layers, foam dressing; Acticoat Absorbant, alginate dressing Category: Mixed "Wound contact layer" and "Alginate, gelling fibre, absorbent fibre"	Compression bandaging	NR	NR	NR

Study	Agent	Dressing type	Secondary dressing	Pre-dressing debridement	Pre-dressing cleaning/irrigation	Intended frequency of dressing change
	Comparator: Cadexomer iodine dressing	Iodosorb ointment or powder Category: Ointments, gels, hydrogels				
Molle 2023 (Molle et al. 2023)	Intervention: Honey	Manuka honey-based dressings Category: Unclear	NR	NR	NR	NR
	Comparator: Silver	Silver-based dressings Category: Unclear				
Mosti et al. 2015 (Mosti et al. 2015)	Intervention: Ionic silver	Aquacel Ag hydrofiber dressing (precise Aquacel product unclear, hydrofiber material is reported thus tagging as absorbent fibre). Category: Alginate, gelling fibre, absorbent fibre	NR	In cases of incomplete wound bed preparation, sharp debridement was performed	Ulcer bed cleansed with Ringer's solution	Daily
	Comparator: DACC	Cutimed Sorbact hydropolymer gel sheet (Cutimed) Category: Wound contact layer				

Study	Agent	Dressing type	Secondary dressing	Pre-dressing debridement	Pre-dressing cleaning/irrigation	Intended frequency of dressing change
Gago 2008 (Gago et al. 2008)	Intervention 1: Ionic silver	Acticoat, polyester core sandwiched between outer layers of a silver coated low-adherent polyethylene net Category: Wound contact layer	Polyurethane foam	NR	NR	Dressings were changed 3 times a week
	Intervention 2: Ionic silver complex Treatment continued throughout the study period using non-silver dressings	Comfeel: hydrocolloid dressing for minimal exudate wounds Biatain Ag: polyurethane foam for moderate to high exudate wounds Category: Mixed, "Hydrocolloid" and "Foams, absorbent pads"	NR			
	Intervention 3: Ionic silver	Aquacel Ag gelling hydrofiber Category: Alginate, gelling fibre, absorbent fibre	Polyurethane foam			

11.3.2 Generalizability of studies that fully met the decision problem

RCTS

Of the 6 RCTs that fully met the decision problem, Miller et al 2010 (Miller et al. 2010, ACTRN12606000094572 2006) assessed silver versus iodine dressings across 2 large community nursing services in the UK. The study included 281 people with lower leg ulcers showing signs of infection. This study was closely applicable to the decision problem, as were 4 further European RCTs of silver dressings; these were conducted in Greece (Dimakakos et al 2009 (Dimakakos et al. 2009), N=42), France (Humbert 2006 (Humbert et al. 2006), N=80), the UK (Meaume et al, 2005 (Meaume et al. 2005), N=71) and across Europe (Molnlycke Health Care (NCT01036438 2009), N=201). They included hospital (Meaume et al. 2005, NCT01036438 2009) and outpatient (Humbert et al. 2006) settings, and the patient population of all 4 trials had infected venous leg ulcers.

The pilot RCT was more limited in applicability to the decision problem.

Mosti et al 2015 (Mosti et al. 2015) was a short pilot RCT assessing silver versus DACC dressings over 4 days in a UK community nursing setting. The study assessed 40 adults with critically colonised or locally infected leg ulcers, of which 20 were VLUs. Not all patients had clinically infected wounds, which limits the applicability of the study to the decision problem.

Non-randomized comparative studies

Gago 2008 (Gago et al. 2008) compared silver dressings with a no-agent comparator in an 8-week prospective cohort study in a Spanish community health centre (N=75). The study was judged to be closely applicable to the decision problem.

Hammerle and Strohal, 2016 (Hammerle and Strohal 2016) compared a mixed intervention arm (some patients received silver foam, others silver alginate, and others no-agent foam, alginate or hydrogel dressings) with octenidine dressings in a 7-week non-randomised trial in an Austrian secondary care centre. The study included 44 adults with VLUs, although only 16 patients had infected wounds. The European secondary care setting means that the study is applicable to the decision problem for the purposes of assessing Octenidine, but the arm including silver dressings was too mixed and had insufficient reporting to provide data to inform this review.

Molle 2023 (Molle et al. 2023) compared honey with silver dressings (N=50) in a 30-day non-randomised trial, reported in a conference abstract. Location and setting were not reported, and it is therefore difficult to assess the applicability of this study to the decision problem.

Single-arm studies

3 prospective case series and 7 single-arm studies assessed silver dressings, with 1 further case series assessing honey dressings.

Of the 3 prospective case series of silver, 2 were published in the 1980s (Degreef and Michiels 1984, Melotte et al. 1985) and may not be generalisable to current practice; both studies were Belgian. The third prospective case series of silver was French and published in 2012 (Truchetet et al. 2012), reporting on 534 patients with VLUs in a private outpatient setting. The 8 single-arm studies of silver were conducted in the UK, Poland, France, Germany, Denmark, Italy, South Africa, the USA, and Canada. The studies reported on between 14 and 42 patients. Despite the issues identified with the studies in silver dressings, the European setting and infected VLU population of all the studies mean that all studies in silver dressings were at least broadly applicable to the decision problem.

Biglari et al 2013 (Biglari et al. 2013) was a prospective case series assessing honey dressings in 121 adult and paediatric patients with infected wounds of various etiologies. The study was conducted at 9 German hospitals and 1 in Austria, with a mean follow up of 5 weeks. The European setting and infected wound population mean that the study is broadly generalizable to the decision problem.

11.3.3 Full risk of bias assessments of studies that fully met the decision problem

Details of the risk of bias assessments conducted for each of the studies that fully met the decision problem are reported in Table 10.4 (RCTs), Table 10.5 (single-arm studies) and Table 10.6 **Error! Reference source not found.** (cohort studies).

RCTs

7 RCTs of eligible interventions were identified that fully met the decision problem, and their risk of bias was assessed using the Cochrane Risk of Bias tool (version 1).

Mosti et al 2015 (Mosti et al. 2015) was a short pilot RCT assessing silver versus DACC dressings. The short follow up meant that the study was judged to be at a high risk of bias.

Miller et al 2010 (Miller et al. 2010, ACTRN12606000094572 2006) assessed silver versus iodine dressings. Although ITT analysis was not conducted, the follow-up rate was almost 95%. The study reported a significant difference between groups in wound size, although as this variable was accounted for in the analysis, it did not impact the risk of bias of the study, which was judged to be low.

4 additional RCTs of silver dressings were included (Dimakakos et al 2009 (Dimakakos et al. 2009), Humbert 2006 (Humbert et al. 2006), Meaume et al, 2005 (Meaume et al. 2005), and Molnlycke Health Care (NCT01036438 2009)). 3 of the RCTs (Dimakakos et al. 2009, Meaume et al. 2005, Humbert et al. 2006) were found to have a moderate risk of bias, largely due to the lack of reporting of allocation generation and concealment. In addition, Humbert 2006 did not fully report all outcomes, and Meaume et al 2005 reported significant differences between intervention and control groups in age and diabetes status. 1 RCT (NCT01036438 2009) was

only published as a clinical trial record, and correspondingly had a high risk of bias due to a lack of detailed reporting, both of methods and outcomes.

The second RCT, Skog 1983 (Skog et al. 1983) assessed iodine versus standard of care and followed up 93 patients with chronic infected venous ulcers for 6 weeks. Details of the setting were unclear. 21 patients were excluded from statistical analysis, and many different kinds of non-antimicrobial dressings in the comparator arm were classed as “standard care”. The study was therefore judged to be at a high risk of bias.

Non-randomized comparative studies

3 studies were non-randomised comparative studies. Risk of bias assessment was conducted using the JBI Cohort studies checklist.

Gago 2008 (Gago et al. 2008) compared silver dressings with a no-agent comparator and had a moderate risk of bias because authors did not clearly report whether a baseline imbalance between groups in prevalence of purulent discharge was accounted for in the analysis.

Hammerle and Strohal, 2016 (Hammerle and Strohal 2016) compared a mixed intervention arm with octenidine dressings. This study was assessed as being at moderate risk of bias, as the authors did not identify possible confounding factors, and no strategy for dealing with such factors was reported. The arm including silver dressings was too heterogenous and had insufficient reporting to provide data to inform this review.

Molle 2023 (Molle et al. 2023) compared honey with silver dressings reported in a conference abstract. Location and setting were not reported, and the study was judged to be at high risk of bias due to limited information available to fully assess risk of bias.

Single-arm studies

4 prospective case series fully met the decision problem and were assessed for risk of bias using the JBI case series checklist. Biglari et al 2013 (Biglari et al. 2013) was a prospective case series of honey dressings and was judged to have a moderate risk of bias due to incomplete inclusion of participants and a lack of outcome reporting for the full population. 3 further prospective case series assessed silver dressings. The studies were assessed using the JBI Case Series Checklist and 2 (Degreef and Michiels 1984, Melotte et al. 1985) were found to have a high risk of bias, largely due to poor or unclear reporting, while the third (Truchetet et al. 2012) had a moderate risk of bias.

7 single-arm studies fully met the decision problem and were also assessed for risk of bias using the JBI case series checklist. All the single-arm studies assessed silver dressings. 3 studies (Harding et al. 2016, Lantis and Gendics 2011, Vanscheidt et al. 2003) were found to have a low risk of bias. 4 studies were found to have a moderate risk of bias: inclusion of participants was not complete and outcomes were not reported for all patients (Jorgensen et al. 2008, Manning et al. 2020, Forlee et al. 2014), and 1 study lacked of reporting of methods, including details of the statistical analysis methods used (Woolstencroft 2018).

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Table 10.4: RCT risk of bias assessment

Study	Judgement / Description	Was the allocation sequence adequately generated?	Was the concealment of treatment allocation adequate?	Was knowledge of the allocated interventions adequately concealed from participants and personnel?	Was knowledge of allocated interventions adequately concealed from outcome assessors?	Were incomplete outcome data adequately addressed?	Are reported of the study free of suggestion of selective outcome reporting?	Was the study apparently free of other problems that could put it at a high risk of bias?	Overall appraisal
(Dimakakos et al. 2009)	J	Unclear	Unclear	Unclear	Unclear	NA	Yes	Yes	Moderate risk of bias
RCT Silver	D	No information on allocation provided	No information on allocation provided	No information on allocation provided	No information on allocation provided	No incomplete outcome data	No evidence of this	No other concerns identified	
(Humbert et al. 2006)	J	Yes	Unclear	NA	NA	Unclear	No	Yes	Moderate risk of bias
	D	Patients site-randomised in blocks of 4	No information on allocation concealment provided	Open label study	Open label study	21 patients withdrew, 19 due to AEs. Study reports that ITT analysis was conducted, but no details of methods are reported. The number of patients included in the analyses for each outcome is not reported, so it is not possible to check whether a full ITT analysis was indeed conducted. For some outcomes it appears not to be the case - for dressing change related outcomes (e.g. pain,	Some outcomes are not fully reported, e.g. the p value for difference in VAS score is reported but not the scores at each timepoint.	No other concerns identified	
RCT Silver									

Study	Judgement / Description	Was the allocation sequence adequately generated?	Was the concealment of treatment allocation adequate?	Was knowledge of the allocated interventions adequately concealed from participants and personnel?	Was knowledge of allocated interventions adequately concealed from outcome assessors?	Were incomplete outcome data adequately addressed?	Are reported of the study free of suggestion of selective outcome reporting?	Was the study apparently free of other problems that could put it at a high risk of bias?	Overall appraisal
						discomfort) the total number of reported dressing changes is lower than the reported total number for each group.			
(Meaume et al. 2005) RCT Silver	J	Unclear	Unclear	NA	NA	Yes	Yes	No	Moderate risk of bias
	D	No detail on randomisation method reported	No detail of allocation concealment is reported	Open label study	Open label study	ITT analysis using LOCF	Pre-specified outcomes were reported	Significant difference between groups in proportion of patients >80 and in diabetes	
(Miller et al. 2010) RCT Silver	J	Yes	Yes	NA	NA	Yes	Yes	No	Low risk of bias
	D	Randomized with MS Excel random number function	Use of opaque numbered envelopes	Open label study	Open label study	Complete case analysis only, however the completion rate was almost 95% (94.6%)	Pre-specified outcomes were reported	Significant difference between groups in wound size - however this variable was accounted for in the analysis.	
(Mo et al. 2015) RCT Chitosan	J	Yes	NA	NA	NA	Yes	Yes	Yes	Low risk of bias
	D	Layered section randomising applied	Open design	Open design	Open design	Outcome data provided for all patients who remained in the study. those who dropped out were excluded `	Pre-specified outcomes were reported	No other concerns identified	
(Mosti et al. 2015)	J	Yes	Unclear	NA	NA	NA	Yes	No	

Study	Judgement / Description	Was the allocation sequence adequately generated?	Was the concealment of treatment allocation adequate?	Was knowledge of the allocated interventions adequately concealed from participants and personnel?	Was knowledge of allocated interventions adequately concealed from outcome assessors?	Were incomplete outcome data adequately addressed?	Are reported of the study free of suggestion of selective outcome reporting?	Was the study apparently free of other problems that could put it at a high risk of bias?	Overall appraisal
RCT Silver	D	Randomized using List Randomizer software	No detail of allocation concealment is reported	Open label study	Open label study	All patients completed the study	Pre-specified outcomes were reported	Pilot study only, short duration.	High risk of bias
(NCT01036438 2009) RCT Silver	J	Unclear	Unclear	Unclear	Unclear	Unclear	No	No	High risk of bias
	D	Not reported	No information on allocation concealment provided	Double-blind study but no information on blinding protocol provided	Double-blind study but no information on blinding protocol provided	10 patients in silver arm (8 AEs, 1 death, 1 no treatment effect); 10 patients in no agent arm (7 AEs, 3 no treatment effect). Results are reported for all patients, but no information on imputation methods are reported.	Infection rate is a listed outcome but no results are reported	Results only published in CT record, limited information available to assess study quality	
(Skog et al. 1983) RCT Iodine	J	Unclear	Yes	Unclear	Unclear	No	Yes	No	High risk of bias
	D	Not reported	Allocated blindly and at random	Described as "allocated blindly" does not specify if clinicians and/or patients were blinded	Described as "allocated blindly" does not specify if outcome assessors were blinded	Drop-outs excluded from statistical analysis	Pre-specified outcomes were reported	Wounds described as infected in methods, but no further detail given. Infection information in results is not sufficient to form any conclusions from (unclear how many patients from	

Study	Judgement / Description	Was the allocation sequence adequately generated?	Was the concealment of treatment allocation adequate?	Was knowledge of the allocated interventions adequately concealed from participants and personnel?	Was knowledge of allocated interventions adequately concealed from outcome assessors?	Were incomplete outcome data adequately addressed?	Are reported of the study free of suggestion of selective outcome reporting?	Was the study apparently free of other problems that could put it at a high risk of bias?	Overall appraisal
								each group were infected with each bacteria at baseline).	
(Vallejo et al. 2022) RCT PHMB	J	Yes	Yes	Unclear	Yes	Yes	Yes	No	Low risk of bias
	D	Computer generated randomisation accounting for wound size.	Group allocation delivered through sealed, opaque envelopes	Reported that patients and clinicians were blinded to treatment, details of blinding not reported.	Wound closure, deterioration and size were validated by the blinded outcome assessor using anonymised photographs and wound tracing software; other outcome data was considered logistically unfeasible to blind assessors to.	5 patients in PHMB arm (2 deteriorated, 1 moved away, 1 due to pain, 1 diagnosed with cancer) and 12 in the no agent arm (11 deteriorated, 1 did not return) did not complete the study; ITT analysis of all randomised patients conducted using LOCF	All outcomes listed in protocol reported	Higher rate of loss to follow-up in the control arm (n=12) vs intervention arm (n=5)	

Table 10.5: Single-arm study risk of bias assessment

Study		Were there clear criteria for inclusion in the case series?	Was the condition measured in a standard, reliable way for all participants included in the case series?	Were valid methods used for identification of the condition for all participants included in the case series?	Did the case series have consecutive inclusion of participants?	Did the case series have complete inclusion of participants?	Was there clear reporting of the demographics of the participants in the study?	Was there clear reporting of clinical information of the participants?	Were the outcomes or follow up of results of cases clearly reported?	Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	Was statistical analysis appropriate?	Overall
(Biglari et al. 2013) Prospective case series Honey	J	Yes	Yes	Yes	Unclear	No	Yes	Yes	No	Yes	Yes	Moderate risk of bias
	D	Infected wounds treated with medihoney at 10 sites	Wound etiology and wound size reported	Wound types and aetiologies reported	Not reported	12/121 patients discontinued; authors report that data is reported for 104 patients but data for a further 2 to 3 patients appear to be absent with no explanation.	Demographic information is clearly reported	Detail of wound types and aetiologies is reported.	Outcomes are clearly defined, however some outcomes (such as wound healing rate) are only reported for subgroup of healed/no n-healed wounds and not the overall population.	Site and location clearly reported	Student's t-test was used to test significance of changes from baseline	
(Bruce 2012) Prospective case series DACC	J	No	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	NA	Moderate risk of bias
	D	Not reported why these particular patients	Wounds were reported to be chronic (apart from 1) but it	No information provided	Not reported	Not reported	Demographic information is clearly reported	Type of wound reported	Clear outcome definitions and reporting	Site and location clearly reported	Descriptive statistics only	

Study		Were there clear criteria for inclusion in the case series?	Was the condition measured in a standard, reliable way for all participants included in the case series?	Were valid methods used for identification of the condition for all participants included in the case series?	Did the case series have consecutive inclusion of participants?	Did the case series have complete inclusion of participants?	Was there clear reporting of the demographics of the participants in the study?	Was there clear reporting of clinical information of the participants?	Were the outcomes or follow up of results of cases clearly reported?	Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	Was statistical analysis appropriate?	Overall
		were chosen	wasn't clear if this was an inclusion criteria. All patients also had different wounds									
(Degreef and Michiels 1984) Prospective case series Silver	J	Yes	Unclear	Unclear	Unclear	No	Yes	No	No	No	NA	High risk of bias
	D	Patients with infected leg ulcers; clear exclusion criteria reported	Not reported	Not reported	Not reported	3 discontinuations due to AEs, 2 due to necrosis	Basic demographic information and etiology reported	Etiology somewhat unclear with regard to number of traumatic ulcers and vascular status. all reported to have vascular or partly vascular etiology but 4 had traumatic ulcer cause, of whom only 3 reported to be worsened	Unclear how discontinued patient outcomes are presented. Further, change in treatment occurred mid-study due to occurrence of pseudo membrane which led to shortening of application duration,	Study site reported but limited information	Descriptive statistics only	

Study		Were there clear criteria for inclusion in the case series?	Was the condition measured in a standard, reliable way for all participants included in the case series?	Were valid methods used for identification of the condition for all participants included in the case series?	Did the case series have consecutive inclusion of participants?	Did the case series have complete inclusion of participants?	Was there clear reporting of the demographics of the participants in the study?	Was there clear reporting of clinical information of the participants?	Were the outcomes or follow up of results of cases clearly reported?	Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	Was statistical analysis appropriate?	Overall
								by vascular status.	unclear how this was accounted for in results			
(Dokic S et al. 2023)	J	No	Unclear	Unclear	Unclear	Unclear	No	No	No	Yes	Unclear	High risk of bias
Prospective case series Copper	D	No information provided	No definition of chronic wound provided	No information provided	Not reported	Not reported	No demographic information reported	No patient clinical information provided	Powerpoint with very limited outcome data	Medical centre name and department named	No statistical analysis reported	
(Durante 2012)	J	Yes	Yes	Yes	Unclear	No	Yes	Yes	Yes	Yes	Yes	Low risk of bias
Prospective case series Enzyme Alginogel	D	Clear reporting of inclusion and exclusion criteria	Wound etiology and area/volume reported for each type of wound	Wound types and aetiologies reported	Not reported	Of 23 patients, 20 were included wound assessment outcomes (1 discontinued dressing due to allergic reaction, 2 had wounds surgically closed prior to end of study).	Demographic information is clearly reported	Detail of wound types, aetiologies and relevant clinical background is reported.	Outcomes are clearly defined and reported	Site and location clearly reported	Non-parametric Wilcoxon signed-rank test was used for comparison between baseline and follow-up values	

Study		Were there clear criteria for inclusion in the case series?	Was the condition measured in a standard, reliable way for all participants included in the case series?	Were valid methods used for identification of the condition for all participants included in the case series?	Did the case series have consecutive inclusion of participants?	Did the case series have complete inclusion of participants?	Was there clear reporting of the demographics of the participants in the study?	Was there clear reporting of clinical information of the participants?	Were the outcomes or follow up of results of cases clearly reported?	Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	Was statistical analysis appropriate?	Overall
						Outcome data was available for 13 at final follow-up of 60 days; reasons for loss to follow-up are not reported.						
(Forlee et al. 2014) Single-arm trial Silver	J D	Yes Clear inclusion and exclusion criteria	Yes Wounds were assessed and measured, swabs and photographs were taken. Assessments at baseline, 4 and 8 weeks also included a tissue sample. Clear wound	Yes Patients had to have category 2, 3 or 4 pressure ulcer, venous leg ulcer or grade 1 or 2 diabetic foot ulcer that showed clinical signs of infection	NA Single-arm trial	No 1 patient discontinued due to unrelated SAE	Yes Baseline characteristics were clearly reported	Yes Baseline medical conditions were clearly reported	No Not all 14 patients are included in all outcome results, e.g. HRQoL scores are reported for 9 patients at final follow-up	No Clinics named but lack of any detailed information	Yes Wilcoxon signed rank test; Kaplan-Meier; McNemar's test; marginal homogeneity test	Moderate risk of bias

Study		Were there clear criteria for inclusion in the case series?	Was the condition measured in a standard, reliable way for all participants included in the case series?	Were valid methods used for identification of the condition for all participants included in the case series?	Did the case series have consecutive inclusion of participants?	Did the case series have complete inclusion of participants?	Was there clear reporting of the demographics of the participants in the study?	Was there clear reporting of clinical information of the participants?	Were the outcomes or follow up of results of cases clearly reported?	Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	Was statistical analysis appropriate?	Overall
			criteria were described for inclusion									
(Harding et al. 2016) Prospective single-arm trial Silver	J	Yes	Yes	Yes	NA	Unclear	Yes	Unclear	Yes	No	Yes	Low risk of bias
	D	Clear inclusion and exclusion criteria provided.	Ulcers had CEAP classification C6.	Diagnosed by clinicians, CEAP classified.	Single-arm trial	Not reported	Gender and age reported	Ulcer status reported, but no causes or comorbidities.	Outcomes and AEs clearly described	Only location given.	Comparison of categorical variables was performed by χ^2 test, and continuous variables were compared by analysis of variance (ANOVA)	
(Jones and Oates 2018) Prospective case series Enzyme Alginogel	J	No	Unclear	Unclear	Yes	Yes	No	Yes	Yes	Yes	No	Moderate risk of bias
	D	Evaluation forms sent to nurses for patients being treated with Flaminal, no information on inclusion criteria	Not reported	Patient wounds considered indicated for Flaminal at primary care, no further details reported	Some information on ulcer location and etiology reported	Clinical outcomes reported in evaluation form are all reported, though data on dressing changes/applications is not	Number of centres and location unclear	Standard binomial test with 95% confidence intervals calculated using the Wilson method and one-tailed p values.	Some information on ulcer location and etiology reported	Clinical outcomes reported in evaluation form are all reported, though data on dressing changes/applications is not	Number of centres and location unclear	
	J	Yes	Yes	No	NA	No	Yes	Yes	Yes	No	Yes	

Study		Were there clear criteria for inclusion in the case series?	Was the condition measured in a standard, reliable way for all participants included in the case series?	Were valid methods used for identification of the condition for all participants included in the case series?	Did the case series have consecutive inclusion of participants?	Did the case series have complete inclusion of participants?	Was there clear reporting of the demographics of the participants in the study?	Was there clear reporting of clinical information of the participants?	Were the outcomes or follow up of results of cases clearly reported?	Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	Was statistical analysis appropriate?	Overall
(Jorgensen et al. 2008) Prospective case series Silver	D	Clear inclusion and exclusion criteria provided.	Ulcer had to have at least one sign of clinical infection.	Not specified, and a patient with an exclusion criteria (ibuprofen use) was included	Single-arm trial	23/24 patients completed the study; one dropped out prematurely due to a dressing-related adverse event (non-allergic skin reaction) and was not included in the analysis.	Gender and age reported	Baseline info reported	Outcomes and AEs clearly described, though 1 participant who discontinued was not included.	No info reported about the clinics participants were recruited from	Only appropriate descriptive statistics are presented	Moderate risk of bias
(King and Rolland 2023) Prospective case series Enzyme Alginogel	J	No	Unclear	Unclear	Unclear	No	No	No	Yes	No	Yes	High risk of bias
	D	Evaluation forms sent to nurses for patients being treated with Flaminal, no information on inclusion criteria	Not reported	Patient wounds considered indicated for Flaminal at primary care, no further details reported	Not reported	Responses are incomplete at different rates for different evaluation questions	No demographic information reported	Limited information on wound types and location reported	Clinical outcomes reported in evaluation form (as it appears in the initial Jones 2018 study) are all	Number of centres and location unclear	Standard binomial test with 95% confidence intervals calculated using the Wilson method and one-tailed p values.	

Study		Were there clear criteria for inclusion in the case series?	Was the condition measured in a standard, reliable way for all participants included in the case series?	Were valid methods used for identification of the condition for all participants included in the case series?	Did the case series have consecutive inclusion of participants?	Did the case series have complete inclusion of participants?	Was there clear reporting of the demographics of the participants in the study?	Was there clear reporting of clinical information of the participants?	Were the outcomes or follow up of results of cases clearly reported?	Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	Was statistical analysis appropriate?	Overall
									reported, though data on dressing changes/applications is not			
(Koullias et al. 2022) Prospective non-interventional study PHMB	J	No	Yes	Yes	Unclear	Unclear	Yes	No	Yes	Yes	NA	Moderate risk of bias
	D	States VLU's, but also "Participating patients may have had any type of wound, other than a third-degree burn"	Wound etiology and wound size reported	Diagnosed by clinicians, CEAP classified.	Not reported	Not reported	Demographic information is clearly reported	only ulcer size reported, number of patients with each type of wound was NR	Clear outcome definitions and reporting	Site and location clearly reported	Descriptive statistics only	
(Lantis and Gendics 2011) Prospective single-arm trial Silver	J	Yes	Yes	Yes	NA	Unclear	Yes	Yes	Yes	No	Yes	Low risk of bias
	D	Clear inclusion and exclusion criteria provided.	Clear parameters reported for inclusion.	Several clinical tests performed to assess suitability.	Single-arm trial	Not reported	Gender and age reported	Baseline characteristics and medical conditions clearly reported.	Outcomes and AEs clearly described	No information given.	Spearman rank correlation coefficients were calculated for risk factor analysis. Kaplan Mier life table	

Study		Were there clear criteria for inclusion in the case series?	Was the condition measured in a standard, reliable way for all participants included in the case series?	Were valid methods used for identification of the condition for all participants included in the case series?	Did the case series have consecutive inclusion of participants?	Did the case series have complete inclusion of participants?	Was there clear reporting of the demographics of the participants in the study?	Was there clear reporting of clinical information of the participants?	Were the outcomes or follow up of results of cases clearly reported?	Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	Was statistical analysis appropriate?	Overall
											analysis was used to assess mean and median times to achieve wound closure and bioburden reduction. McNemars test for difference was used to assess changes in primary and secondary endpoints over time.	
(Manning et al. 2020) Prospective single-arm trial Silver	J D	Yes Clear eligibility criteria reported	Yes Patients with chronic/infected wounds presenting to hospital wound centre, ulcer size/area and	Yes Patients presenting with infected wounds diagnosed and measured at hospital wound centre	NA Single-arm trial, patients selected by inclusion criteria from those presenting at surgical department	No 3 patients from the VLU group were lost to follow up and are not reported	No Age is reported but no other demographic information (e.g. gender)	Yes Wound etiology and duration is reported for each wound type	No Of the 16 VLU patients available to follow-up the wound healing rate is only reported for 11 whose	Yes Study site and location reported	NA Descriptive statistics only	Moderate risk of bias

Study		Were there clear criteria for inclusion in the case series?	Was the condition measured in a standard, reliable way for all participants included in the case series?	Were valid methods used for identification of the condition for all participants included in the case series?	Did the case series have consecutive inclusion of participants?	Did the case series have complete inclusion of participants?	Was there clear reporting of the demographics of the participants in the study?	Was there clear reporting of clinical information of the participants?	Were the outcomes or follow up of results of cases clearly reported?	Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	Was statistical analysis appropriate?	Overall
			duration reported						wounds are said to have improved. It is unclear whether the remaining 5 patients had stagnant or deteriorating wounds. Figure 3 suggests that 3 patients experienced significant growth of wound area, but it is not reported which wound type these patients had.			

Study		Were there clear criteria for inclusion in the case series?	Was the condition measured in a standard, reliable way for all participants included in the case series?	Were valid methods used for identification of the condition for all participants included in the case series?	Did the case series have consecutive inclusion of participants?	Did the case series have complete inclusion of participants?	Was there clear reporting of the demographics of the participants in the study?	Was there clear reporting of clinical information of the participants?	Were the outcomes or follow up of results of cases clearly reported?	Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	Was statistical analysis appropriate?	Overall
(Melamed et al. 2021) Prospective single-arm trial Copper	J	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Low risk of bias
	D	Clear inclusion and exclusion criteria were provided	Wounds were screened and assessed in the same way	Patients were identified from an outpatient hospital clinic	Not reported	Not reported	Demographic information is clearly reported in supplementary material	Disease background, wound size and location all provided	Clear outcome definitions and reporting	Site and location clearly reported	ANOVA and t tests carried out, p values provided	
(Melotte et al. 1985) Prospective case series Silver	J	Yes	Yes	No	Unclear	No	Yes	Unclear	No	No	No	High risk of bias
	D	Exclusion reasons provided	Patients with leg ulcers	No information provided	Not reported	A number of participants were excluded after discontinuing due to treatment failure	Gender and age reported	Bacteria swab cultures reported but nothing else about the wound e.g size, location or appearance	Patients were excluded where they discontinued due to failure to improve and appear not to have been included in outcomes such as bacterial swabbing.	No information given.	No statistical analysis conducted	
	J	Yes	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	

Study		Were there clear criteria for inclusion in the case series?	Was the condition measured in a standard, reliable way for all participants included in the case series?	Were valid methods used for identification of the condition for all participants included in the case series?	Did the case series have consecutive inclusion of participants?	Did the case series have complete inclusion of participants?	Was there clear reporting of the demographics of the participants in the study?	Was there clear reporting of clinical information of the participants?	Were the outcomes or follow up of results of cases clearly reported?	Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	Was statistical analysis appropriate?	Overall
(Moghazy et al. 2010) Prospective single-arm trial Honey	D	Clear inclusion and exclusion criteria reported	Patients with infected DFUs presenting to surgical department, ulcer size/area measured and reported	Patients with infected DFUs presenting to surgical department	Single-arm trial, patients selected by inclusion criteria from those presenting at surgical department	Data reported for all patients, including 2 patients who underwent amputation at 1 month and 2 who received skin grafts	Demographic information is clearly reported	Detail of wound etiology is reported, along with relevant clinical background	Clear outcome definitions and reporting	Site and location clearly reported	Chi-squared test to test difference in proportion of patients at stages of healing at each timepoint	Low risk of bias
(Orig and Singleton 2016) Prospective case series Silver	J D	Yes Patients with critically colonised or infected wounds requiring tissue viability nurse assessment were included; clear exclusion criteria reported.	Unclear Unclear, broad wound types included	Yes Patients with critically colonised or infected wounds requiring tissue viability nurse assessment	Unclear Not reported	Unclear No details of any discontinuations (or lack thereof) is reported	Yes Basic demographic information reported	Yes Detailed breakdown of wound type, location and relevant health conditions is reported	No Limited reporting of healing and infection outcomes	Yes Study site reported, described as acute hospital ward. Details of discharge to community care reported where applicable.	NA Descriptive statistics only	High risk of bias
	J	Unclear	Yes	Unclear	Unclear	Unclear	No	No	Yes	Yes	NA	

Study		Were there clear criteria for inclusion in the case series?	Was the condition measured in a standard, reliable way for all participants included in the case series?	Were valid methods used for identification of the condition for all participants included in the case series?	Did the case series have consecutive inclusion of participants?	Did the case series have complete inclusion of participants?	Was there clear reporting of the demographics of the participants in the study?	Was there clear reporting of clinical information of the participants?	Were the outcomes or follow up of results of cases clearly reported?	Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	Was statistical analysis appropriate?	Overall
(Treadwell T et al. 2022) Prospective case series Copper	D	No inclusion criteria provided	All wounds included had failed standard care for one month	No information provided	Not reported	Not reported	Only age reported	only ulcer size reported, number of patients with each type of wound was NR	Healing outcome reported	Reported on the poster	Descriptive statistics only	Moderate risk of bias
(Truchetet et al. 2012) Prospective case series Silver	J	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	No	No	Yes	Moderate risk of bias
	D	Clear inclusion and exclusion criteria provided.	Wounds were checked for 10 signs compatible with wound infection	Participating physicians were asked to include in the study the first 2 consecutive patients they prescribed the silver dressing	Yes first 2 patients from each physician were included	Not reported	Gender, age and wound baseline characteristics	Baseline info reported	Not all outcomes available for the VLU subgroup. Reasons for discontinuation are not fully available, could potentially include wound deterioration.	No info reported about the clinics participants were recruited from	The primary analysis was purely descriptive. Univariate analysis of variance (ANOVA) was used to compare some wound-aspect parameters between groups (VLUs and acute wounds)	
	J	Yes	Unclear	Yes	NA	Unclear	Yes	Yes	Yes	No	Yes	

Study		Were there clear criteria for inclusion in the case series?	Was the condition measured in a standard, reliable way for all participants included in the case series?	Were valid methods used for identification of the condition for all participants included in the case series?	Did the case series have consecutive inclusion of participants?	Did the case series have complete inclusion of participants?	Was there clear reporting of the demographics of the participants in the study?	Was there clear reporting of clinical information of the participants?	Were the outcomes or follow up of results of cases clearly reported?	Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	Was statistical analysis appropriate?	Overall
(Vanscheidt et al. 2003) Prospective single-arm trial Silver	D	Clear inclusion and exclusion criteria provided	Not clear how infection was defined "based purely on generally accepted clinical criteria"	Several clinical tests performed to assess suitability.	Single-arm trial	Not reported	Gender and age reported	Baseline info reported	Outcomes and AEs clearly described	No info reported	Fisher's exact test, Cochran-Mantel-Haenzel test.	Low risk of bias
(Woolstencroft 2018) Prospective single-arm study Silver	J	Yes	Yes	No	Unclear	Unclear	Yes	Unclear	No	No	No	Moderate risk of bias
	D	Clear inclusion and exclusion criteria provided.	Wound infections were identified through clinical diagnosis	No information on why these specific patients were chosen	Not reported	Not reported	Gender and age reported	Reported for some but not all participants	31 evaluation forms were received but certain outcomes do not report results for all 31 patients	Described as being from clinics - no other information provided	No statistical analysis reported yet things are reported to be significant	
(Yang K et al. 2015)	J	Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes	No	No	Unclear	Moderate risk of bias
	D	Chronically infected	Wound etiology	Not reported	Not reported	The occurrence	Demographic	Detail of wound types	Conference poster	Not reported	Conference poster only,	

Study		Were there clear criteria for inclusion in the case series?	Was the condition measured in a standard, reliable way for all participants included in the case series?	Were valid methods used for identification of the condition for all participants included in the case series?	Did the case series have consecutive inclusion of participants?	Did the case series have complete inclusion of participants?	Was there clear reporting of the demographics of the participants in the study?	Was there clear reporting of clinical information of the participants?	Were the outcomes or follow up of results of cases clearly reported?	Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	Was statistical analysis appropriate?	Overall
Prospective single-arm study Honey		VLUs were included	and wound size reported			of any discontinuations is not reported	information is clearly reported	and aetiologies is reported.	only, therefore limited data on the secondary outcomes (primary outcome of cytokine reduction is ineligible). Only percentage reduction in wound size and significance is reported.		limited information	

Table 10.6: Cohort study risk of bias assessment

Study		Were the 2 groups similar and recruited from the same population?	Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Was the exposure measured in a valid and reliable way?	Were confounding factors identified?	Were strategies to deal with confounding factors stated?	Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Were the outcomes measured in a valid and reliable way?	Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	Were strategies to address incomplete follow up used?	Was appropriate statistical analysis used?	Overall appraisal
(Gago et al. 2008) Prospective cohort Silver	J	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	NA	Yes	Moderate risk of bias
	D	Patients all had similar baseline characteristics and were recruited from the same population	Details of all dressings were described and they were used in the same way	Yes - details of dressing material and process at each application are reported	Study mentions baseline differences and that there were statistically significant differences in exudate, with group 2 having fewer patients with purulent exudate at baseline (p=0.013)	Difference in purulent exudate levels at baseline; authors report that baseline factors associated with outcomes were adjusted for, but limited information as to which factors specifically were adjusted for.	Patients were enrolled on presenting to clinics with infected leg wounds.	Outcomes clearly defined and measure, e.g. infection presence measured by checking for a list of clinical features and healing was measured in cm2	8 week follow up reported which is appropriate timeframe	Follow up was complete	NA	Cox regression proportional hazard and Kaplan-Meier plots were reported and justification provided	
	J	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	

(Hammerle and Strohal 2016) Non-randomised trial Silver	D	Patients requited from the same hospital	Details of dressings provided	Yes - details of dressing material and process at each application are reported	Healing measured as wound size/area in cm2 at weekly visits by an investigator. Other outcomes included percentage of wound area granulating, etc.	42 day study period	Follow up was complete for all patients	Healing measured as wound size/area in cm2 at weekly visits by an investigator. Other outcomes included percentage of wound area granulating, etc.	42 day study period	Follow up was complete for all patients	No incomplete follow up	ANOVA and Tukey analyses carried out	Moderate risk of bias
(Molle et al. 2023) Non-randomised trial Silver	J D	Unclear Conference abstract only, limited reporting	Unclear Conference abstract only, limited reporting	Unclear Conference abstract only, limited reporting	Unclear Conference abstract only, limited reporting	Unclear Conference abstract only, limited reporting	Yes Patients with infected VLUs included, wounds extant at baseline	Unclear Conference abstract only, limited reporting. Only reported as percentage wound size reduction, unclear if this is area cm2, etc.	Yes 30 day follow-up	Unclear Conference abstract only, limited reporting	Unclear Conference abstract only, limited reporting	Unclear Conference abstract only, limited reporting	High risk of bias

11.4 *Appendix D: Feasibility of quantitative analysis*

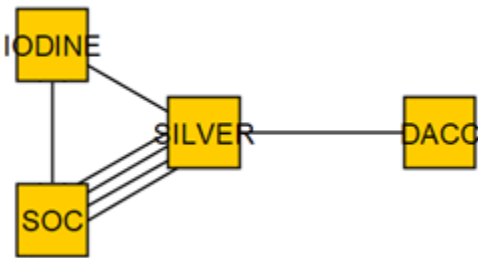
The feasibility of quantitative analysis of data from randomized controlled trials that fully met the decision problem was assessed. 7 such RCTs were identified (see Table 10.7). Non-randomized evidence was not considered for inclusion in a quantitative analysis, as results from different study designs should be expected to differ systematically, resulting in increased heterogeneity (Cochrane 2024).

Table 10.7: RCTs suitable for use in a quantitative analysis

TRIAL	Intervention	Comparator
Dimakakos 2009	SILVER Silver releasing foam dressing	STANDARD OF CARE No agent (non-adhesive foam dressing)
Humbert 2006	SILVER Silver (Biatain AG) foam dressing	STANDARD OF CARE No agent (calcium alginate fibre dressing, Algosteril Brothier Laboratories)
Meaume 2005	SILVER Silver-releasing hydroalginate dressing (Silvercel)	STANDARD OF CARE No agent (pure calcium alginate dressing (Algosteril)
Miller 2011	SILVER Nanocrystalline silver dressing (Acticoats)	IODINE Cadexomer iodine dressing (Iodosorbs) with compression bandaging
Molnlycke Health Care AB 2014	SILVER Absorbent foam silver dressing, Mepilex	STANDARD OF CARE No agent (absorbent foam dressing, Mepilex without silver)
Mosti 2015	SILVER Silver-containing hydrofiber (Aquacel Ag)	DACC DACC (microorganism-binding, Cutimed Sorbact)
Skog 1983	IODINE Cadexomer iodine (Iodosorb)	STANDARD OF CARE (mixed) Paraffin-impregnated dressings were most commonly used, but saline dressings and bland ointments were also used occasionally. Additional agents (not specifically antimicrobials) employed included merbrominc, Salvstrumpa, and systemic antibiotics

The RCTs formed the following theoretical network (Figure 11.2).

Figure 11.2: Theoretical network of RCTs



This network was based on a number of assumptions, which were later examined in more detail. The network assumed:

- That all non-antimicrobial dressing arms are clinically similar and can be grouped together.
- That all silver dressings are clinically similar and can be grouped together.
- That all studies report data for the same outcome(s).
- That all studies report data with clinically comparable timepoints.

Similarity of “standard of care” arms

Clinical feedback suggested that the dressing types used as “standard of care” or “comparator” arms were not sufficiently similar to combine, as different dressing types have very different clinical indications for use. This means that the wound types treated with each group of dressings are clinically heterogeneous, and thus cannot be combined in a single network meta-analysis.

The only 2 studies with comparable non-antimicrobial dressing arms, suitable for combining in a meta-analysis, are Humbert 2006 and Meaume 2005, both of which assess a silver dressing versus the calcium alginate fibre dressing Algosteril.

Similarity of silver arms

Following clinical feedback, the various types of silver dressings assessed by the RCTs could be grouped into a) foams, b) fibres and hydro alginates, and c) nanocrystalline dressings. Within each of these 3 groups, clinicians felt that similar results would be expected. This means that dressings within each group could be pooled for the purposes of network meta-analysis, giving us nodes a, b and c. However, described above, “each group (of dressing types) has very different clinical indications for use”, meaning that the patient populations of each group are clinically heterogeneous, and thus cannot be compared. The only option for quantitative analysis that this leaves is to analyse within each group, i.e. within each patient population. This results in a series of small fragmented “sub networks”, of limited value.

The silver dressings assessed by Humbert 2006 and Meaume 2005 are foam and hydro alginate respectively, with clinical opinion suggesting that these 2 dressings would fall into different use groups and could not be considered similar. No meta-analysis of these 2 trials is therefore possible.

Clinical comparability of timepoints

Although it was already established that no quantitative analysis was possible due to a lack of homogeneity in dressings assessed and wound types treated, clinical opinion was also sought as to whether similarity could be assumed across the various timepoints at which the RCTs reported outcome data.

Feedback suggested that at timepoints of 4,6,8 and 9 weeks, differences in healing would be expected regardless of treatment / dressing, so data reported across these timepoints would not be comparable. As the majority of studies reported outcome data at a variety of short to medium term timepoints (i.e. up to and including 24 weeks), comparison of outcome data across RCTs was not possible.

11.5 *Appendix E: Ongoing studies*

The EAG searches identified 4 eligible ongoing studies (in 6 documents):

- 1 single-arm trial evaluating DURAFIBER Ag in people with infected VLUs (NCT03277131, (NCT03277131 2017)).
- 1 RCT comparing Cutimed Sorbact and Aquacel Ag in people with infected VLUs (NCT03667937 (NCT03667937 2019), protocol references (Morilla-Herrera et al. 2020, Morilla-Herrera et al. 2023)).
- 1 single-arm trial evaluating Biatain Ag in people with infected VLUs (NCT05873257, (NCT05873257 2023))
- 1 single-arm trial comparing AQUACEL Ag+ and Kollagenase in people with infected VLUs (RBR-4kkq2h, (RBR-4kkq2h 2019)).

11.6 *Appendix F: Efficacy and safety outcome summaries*

11.6.1 *Infection*

11.6.1.1 *Infection: Local infection*

11.6.1.1.1 Studies that fully met the decision problem

The presence of signs of local infection or resolution of infection was reported by 10 studies that fully met the decision problem, including 4 comparative studies and 6 single-arm studies. The comparative studies included 2 RCTs, 1 in an unclear setting and location comparing **monofloral honey, dressing type unspecified** and **unspecified silver sub-agent and dressing type (n=25 in each arm)** (Molle et al. 2023)) and 1 in mixed Swedish settings comparing **cadexomer iodine Iodosorb powder, dressing category: ointments, gels, hydrogels** to non-antimicrobial dressings (n=93 (Skog et al. 1983)). The other comparative studies included 1 Spanish community health centre cohort study comparing 3 forms of silver dressing (n=25 in each arm) with **various sub-agent and dressing types** (Gago et al. 2008) and 1 non-randomised trial in an Austrian secondary care setting (n=16) comparing **octenidine (dressing category: ointments, gels, hydrogels)** with different secondary dressings (Hammerle and Strohal 2016).

The 6 single-arm studies included 2 Belgian studies evaluating **1% silver sulfadiazine cream (dressing category: ointments, gels, hydrogels)**, 1 hospital setting, n=29 (Degreef and Michiels 1984); 1 unclear setting, n=19 (Melotte et al. 1985)), and 1 study each evaluating **DURAFIBER Ag ionic silver gelling fibre (dressing category: alginate, gelling fibre, absorbent fibre)**, South African secondary care centre, n=14) (Forlee et al. 2014), **ionic silver Aquacel Ag (dressing category: alginate, gelling fibre, absorbent fibre)**, France and Germany in unclear treatment settings, n=18) (Vanscheidt et al. 2003), **silver sulphadiazine Allevyn Ag foam dressing (dressing category: foams, absorbent pads)**, USA tertiary care setting, n=24) (Lantis and Gendics 2011) and **Mepilex Ag silver sulphate foam (dressing category: foams, absorbent pads)**, French private outpatient setting, n=534) (Truchetet et al. 2012). Timepoints and outcome definitions varied. We have included microbial burden outcomes in the summary below; though microbial burden is not itself a sign of infection, the IWII 2022 principles of best practice (International Wound Infection Institute (IWII) 2022) states that controlling wound bioburden is part of the management of infected wounds, thus these were considered outcomes of interest.

Silver vs honey (monofloral honey, dressing types unspecified; silver unspecified sub-agent and dressing type (Molle et al. 2023)):

- 1 RCT in an unclear setting and location comparing Manuka honey and silver (**monofloral honey, dressing types unspecified; silver unspecified sub-agent and dressing type**) (n=25 in each arm) reported that 84% of patients in the honey arm and 44% of patients in the silver arm had negative bacterial swab tests after 15 days; no statistical comparison was reported (Molle et al. 2023).

Iodine (cadexomer iodine Iodosorb powder, dressing category: ointments, gels, hydrogels vs various standard dressings including paraffin- or saline- impregnated dressings, ointments etc. (Skog et al. 1983)):

1 RCT in an unclear setting and location reported the number of patients with the most common bacterial infection (*staphylococcus aureus*) with reduced or clear swab results after treatment (Skog et al. 1983). In a complete case analysis statistically significantly more patients in the iodine arm had no presence of *S. aureus* at 3 weeks, as 17/24 patients had clear or reduced swab results versus 2/20 patients in the no agent arm ($p < 0.001$).

Silver (various sub-agents and dressing types (Gago et al. 2008, Forlee et al. 2014, Lantis and Gendics 2011, Vanscheidt et al. 2003, Truchetet et al. 2012, Degreef and Michiels 1984))

Change in the proportion of patients with resolved infections from baseline to 4 weeks was reported by 4 non-UK studies: 1 prospective cohort study in a Spanish community health centre (Gago et al. 2008) and 3 single-arm trials (1 in a South African hospital setting (Forlee et al. 2014), 1 in a US tertiary wound care practice (Lantis and Gendics 2011) and 1 in unclear French and German settings (Vanscheidt et al. 2003)):

- The cohort study compared different brands of silver dressing and reported that all patients in the **ionic silver Acticoat (dressing category: wound contact layer, gauze)**, **ionic silver complex Comfeel and Biatain Ag (dressing category: mixed)**, and **ionic silver Aquacel Ag hydrofiber (dressing category: alginate, gelling fibre, absorbent fibre)** groups ($n=25$ in each group) were free of signs of infection at 4 weeks; authors reported that infections signs resolved statistically significantly faster in the Acticoat arm (week 2 15/25 vs 1/25 and 2/25 respectively, week 3 15/25 vs 2/25 and 3/25 respectively, $p < 0.05$) (Gago et al. 2008).
- Both single-arm trials reported a statistically significant reduction from baseline in the proportion of patients with at least 1 sign of infection (14/14 vs 4/13, $p=0.002$ for **ionic silver DURAFIBRE™ Ag (dressing category: alginate, gelling fibre, absorbent fibre)** (Forlee et al. 2014); 24/24 vs 18/23 $p=0.033$ for **silver sulphadiazine Allevyn Ag (dressing category: foams, absorbent pads)** (Lantis and Gendics 2011)).
- 1 single-arm trial in unclear German and French settings reported that infection resolved in 2/11 patients after 28 days of treatment with Aquacel Ag (**ionic silver sodium carboxymethylcellulose fibre, dressing category: alginate, gelling fibre, absorbent fibre**) (Vanscheidt et al. 2003).

1 single-arm study reported change in microbial burden:

- 1 prospective case series in a Belgian hospital setting reported that among 29 patients with infected VLU's receiving **1% silver sulfadiazine cream (dressing category:**

ointments, gels, hydrogels) 19/29 (65.5%) had negative bacteria swabs at week 4 (Degreef and Michiels 1984).

3 studies reported the mean time to resolution of infection in days:

- 1 cohort study (n=25 in each arm) compared hazard ratios for time to infection resolution in different brands of silver dressing in a Spanish community health setting. This study reported that all patients in the Acticoat (**ionic silver, dressing category: wound contact layer, gauze**) group experienced infection resolution statistically significantly faster than those in the Comfeel/Bioatain Ag (**ionic silver complex hydrocolloid and foam dressings, dressing category: mixed**) and Aquacel Ag (**ionic silver, dressing category: alginate, gelling fibre, absorbent fibre**) groups as patients were more likely to have infections resolved at any time within the first 4 weeks of treatment (hazard ratio 1.96, p=0.018, 95% CI 1.12 to 3.43 and 1.89, p=0.025 95% CI 1.08 to 3.31 respectively) (Gago et al. 2008).
- 1 single-arm trial (n=14) in South African secondary care centres (**DURAFIBER Ag ionic silver gelling fibre, dressing category: alginate, gelling fibre, absorbent fibre**) reported that the mean time to resolution of clinical infection signs was 29.5 days (95% CI 14 to 49) (Forlee et al. 2014).
- 1 prospective case series (n=19) in an unclear Belgian setting (**1% silver sulfadiazine cream, dressing category: ointments, gels, hydrogels**) reported that in 4/19 patients who experienced infection resolution by 6 weeks, the mean time to resolution was 14 days (range 7 to 33) (Melotte et al. 1985).

1 study reported the change in the mean number of infection signs per patient:

- 1 prospective case series in a French outpatient setting (**Mepilex Ag silver sulphate foam, dressing category: foams, absorbent pads**) reported that the mean number of infection signs among 534 infected leg ulcer patients statistically significantly fell by (-2.2, SD 1.5, p<0.001) after a median follow up period of 19 days (Truchetet et al. 2012).

Octenidine (dressing category: ointments, gels, hydrogels (Hammerle and Strohal 2016))

1 non-randomised trial in an Austrian secondary care centre reported that among a subgroup of patients with infected leg ulcers (n=5 and 1 lost to follow up by day 42 in each arm) statistically significantly more patients had no sign of infection in the **octenidine gel with non-adherent contact layer and suction gauze** compared to the **octenidine gel plus secondary foam/alginate arm (both dressing category: ointments, gels, hydrogels)** (non-adherent layer and gauze 4/4 vs foam or alginate 1/4 p=0.038) at day 42 (Hammerle and Strohal 2016).

11.6.1.1.2 Studies that partly met the decision problem

4 single-arm studies that partly met the decision problem reported infection outcomes including 3 evaluating **enzyme alginate gel, dressing category: ointments, gels, hydrogels** (2 in UK

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primary care settings n=356 (Jones and Oates 2018) and n=1657 (King and Rolland 2023); 1 in Israel in a hospital outpatient setting n=23 (Durante 2012)) and 1 study in a Slovenian hospital setting evaluating **cupric oxide (dressing category: wound contact layer, n=12 (Dokic S et al. 2023))**.

Enzyme alginogel, dressing category: ointments, gels, hydrogels, n=356 (Jones and Oates 2018) and n=1657 (King and Rolland 2023)),

- Both UK primary care studies reported clinician-assessed improvement in signs of infection or critical colonisation after treatment with enzyme alginogels and both reported statistically significantly higher percentages of patients with improved signs of infection ((254/340 74.41% (Jones and Oates 2018) and 1114/1528 72.9% (King and Rolland 2023)) compared to the 50% of patients that authors would expect to have improved infections by chance ($p < 0.001$ in both cases).
- 1 prospective case series in an Italian hospital setting reported that all 3 patients with infected wounds at baseline were free of infection after 60 days of using enzyme alginogel (Durante 2012).

Copper (cupric oxide, dressing category: wound contact layer (Dokic S et al. 2023))

- 1 prospective case series in a Slovenian hospital setting reported that all 12 patients treated with copper dressings were free of infection after 3 months, though the number of patients with infected wounds at baseline was unclear (Dokic S et al. 2023).

11.6.1.2 Infection: Wound severity scores

11.6.1.2.1 Studies that fully met the decision problem

Wound severity scores were reported by 1 RCT that fully met the decision problem (Meaume et al. 2005).

Silver (metallic silver Silvercel hydro-alginate, dressing category: alginate, gelling fibre, absorbent fibre vs Algosteril, pure calcium alginate (Meaume et al. 2005))

- 1 RCT in a UK hospital setting reported a greater though non-statistically significantly greater mean score reduction in Wound Severity Score days in the whole study population of both leg ulcers and pressure ulcers at 4 weeks in the Silvercel group compared to usual care (ITT analysis n=51 Silvercel and n=48 no AMD, -5.6 SD 3.2 vs -4.1 SD 4.3, $p=0.063$), while the percentage decrease in score was statistically significantly greater in the Silvercel group (-32.1% SD 17.4% vs -22.6% SD 25.3%, $p=0.034$) (Meaume et al. 2005). The change in mean score and percentage differences were reported for patients with leg ulcers only (ITT analysis n=38 Silvercel and n=33 no AMD, -5.7 SD 2.8, -32.6% SD 15.4 vs -4.4 SD 4.3, -25.0% SD 21.8%), though no comparison was reported.

- This study also reported no statistically significant difference in modified ASEPSIS score at 14 between Silvercel and no AMD (ITT analysis n=51 Silvercel and n=48 no AMD, 104.2 (SD 72.8) vs 95.4 (SD 62.2), p=0.791) (Meaume et al. 2005). The modified score was reported for the leg ulcers patients alone, though no statistical comparison was reported (ITT analysis n=38 Silvercel and n=33 no AMD, 111.8 (SD 79.1) vs 86.3 (51.0).

11.6.1.2.2 Studies that partly met the decision problem

No studies that partly met the decision problem reported a wound severity score.

11.6.2 *Clinical Signs of Infection*

11.6.2.1 *Clinical signs of infection: Covert*

11.6.2.1.1 Studies that fully met the decision problem

2 single-arm studies (South Africa and US, secondary and tertiary care) that fully met the decision problem reported covert clinical signs of infection with use of a silver dressing, including 1 evaluating **ionic silver DURAFIBRER Ag gelling fibre (dressing category: alginate, gelling fibre, absorbent fibre, n=14)** (Forlee et al. 2014) and 1 evaluating **silver sulphadiazine Allevyn Ag foam dressing (dressing category: foams, absorbent pads, n=24)** (Lantis and Gendics 2011).

Silver (various sub-agents, dressing types (Forlee et al. 2014, Lantis and Gendics 2011))

- **Silver (ionic silver DURAFIBRER Ag Gelling fibre, dressing category: alginate, gelling fibre, absorbent fibre):** The South African study (n=14) (Forlee et al. 2014) reported friable granulation tissue at baseline in 2 (14.3%) patients and at final assessment (up to 8 weeks) in 0 (0%).
- **Silver (silver sulphadiazine Allevyn Ag foam dressing, dressing category: foams, absorbent pads):** The US single-arm trial (n=24 (Lantis and Gendics 2011)) reported friable granulation tissue at baseline (week 0) in 5 (20.8%) patients; week 2: 4 (16.7%); week 4 (n=23): 5 (21.7%); and week 8 (n=23): 4 (17.4%) and treatment discontinuation in 3 (12.5%).

11.6.2.1.2 Studies that partly met the decision problem

No studies that partly met the decision problem reported this outcome.

11.6.2.2 *Clinical signs of infection: Overt*

Studies that fully met the decision problem

8 studies that fully met the decision problem reported overt signs of infection including 2 RCTs comparing eligible agents to non-antimicrobial dressings (1 Swedish RCT in a mixed treatment setting comparing **cadexomer iodine Iodosorb powder, dressing category: ointments, gels, hydrogels**, n=74 (Skog et al. 1983); 1 French RCT in secondary care settings evaluating **ionic silver complex Biatain Ag foam (dressing category: foams, absorbent pads**, n=80 (Humbert et al. 2006)). The remaining 6 studies were single-arm, including: 1 in South Africa (in 3 secondary care centres) evaluating **ionic silver DURAFIBRER Ag gelling fibre (dressing category: alginate, gelling fibre, absorbent fibre, n=14)** (Forlee et al. 2014); 1 in the UK (10 clinics) evaluating a **silver oxysalts KerraContact Ag polyethylene mesh (dressing category: alginate, gelling fibre, absorbent fibre, n=31)** (Woolstencroft 2018); 1 in Denmark and Canada (outpatient clinics at 4 centres) evaluating **Physiotulle Ag (silver sulphadiazine, dressing category: wound contact layer, n=24)** (Jorgensen et al. 2008); 1 in the US (tertiary care wound practice) evaluating **silver sulphadiazine Allevyn Ag foam dressing (dressing category: foams, absorbent pads, n=24)** (Lantis and Gendics 2011); 1 in France (private outpatient setting) evaluating **silver sulphate Mepilex ag foam (dressing category: foams, absorbent pads, n=534)** (Truchetet et al. 2012); and 1 in France and Germany (unclear setting) evaluating **ionic silver Aquacel Ag absorbent fibre (dressing category: alginate, gelling fibre, absorbent fibre, n=11)** (Vanscheidt et al. 2003).

Iodine (cadexomer iodine Iodosorb powder, dressing category: ointments, gels, hydrogels)

1 RCT (Sweden, mixed treatment setting) compared **cadexomer iodine Iodosorb powder** (n=38) with standard treatment (n=36) (Skog et al. 1983). Erythema and pus/ debris scores fell more at 6 weeks with iodine than with standard treatment ($p < 0.005$ for both scores).

Silver (various sub-agents and dressing types (Humbert et al. 2006, Lantis and Gendics 2011, Truchetet et al. 2012, Jorgensen et al. 2008, Forlee et al. 2014, Vanscheidt et al. 2003, Woolstencroft 2018))

7 studies assessing silver reporting overt signs of infection fully met the decision problem. These included an RCT (**foam** (Humbert et al. 2006)) and 6 single-arm studies (**foam** (Lantis and Gendics 2011, Truchetet et al. 2012), **hydrocolloid** (Jorgensen et al. 2008), **gelling fibre** (Forlee et al. 2014, Vanscheidt et al. 2003), **mesh** (Woolstencroft 2018)):

- 1 RCT (France, mainly outpatients) compared **ionic silver complex Biatain Ag foam (dressing category: foams, absorbent pads, n=40)** with calcium alginate fibre dressing (n=40) (Humbert et al. 2006). The proportion of patients with wound malodour reduced at day 14 (from 87.5% to 28.2% with silver [change from baseline -59.3%]; from 82.5% to 47.2% with calcium alginate [change from baseline -35.3%]; between arm comparison was not reported).

- 5 single-arm trials of **silver** reported reductions in the proportion of patients with:
 - Erythema: **ionic silver gelling fibre**, from 42.9% at baseline to 7.1% at 8 weeks (Forlee et al. 2014); **silver sulphadiazine polyurethane foam**, from 75% at baseline to 66.7% at week 2, 43.5% at week 4 and 34.8% at week 8 (Lantis and Gendics 2011) and **silver sulphate silicone foam**, from 74% at baseline to 52% at mean follow-up of 19 days (Truchetet et al. 2012)).
 - Temperature around the wound: (**ionic silver gelling fibre**, from 35.7% at baseline to 0% at 8 weeks (Forlee et al. 2014); **silver sulphadiazine polyurethane foam**, from 16.7% at baseline to 4.2% at week 2 and 0% at weeks 4 and 8 (Lantis and Gendics 2011));
 - Purulent discharge: **ionic silver gelling fibre**, from 21.4% at baseline to 0% at 8 weeks (Forlee et al. 2014); **silver sulphadiazine polyurethane foam**, from 16.7% at baseline to 4.2% at week 2 and 0% at weeks 4 and 8 (Lantis and Gendics 2011)).
 - Malodour: **ionic silver gelling fibre**, from 42.9% at baseline to 0% at 8 weeks (Forlee et al. 2014); **silver sulphadiazine hydrocolloid**, from 37% at baseline to 8% at day 9 and 4% at 31 (Jorgensen et al. 2008); **silver sulphadiazine polyurethane foam**, from 41.7% at baseline to 37.5% at week 2, 34.8% at week 4 and 17.4% at week 8 (Lantis and Gendics 2011) and **silver oxysalts polyethylene mesh**, with wound odour “reduced significantly” in 64.4% of patients at 4 weeks (Woolstencroft 2018)).
 - 1 study (France and Germany, setting not reported) evaluating **ionic silver Aquacel Ag absorbent fibre** did not report erythema directly but reported that 3/11 patients (27%) had redness and inflammation at 28 days (Vanscheidt et al. 2003).

11.6.2.2.1 Studies that partly met the decision problem

2 single-arm studies that partly met the decision problem reported overt signs of infection including 1 in community centres and acute hospitals in the UK and Ireland evaluating **DACC (dressing category: wound contact layer; n=14 wounds in 13 patients (Bruce 2012))** and 1 in an Egyptian outpatient setting evaluating **monofloral honey, dressing category: wound contact layers, gauze, n=30 (Moghazy et al. 2010))**.

DACC (dressing category: wound contact layer (Bruce 2012))

1 prospective single-arm study (UK and Ireland, community centres and acute hospitals) of **DACC (dressing category: wound contact layer; n=14 wounds in 13 patients (Bruce 2012))** reported that after 28 days' follow-up (or until infection reduced), erythema had resolved in the 9 wounds initially affected, raised temperature had resolved in the 6 wounds initially affected,

and of the 12 wounds with malodour at the start of treatment, only 3 had malodour at the end of treatment.

Honey (monofloral honey, dressing category: wound contact layers, gauze (Moghazy et al. 2010))

1 prospective single-arm study (n=30) of **monofloral honey (dressing category: Wound contact layers, gauze)** in infected DFUs (Egypt, outpatient department) (Moghazy et al. 2010) reported statistically significant reductions in the number of patients with inflammation from baseline to 1 month (100% to 3.3%) and 2 or 3 months (0%, $p<0.001$). Similarly, the number of patients with foul/purulent exudate was statistically significantly reduced at 1, 2 or 3 months (from 76.7% to 0%, $p<0.01$).

11.6.3 Wound Healing

11.6.3.1 Wound healing: Time to healing

11.6.3.1.1 Studies that fully met the decision problem

2 studies fully that fully met the decision problem reported wound healing using a silver impregnated dressing, including 1 UK RCT (community nursing setting, n=133 in each arm) comparing **ionic silver Acticoat/Acticoat 7 or Acticoat Absorbent (barrier dressings and alginate dressings, dressing category: mixed wound contact layer, gauze and alginate, gelling fibre, absorbent fibre)** with **Iodosorb cadexomer iodine (ointment or powder, dressing category: ointments, gels, hydrogels)** (Miller et al. 2010) and 1 US prospective single-arm trial (tertiary care wound practice, n=24) evaluating **silver sulphadiazine Allevyn Ag (polyurethane foam, dressing category: foams, absorbent pads)** (Lantis and Gendics 2011).

- **Ionic silver (barrier and alginate, dressing category: mixed) versus cadexomer iodine (ointment or powder):** The UK RCT (n=133 in both arms (Miller et al. 2010)) conducted a survival analysis for the total number of days to wound healing. No statistically significant difference was found between groups (log-rank $p=0.7$, wilcoxon $p=0.8$; days to wound healing NR for either arm).
- **Silver sulphadiazine (polyurethane foam, dressing category: foams, absorbent pads):** The US single-arm trial (n=24 (Lantis and Gendics 2011)) reported the median time to wound closure and treatment cessation (among 50% of patients with fully healed wounds) to be 91 days (13 weeks) (range NR). Among these patients the mean treatment duration was 57.3 days (SD NR).

11.6.3.1.2 Studies that partly met the decision problem

1 further prospective single-arm study that partly met the decision problem reported on a **monofloral honey dressing (dressing category: wound contact layer, gauze)** in infected

DFUs in an Egyptian outpatient department (n=30 (Moghazy et al. 2010)) The mean duration of healing was reported to be 2.3 weeks (SD 0.94) (Moghazy et al. 2010)).

11.6.3.2 Wound healing: Complete healing

11.6.3.2.1 Studies that fully met the decision problem

13 studies that fully met the decision problem reported complete healing. This included 1 RCT comparing two eligible agents (**UK community nurse setting, Iodosorb cadexomer iodine powder/ointment, dressing category: ointments, gels, hydrogels vs ionic Acticoat/Acticoat 7 or Acticoat Absorbent, dressing category: mixed n=133 in each arm (Miller et al. 2010))**) and 2 RCTs comparing silver with no agent (1 UK hospital setting evaluating **metallic silver dressing category: alginate, gelling fibre, absorbent fibre, n=99 (Meaume et al. 2005)**; 1 Greek unclear setting evaluating **ionic silver complex Contreet Ag/Biatain Ag foam, dressing category: foams, absorbent pads, n=42 (Dimakakos et al. 2009))**). Of 3 non-randomised comparative studies, 1 compared eligible agents (1 cohort study in an unclear location and setting comparing **monofloral honey, dressing type unspecified and silver unspecified sub-agent and dressing type, n=25 in each arm (Molle et al. 2023))**) and 2 compared the same agent in different forms (1 Austrian non-randomised trial in secondary care comparing **octenidine, dressing category: ointments, gels, hydrogels** with different secondary dressings n= 29 in each arm (Hammerle and Strohal 2016); 1 Spanish community health centre cohort study comparing 3 forms of silver dressing with **various sub-agent and dressing types, n=25 in each arm (Gago et al. 2008))**). The other 8 studies were single-arm studies including 2 Belgian studies evaluating **1% silver sulfadiazine cream (dressing category: ointments, gels, hydrogels, 1 hospital setting, n=29 (Degreef and Michiels 1984)**; 1 unclear setting, n=19 (Melotte et al. 1985)), 1 French study in an outpatient setting evaluating **silver sulphate (dressing category: foams, absorbent pads, n=534) (Truchetet et al. 2012)**, 1 US single-arm study in a tertiary care setting evaluating **silver sulphadiazine Allevyn Ag foam (dressing category: foams, absorbent pads, n=24 (Lantis and Gendics 2011)**, 1 UK study in a tertiary care setting evaluating silver oxysalt KerraContact Ag (**dressing category: alginate, gelling fibre, absorbent fibre, n=30 (Woolstencroft 2018)**, 1 UK and Poland study in an unclear treatment setting evaluating **ionic silver with antibiofilm agent Aquacel Ag+ Hydrofiber, dressing category: alginate, gelling fibre, n=10 (Harding et al. 2016))** and 1 South African study in a secondary care setting evaluating **ionic silver DURAFIBRER Ag gelling fibre (dressing category: alginate, gelling fibre, absorbent fibre, n=14 (Forlee et al. 2014))**.

Honey versus silver (monofloral honey, dressing type unspecified; silver unspecified sub-agent and dressing type (Molle et al. 2023)):

- A non-randomised clinical trial (Molle et al. 2023) of honey (n=25 ulcers) vs silver (n=25 ulcers) dressings reported that at day 30, 13.6% and 64% of ulcers respectively had

healed. P values against baseline were statistically significant for both arms (p=0.001 and p<0.0001 respectively).

Iodine (Iodosorb cadexomer iodine powder/ointment, dressing category: ointments, gels, hydrogels) versus silver (ionic Acticoat/Acticoat 7 or Acticoat Absorbent, dressing category: mixed (Miller et al. 2010)):

- An RCT of iodine (Miller et al. 2010) (n=133) comparing with silver (n=133) dressings reported that at 12 weeks' follow up, the proportion of patients with healed wounds (100% closure) was 85 (64%) in the silver arm and 84 (63%) in the iodine arm (p >0.05). Subgroup analysis found no difference between the treatment groups in the number of wounds healed overall for young vs old (wounds with duration less than or greater than 12 weeks) or small vs big (wound area less than or greater than 3.6cm²) wounds.

Octenidine (dressing category: ointments, gels, hydrogels (Hammerle and Strohal 2016)):

- A non-randomised trial, assessed Octenidine plus a foam / alginate dressing (n=17 ulcers) against Octenidine plus a wound contact layer (n=15 ulcers). After 26 days, the number healed ulcers with a foam / alginate dressing was 2/17 (11.7%) and with octenidine with a wound contact layer was 3/15 (20%) (Hammerle and Strohal 2016). No statistical comparison was reported.

Silver (Silvercel metallic silver hydroalginate, dressing category: alginate, gelling fibre, absorbent fibre (Meaume et al. 2005); ionic silver complex Contreet/Biatain Ag foam, dressing category: foams, absorbent pads (Dimakakos et al. 2009)) versus no agent:

- 2 studies assessed silver dressings against a no-agent comparator. The first study of silver alginate (Meaume et al. 2005) reported that at 4 weeks, 1/51 patients in the silver arm had experienced wound closure, and 1/48 patients in the comparator arm.
- The second study of silver foam (Dimakakos et al. 2009) reported that at week 9, 17/21 (81%) of patients in the silver arm had experienced complete wound healing, compared with 10/21 (48%) in the comparator arm, a statistically significant difference between arms (p=0.02).

Silver versus silver (ionic silver, various dressing types (Gago et al. 2008))

- A final comparative study of silver (Gago et al. 2008) assessed 3 different types of dressings. The number of wounds healed at 8 weeks in each group was:

¹ P value is as-reported in the paper, presumed to be p<0.001

- 14/25 (56%) in group 1 (**ionic silver Acticoat polyethylene dressing, dressing category: wound contact layer, gauze**).
- 6/25 (24%) in group 2 (**ionic silver Comfeel™ hydrocolloid or Biatain™ Ag foam, dressing category: mixed**).
- 7/25 (28%) in group 3 (**ionic silver Aquacel Ag hydrofiber, dressing category: alginate, gelling fibre, absorbent fibre**).
- Time to complete healing was also faster in group 1 compared to group 2 and 3 ($p < 0.05$), after adjusting for baseline wound area.

Silver (single-arm studies)

- A further 6 single-arm studies of silver dressings reported wound closure / healing rates of:
 - 1/29 (3.4%) at two weeks (**1% silver sulfadiazine cream, dressing category: ointments, gels, hydrogels**) (Degreef and Michiels 1984)
 - 9.8% of 534 patients at a median of 19 days (2.7 weeks) (**Mepilex Ag silver sulphate, dressing category: foams, absorbent pads**) (Truchetet et al. 2012)
 - 2/30 (7%) at 4 weeks (**Kerracontact Ag silver oxysalts polyethylene dressing, dressing category: alginate, gelling fibre, absorbent fibre**) (Woolstencroft 2018)
 - 1/10 (10%) (**Aquacel Ag+ ionic silver with antibiofilm agent, dressing category: alginate, gelling fibre, absorbent fibre for 4 weeks followed by 4 weeks non-antimicrobial Aquacel**) and 7/14 (50%); **DURAFIBRE Ag ionic silver, dressing category: alginate, gelling fibre, absorbent fibre**) at 8 weeks (Harding et al. 2016, Forlee et al. 2014)
 - 11/24 (45.8%) at a median of 80.5 days (11.5 weeks) (**Allevyn Ag foam dressing, dressing category: foams, absorbent pads**) (Lantis and Gendics 2011).
- A seventh single-arm study (**1% silver sulfadiazine cream, dressing category: ointments, gels, hydrogels**) found that 11/19 patients healed within an average of 19 days (7-39 days) (Melotte et al. 1985).

11.6.3.2.2 Studies that partly met the decision problem

A further 9 studies that partly met the decision problem and reported on complete healing rates including 2 RCTs (1 in a Chinese hospital setting comparing **chitosan , dressing category: alginate, gelling fibre, absorbent fibre** to a non-antimicrobial dressing, n=79 (Mo et al. 2015);

1 in an Australian wound care clinic setting comparing **PHMB dressings of various dressing types, n=79** (Vallejo et al. 2022)). 7 studies were single-arm including 1 in an acute hospital setting in an unclear location evaluating **chitosan (dressing category: alginate, gelling fibre, absorbent fibre, n=20)** (Orig and Singleton 2016), 2 studies evaluating **cupric oxide (dressing type: wound contact layer, 1 in a Slovenian hospital setting, n=12 (Dokic S et al. 2023); 1 in Israel in an outpatient treatment setting, n=13 (Melamed et al. 2021))**, 1 in an Italian hospital setting evaluating **enzyme alginogel (dressing category: ointments, gels, hydrogels, n=23 (Durante 2012))** and 2 evaluating honey dressings (1 German and Austrian study in hospital settings evaluating **manuka MediHoney topical or gel, dressing category: ointments, gels, hydrogels, n=154** (Biglari et al. 2013); 1 Egyptian outpatient setting study evaluating **monofloral honey, dressing category: wound contact layers, gauze, n=30** (Moghazy et al. 2010))

Chitosan (dressing category: alginate, gelling fibre, absorbent fibre (Mo et al. 2015) and (Orig and Singleton 2016)):

- An RCT of chitosan vs a no-agent dressing (Mo et al. 2015) reported that in infected wounds 8/35 (23%) in the chitosan group achieved complete healing at 4 weeks, compared with 1/34 (2.9%) in the comparator group.
- A second single-arm study of chitosan found that at discharge (mean 8.18 days) 4/20 patients (20%) had healed wounds (Orig and Singleton 2016).

Copper (cupric oxide, dressing type: wound contact layer (Dokic S et al. 2023, Treadwell T et al. 2022)):

- 2 prospective case series of copper reported that 12/12 (100%) of patients had complete healing at 3 months (Dokic S et al. 2023), and that 8/25 patients (31%) “healed during the course of therapy” (Treadwell T et al. 2022) although duration of follow up was not reported for the second study.

Enzyme Alginogel (dressing category: ointments, gels, hydrogels (Durante 2012)):

1 prospective case series (Durante 2012) reported complete healing rates of 1/23 at day 14, 7/23 at day 30, and 12/23 at day 60.

Honey (manuka MediHoney topical or gel, dressing category: ointments, gels, hydrogels (Biglari et al. 2013), or monofloral honey, dressing category: wound contact layer, gauze (Moghazy et al. 2010)):

- 1 single-arm study of manuka honey gel dressings (Biglari et al. 2013) reported 32/101 patients (31.4%) with completely healed wounds at a mean follow up of 4.88 (SD 4.4) weeks.

- A second single-arm study reported that patients with closed wounds increased with time from 0/30 (0%) at baseline to 4/30 (13.3%) at 1 and 2 months, 5/30 (16.7%) at 3 months (Moghazy et al. 2010).

PHMB (dressing category: mixed (Vallejo et al. 2022); PHMB, dressing category: wound contact layer, gauze (Koullias et al. 2022)):

- An RCT of PHMB (Vallejo et al. 2022) found no statistically significant difference in the number of healed wounds between PHMB and the no-agent comparator arm at 12 weeks (PHMB 4/25 (16%) and comparator 6/25 (24%); $p=0.47$).
- A second single-arm study of PHMB ($n=67$) reported that the proportion of patients with wound closure increased with time from baseline to 9% at 4 weeks, 33.14% at 8 weeks, 41.76% at 12 weeks, 45.35% at 16 weeks, 53.1% at 16 weeks, and 72.64% at 32 weeks (Koullias et al. 2022).

11.6.3.3 Wound healing: Partial healing

11.6.3.3.1 Studies that fully met the decision problem

5 studies that fully met the decision problem reported partial healing, all of which evaluated silver dressings. They included 1 RCT in a UK hospital comparing a **metallic silver Silvercel hydroalginate dressing (dressing category: alginate, gelling fibre, absorbent fibre; $n=51$)** with a pure calcium alginate dressing ($n=48$) (Meaume et al. 2005) and 4 prospective single-arm studies assessing **silver sulphate Mepilex Ag foam (dressing category: foams, absorbent pads, France, $n=534$) (Truchetet et al. 2012)**, **ionic and metallic silver polymeric matrix (dressing category: unclear, USA, $n=16$) (Manning et al. 2020)**, **silver oxysalt KerraContact Ag polyethylene mesh (dressing category: alginate, gelling fibre, absorbent fibre, UK, $n=31$) (Woolstencroft 2018)**, and **ionic silver with antibiofilm agent Aquacel Ag+ hydrofiber (dressing category: alginate, gelling fibre, absorbent fibre, UK and Poland, $n=10$) (Harding et al. 2016)**.

Silver; metallic silver Silvercel hydroalginate dressing (dressing category: alginate, gelling fibre, absorbent fibre) (Meaume et al. 2005), silver sulphate Mepilex Ag foam (dressing category: foams, absorbent pads)(Truchetet et al. 2012), ionic and metallic silver polymeric matrix (dressing category: unclear) (Manning et al. 2020), silver oxysalt KerraContact Ag polyethylene mesh (dressing category: alginate, gelling fibre, absorbent fibre) (Woolstencroft 2018), and ionic silver with antibiofilm agent Aquacel Ag+ hydrofiber (dressing category: alginate, gelling fibre, absorbent fibre)(Harding et al. 2016)):

- The UK RCT (Meaume et al. 2005) found no statistically significant difference ($p=0.425$) between arms in the proportion of wounds considered closed or improved (silver 34/51 67% vs no agent 26/48 54%, $p=0.45$) at 4 weeks.

- 4 prospective single-arm studies reported partial healing. 2 studies reported wounds to be improved in 68.75% (11/16) to 77% (of n=534) of patients at approximately 3 weeks (Truchetet et al. 2012, Manning et al. 2020)). 1 study reported that at 4 weeks 60% and 30% (of n=31) experienced “significant wound improvement” or “wound improvement” respectively (Woolstencroft 2018), and 1 reported that at 8 weeks 8/10 (80%) and 1/10 (10%) patients experienced “marked” or “mild” wound improvement respectively (Harding et al. 2016).

11.6.3.3.2 Studies that partly met the decision problem

10 studies partly met the decision problem and reported on complete healing rates including 2 RCTs (1 in a Chinese hospital setting comparing **Kytocel chitosan, dressing category: alginate, gelling fibre, absorbent fibre** to a non-antimicrobial dressing, n=79 (Mo et al. 2015); 1 in an Australian wound care clinic setting comparing **PHMB dressings of various dressing types, n=79** (Vallejo et al. 2022)). 8 studies were single-arm including and 2 studies evaluating honey dressings (1 German and Austrian study in hospital settings evaluating **manuka MediHoney topical or gel, dressing category: ointments, gels, hydrogels, n=154** (Biglari et al. 2013); 1 Egyptian outpatient setting study evaluating **monofloral honey, dressing category: wound contact layers, gauze, n=30** (Moghazy et al. 2010)), 1 study in an acute hospital setting in an unclear location evaluating **chitosan (dressing category: alginate, gelling fibre, absorbent fibre, n=20)** (Orig and Singleton 2016), 1 study in the USA in an unclear setting evaluating **cupric oxide (dressing category: dressing category: wound contact layer, gauze, n=25** (Treadwell T et al. 2022)), 1 in the UK and Ireland in mixed community centre and hospital settings evaluating **DACC (dressing category: wound contact layer, gauze, n=23** (Bruce 2012)), and 3 studies evaluating enzyme alginogel (dressing category: ointments, gels, hydrogels: 2 in UK primary care settings, n=356 (Jones and Oates 2018) and n=1657 (King and Rolland 2023); 1 in an Italian hospital setting, n=23 (Durante 2012)).

Chitosan (both, dressing category: alginate, gelling fibre, absorbent fibre (Orig and Singleton 2016, Mo et al. 2015)):

- A Chinese RCT (hospital setting) (Mo et al. 2015) in patients with any infected wound reported that more patients achieved healing of at least 80% in the chitosan arm (7/35 20%) than the comparator (3/34 9%), although statistical significance was not reported.
- A shorter-term prospective single-arm study (Orig and Singleton 2016) in patients with infected wounds on an acute hospital ward (country not reported), reported that 11/20 (55%) patients experienced an improvement in quality of granulation tissue at a mean evaluation time of 8.18 days (SD NR).

Copper (cupric oxide, dressing category: wound contact layer, gauze (Treadwell T et al. 2022)):

- 1 prospective case series of copper (Treadwell T et al. 2022) in hard to heal wounds at a US medical centre reported that at an unspecified follow-up, 17/25 (68%) patients experienced healing of at least 50% of the wound.

DACC (dressing category: wound contact layer, gauze (Bruce 2012)):

- 1 prospective case series of DACC (n=14 wounds in 13 patients (Bruce 2012)) in chronic wounds in UK and Irish community centres and acute hospitals reported that after 28 days' follow-up (or until infection reduced), the number of wounds with inflammation had reduced from 11 to 4.

Enzyme Alginogel (dressing category: ointments, gels, hydrogels (Durante 2012, Jones and Oates 2018, King and Rolland 2023)):

- After 60 days' follow-up, 1 prospective case series (Durante 2012) of acute or chronic wounds treated in Italian hospitals reported that 20/20 patients experienced a statistically significant decrease ($p < 0.001$) in wound area and volume. The second and third studies (infected wounds in UK primary care) did not report a follow up timepoint, but all wounds in the second study (n=352 (Jones and Oates 2018)) were reported to be "improved" (78.4%) or unchanged (21.6%). Of 1587 participants in the third study (King and Rolland 2023), 77.5% of wounds were "improved" and 22.5% showed no change or worsening.

Honey (monofloral honey, dressing category: wound contact layers, gauze (Moghazy et al. 2010) and manuka MediHoney topical or gel, dressing category: ointments, gels, hydrogels (Biglari et al. 2013)):

- At a mean follow-up of 4.4 weeks, 1 prospective case series of general infected wounds in German and Austrian hospitals (Biglari et al. 2013) reported that of 101 patients, 53.3% showed improvement (i.e. a reduced wound area), 9.2% had "stagnant" (+/- 10% size of wound area) wounds, and 6.1% had deteriorating wounds. At 3 months' follow-up, a prospective single-arm trial in infected DFUs in Egyptian outpatients (Moghazy et al. 2010) (n=30) reported that partial healing had occurred in 43.3%, while 93.3% had experienced a reduction in size of the wound.

PHMB (dressing category: mixed (Vallejo et al. 2022)):

- 1 comparative study of PHMB versus no-agent comparator (n=25 (Vallejo et al. 2022)) reported that after 12 weeks, there was no statistically significant difference in ulcer healing between arms ($p=0.53$), measured using the Pressure Ulcer Scale for Healing (PUSH) Tool.

11.6.4 Wound size and area

11.6.4.1 Wound size / area: Change

11.6.4.1.1 Studies that fully met the decision problem

5 comparative studies that fully met the decision problem (1 **cadexomer iodine**, 1 **octenidine**, 3 **various silver sub-agents**) and 6 single-arm studies (all evaluating **silver**) reported change in wound size / area.

The 5 comparative studies included 4 RCTs compared eligible agents to non-antimicrobial dressings: 1 in mixed Swedish settings comparing **cadexomer iodine Iodosorb powder**, **dressing category: ointments, gels, hydrogels** n=93 (Skog et al. 1983); 1 in a UK hospital setting evaluating **metallic silver dressing category: alginate, gelling fibre, absorbent fibre**, n=99 (Meaume et al. 2005); 1 in French secondary care settings evaluating **ionic silver complex (Biatain AG) foam (dressing category: foams, absorbent pads**, n=80) (Humbert et al. 2006); and 1 in European hospital settings evaluating **silver sulphate Mepilex Ag foam**, **dressing category: foams, absorbent pads** n=201) (NCT01036438 2009). The remaining comparative study was an Austrian non-randomised trial in secondary care comparing **octenidine**, **dressing category: ointments, gels, hydrogels** with different secondary dressings n= 29 in each arm (Hammerle and Strohal 2016).

Iodine (cadexomer iodine Iodosorb powder (dressing category: ointments, gels, hydrogels (Skog et al. 1983))

1 RCT (location and setting not stated) using **cadexomer iodine Iodosorb powder (dressing category: ointments, gels, hydrogels**; n=38) compared with standard treatment (n=36) (Skog et al. 1983) and reported a statistically significant reduction in ulcer size in patients receiving the iodine dressing (34% vs increase of 5% in the standard treatment group, p<0.02).

Octenidine (dressing category: ointments, gels, hydrogels (Hammerle and Strohal 2016))

1 non-randomised comparative study (Austria, secondary care) compared **octenidine (dressing category: ointments, gels, hydrogels)** (n=14 patients, 17 venous leg ulcers); with a comparator group: **octenidine (dressing category: ointments, gels, hydrogels) plus wound contact layer and gauze** (n=15 patients, 15 venous leg ulcers) (Hammerle and Strohal 2016). The percent reduction in wound area at day 42 was not statistically significantly different between the **octenidine with foam/alginate** group and the **octenidine with gel plus gauze** group (-64.1% vs -96.2%, p=0.845).

Silver (various sub-agents and dressing types (Humbert et al. 2006, NCT01036438 2009, Meaume et al. 2005, Lantis and Gendics 2011, Jorgensen et al. 2008, Manning et al. 2020, Harding et al. 2016, Vanscheidt et al. 2003))

3 RCTs of **silver**: 1 (France, mainly outpatients) comparing **ionic silver complex (Biatain AG) foam (dressing category: foams, absorbent pads, n=40)** with calcium alginate fibre dressing (n=40) (Humbert et al. 2006); 1 (European hospital setting, not including the UK) comparing **silver sulphate Mepilex Ag foam (dressing category: foams, absorbent pads) n=100)** with an absorbent foam dressing without silver (n=101) (NCT01036438 2009); and 1 (UK, hospital) comparing **metallic Silvercel hydroalgininate (dressing category: alginate, gelling fibre, absorbent fibre) (n=51)** with a pure calcium alginate dressing (n=48) (Meaume et al. 2005).

- The RCT in France comparing **ionic silver complex (Biatain AG) foam (dressing category: foams, absorbent pads, n=40)** with calcium alginate fibre dressing (n=40) (Humbert et al. 2006) reported the reduction in wound surface area at 6 weeks was 2.6 times greater in silver group (37.3% vs 14.2%, p=0.04). The multinational RCT comparing the **silver sulphate Mepilex Ag foam (dressing category: foams, absorbent pads, n=100)** with non-silver foam (n=101) (NCT01036438 2009) reported a mean (SD) change in wound area at 8 weeks of -5.09 (14.23) cm² in the silver group vs -4.65 (15.43) cm² in the control group (p value not stated).
- The UK RCT comparing a **metallic Silvercell hydroalgininate (dressing category: alginate, gelling fibre, absorbent fibre, n=51)** with a pure calcium alginate dressing (n=48) (Meaume et al. 2005) reported the wound area change at week 4 was not statistically significantly different between the groups (-23.7% vs -24.0%).

6 single-arm studies that fully met the decision problem reported reduction in wound area using a **silver** dressing, including 1 (South Africa, secondary care) evaluating a **ionic silver DURAFIBRER Ag gelling fibre (dressing category: alginate, gelling fibre, absorbent fibre, n=14)** (Forlee et al. 2014); 1 (US, tertiary care) evaluating **silver sulphadiazine Allevyn Ag foam dressing (dressing category: foams, absorbent pads, n=24)** (Lantis and Gendics 2011); 1 (Denmark and Canada, outpatients) evaluating **Physiotulle Ag (silver sulphadiazine, dressing category: wound contact layer, n=24)** (Jorgensen et al. 2008); 1 (USA, secondary care) evaluating a **ionic and metallic silver polymeric matrix (dressing category: unclear, n=16)** (Manning et al. 2020), 1 (UK and Poland, setting not stated) evaluating **ionic silver with antibiofilm agent Aquacel Ag+ hydrofiber (dressing category: alginate, gelling fibre, absorbent fibre, n=10)** (Harding et al. 2016), and 1 (France and Germany, setting not reported) evaluating **ionic silver dressing (Aquacel Ag) absorbent fibre (dressing category: alginate, gelling fibre, absorbent fibre, n=11)** (Vanscheidt et al. 2003).

- Reductions in wound area were reported as 78.3% at Week 8 (**ionic silver DURAFIBRER Ag gelling fibre; dressing category: alginate, gelling fibre, absorbent fibre, n=14**) (Forlee et al. 2014)); 81.5% at 12 weeks (**silver sulphadiazine foam Allevyn Ag; dressing category foams, absorbent pads, 24**) (Lantis and Gendics 2011)); 42% at day 31 (**Physiotulle Ag; silver sulphadiazine, dressing category: wound contact layer, n=24**) (Jorgensen et al. 2008); 85.0% at day 28 (**metallic silver Hyalosilver topical spray powder; >75% at 12 weeks (ionic and**

metallic silver polymeric matrix, dressing category: unclear, n=16 (Manning et al. 2020); 70.2% at 8 weeks (**ionic silver with antibiofilm agent Aquacel Ag+ dressing category: alginate, gelling fibre, absorbent fibre**) (Harding et al. 2016); and 32.5% at 28 days (**ionic silver Aquacel AG hydrofiber; dressing category: alginate, gelling fibre, absorbent fibre, n=11**) (Vanscheidt et al. 2003).

11.6.4.1.2 Studies that partly met the decision problem

A further 8 studies partly met the decision problem and reported change in wound size / area including 2 RCTs (1 in a Chinese hospital setting comparing **chitosan, dressing category: alginate, gelling fibre, absorbent fibre** to a non-antimicrobial dressing, n=79 (Mo et al. 2015); 1 in an Australian wound care clinic setting comparing **PHMB dressings of various dressing types, n=79** (Vallejo et al. 2022)). 6 studies were single-arm including 1 evaluating **cupric oxide (dressing type: wound contact layer, in a Slovenian hospital setting, n=12** (Dokic S et al. 2023)); 1 in the UK and Ireland in mixed community centre and hospital settings evaluating **DACC (dressing category: wound contact layer, gauze, n=23** (Bruce 2012)); 1 in an Italian hospital setting evaluating **enzyme alginogel (dressing category: ointments, gels, hydrogels, n=23** (Durante 2012)); 1 in the USA in unclear settings evaluating **PHMB (unclear agent subtype, dressing category: wound contact layers, gauze, n=67** (Koullias et al. 2022)); and 2 evaluating **manuka MediHoney topical or gel, dressing category: ointments, gels, hydrogels** (1 German and Austrian study in hospital settings n=154 (Biglari et al. 2013); 1 in hospitals in the USA (Yang K et al. 2015).

Chitosan (chitosan, dressing category: alginate, gelling fibre, absorbent fibre (Mo et al. 2015))

1 RCT (3 university hospital centres in China) compared **chitosan (dressing category: alginate, gelling fibre, absorbent fibre)** (n=45) vs no agent (Vaseline gauze, n=45) for 4 weeks (Mo et al. 2015). The **percentage reduction in mean wound area from baseline in cm²** was statistically significantly greater with chitosan than no agent from Week 2 onwards (week 2 chitosan -36.01% vs no agent -24.32%, p<0.033; week 3 chitosan -53.77% vs no agent 36.02%, p<0.003; week 4 chitosan -65.97% vs no agent 39.95%, p<0.0014) (Mo et al. 2015).

Copper (cupric oxide, dressing category: wound contact layer, gauze (Melamed et al. 2021))

1 single-arm study assessed **cupric oxide (dressing category: wound contact layer, gauze)** in an outpatient hospital clinic in Israel (n=13) for 4 weeks (Melamed et al. 2021). During treatment, the **mean wound size reduction** among all patients was 53.2% (p=0.003); it was greater for non-weight bearing wounds than weight-bearing wounds (66.9% [p<0.001 vs baseline] vs 25% [not statistically significant vs baseline]).

DACC (dressing category: wound contact layer, gauze (Bruce 2012))

1 single-arm study assessed **DACC (dressing category: wound contact layer, gauze)** in chronic wounds in UK and Irish community centres and acute hospitals (n=14 wounds in 13 patients (Bruce 2012)). It reported that after 28 days' follow-up (or until infection reduced), 11/14 (79%) of wounds had a **reduction of wound size**; 6 (43%) had a **75% reduction in wound size** and 1 (7%) had a **25 to 49% reduction in wound size** (the reductions in wound size was not reported for the other 4 wounds).

Enzyme Alginogel (dressing category: Ointments, gels, hydrogels (Durante 2012))

1 prospective case series of 23 patients with acute or chronic wounds treated in Italian hospitals assessed **enzyme alginogel (dressing category: Ointments, gels, hydrogels)** (Durante 2012). After 60 days' follow-up (complete case analysis, n=13), the wound surface area (cm²) and volume (cm³) both reduced statistically significantly from baseline (mean surface area from 2.6cm² to 0.4cm² and volume from 2.6cm³ to 0.1cm³, p=0.001 for both results).

Honey (manuka hone, dressing category: ointments, gels, hydrogels (Biglari et al. 2013, Yang K et al. 2015))

3 prospective case series assessed honey: 1 **manuka MediHoney topical or gel, dressing category: ointments, gels, hydrogels** in infected general wounds (n=101) in German and Austrian hospitals (Biglari et al. 2013); 1 **topical manuka honey(dressing category: ointments, gels, hydrogels)** in patients with ulcerated stasis dermatitis due to chronic venous insufficiency (n=20) in hospitals in the USA (Yang K et al. 2015); and 1 **monofloral honey (dressing category: wound contact layers, gauze)** in infected DFUs (n=30) in an Egyptian outpatient department (Moghazy et al. 2010). All reported statistically significant reductions (p≤0.05) in wound area by the end of the studies (**manuka MediHoney** mean wound area reduced from 29.66cm² (SD 57.57) at baseline to 11.32cm² (SD 33.3) at mean 4.88 (SD 4.4) week follow-up (Biglari et al. 2013); **manuka honey** -21% change in wound area from baseline to 4 weeks (Yang K et al. 2015); **monofloral honey**, significant reduction in proportion of patients with larger wound sizes on an ordinal scale from baseline to 3 months (Moghazy et al. 2010)).

PHMB (various dressing types, (Vallejo et al. 2022, Koullias et al. 2022))

1 RCT assessed **PHMB (dressing category: mixed, n=25)** vs no agent (cleansing of the wound after and between treatments with clean water or saline, then non-medicated dressing products, n=25) in a community wound clinic in Australia with a follow up of 12 weeks (Vallejo et al. 2022).

1 prospective non-interventional study involving patients from the RESPOND Registry in the US (n=67) treated with **PHMB (dressing category: wound contact layers, gauze)** and followed up for 32 weeks (Koullias et al. 2022).

- The RCT that assessed **PHMB (dressing category: mixed, n=25)** vs no agent (clean water or saline, then non-medicated dressing products, n=25) reported the proportion of wounds reduced in size (any reduction) at 12 weeks as 61% with PHMB vs 12.7% with control; p=0.019 (Vallejo et al. 2022).
- The prospective non-interventional study involving patients from the RESPOND Registry in the US (n=67) treated with a **PHMB (unclear agent subtype, dressing category: wound contact layers, gauze)** and followed up for 32 weeks (Koullias et al. 2022) reported a >60% reduction in area in 77.61% of patients; a >60% reduction in depth in 70.15% and a >75% reduction in volume in 86.57% of patients.

11.6.4.2 Wound size / area: Rate of change

11.6.4.2.1 Studies that fully met the decision problem

3 studies that fully met the decision problem reported the rate of change in wound size / area including 2 UK RCTs: 1 in a hospital setting (n=99) comparing **metallic silver Silvercell (dressing category: alginate, gelling fibre, absorbent fibre to a non-antimicrobial dressing)** (Meaume et al. 2005) and 1 in a community setting comparing **ionic silver Acticoat dressings (dressing category: mixed)** with **cadexomer iodine (dressing category: ointments, gels, hydrogels)** (Miller et al. 2010). The remaining study was a single-arm study in Danish and Canadian outpatient settings (n=24) evaluating **Physiotulle Ag (silver sulphadiazine; dressing category: wound contact layer)** (Jorgensen et al. 2008).

Silver (metallic silver Silvercell hydroalginate (Meaume et al. 2005), ionic silver Acticoat dressings (Miller et al. 2010), and silver sulphadiazinehydrocolloid (Jorgensen et al. 2008)):

- The RCT in a UK hospital comparing **metallic silver Silvercell hydroaliginate (dressing category: alginate, gelling fibre, absorbent fibre)** (n=51) with a pure calcium alginate dressing (n=48) (Meaume et al. 2005) reported that the healing rate at week 4 was greater with silver (silver-0.32, SD 0.57 vs no agent -0.16 SD 0.4, p=0.024).
- 1 UK RCT (community nursing setting) compared **ionic silver dressing Acticoat, Acticoat Absorbant and Acticoat 7 (dressing category: mixed)** with **cadexomer iodine (dressing category: ointments, gels, hydrogels)** (Miller et al. 2010). The study reported that the daily healing rate (% change in wound size divided by the number of days between measurement; mean [SD]) at Week 2 for silver (n=129) was 2.12 (2.94) vs iodine (n=127) -0.22 (8.18) (p<0.01). There was no difference between groups at the later time points.
- 1 single-arm study (n=24) that fully met the decision problem was conducted in Denmark and Canada (outpatient clinics at 4 centres) evaluating **Physiotulle Ag (silver sulphadiazine; dressing category: wound contact layer)** (Jorgensen et al. 2008). This study reported a linear healing rate of 0.32 cm over the 4-week study period, where

the linear healing rate was defined as the reduction in wound area divided by mean wound circumference, where the reduction in area is divided by the mean of the wound circumference.

11.6.4.2.2 Studies that partly met the decision problem

1 prospective single-arm study of copper partly met the decision problem and reported a rate of change in wound size / area.

Copper (cupric oxide, dressing category: wound contact layer, gauze (Melamed et al. 2021))

- 1 prospective single-arm study of **cupric oxide (dressing category: wound contact layer, gauze)** in an outpatient hospital clinic in Israel (n=13) (Melamed et al. 2021) reported statistically significant reduction in the mean wound area from baseline to 4 weeks (4 weeks with copper dressing, -53.2%, p=0.003) and 6 weeks (including 2 further weeks with unspecified “standard care dressings”, -65% p<0.001)

11.6.5 *Change in wound bed condition*

8 studies that fully met the decision problem reported complete healing including 2 RCTs comparing eligible agents to non-antimicrobial dressings: 1 in mixed Swedish settings evaluating **cadexomer iodine Iodosorb powder, dressing category: ointments, gels, hydrogels** n=93 (Skog et al. 1983); and 1 in French secondary care settings evaluating **ionic silver complex (Biatain AG) foam (dressing category: foams, absorbent pads, n=80)** (Humbert et al. 2006). 1 non-randomised comparative study compared the same agent in different forms (1 Austrian non-randomised trial in secondary care comparing **octenidine, dressing category: ointments, gels, hydrogels** with different secondary dressings n= 29 in each arm (Hammerle and Strohal 2016). The other 5 studies were single-arm, including 1 French study in an outpatient setting evaluating **silver sulphate (dressing category: foams, absorbent pads, n=534)** (Truchetet et al. 2012), 1 US single-arm study in a tertiary care setting evaluating **silver sulphadiazine Allevyn Ag foam (dressing category: foams, absorbent pads, n=24)** (Lantis and Gendics 2011), 1 UK study in a tertiary care setting evaluating **silver oxysalt KerraContact Ag (dressing category: alginate, gelling fibre, absorbent fibre, n=30)** (Woolstencroft 2018), 1 South African study in a secondary care setting evaluating **ionic silver DURAFIBRER Ag gelling fibre (dressing category: alginate, gelling fibre, absorbent fibre, n=14)** (Forlee et al. 2014)); and 1 in Denmark and Canada (outpatient clinics at 4 centres) evaluating **Physiotulle Ag (silver sulphadiazine, dressing category: wound contact layer, n=24)** (Jorgensen et al. 2008).

8 studies that partly met the decision problem reported change in wound bed condition, including 1 RCT in a Chinese hospital setting comparing **chitosan, dressing (dressing category: alginate, gelling fibre, absorbent fibre** to a non-antimicrobial dressing, n=79 (Mo et al. 2015)). The other 7 studies were single-arm, including 2 studies evaluating **cupric oxide (dressing type: wound contact layer**, 1 in a Slovenian hospital setting, n=12 (Dokic S et al.

2023); 1 in Israel in an outpatient treatment setting, n=13 (Melamed et al. 2021)); 2 evaluating honey dressings (1 German and Austrian study in hospital settings evaluating **manuka MediHoney topical or gel, dressing category: ointments, gels, hydrogels, n=154** (Biglari et al. 2013); 1 Egyptian outpatient setting study evaluating **monofloral honey, dressing category: wound contact layers, gauze, n=30** (Moghazy et al. 2010)); and 3 evaluating enzyme alginogel (dressing category: ointments, gels, hydrogels: 2 in UK primary care settings, n=356 (Jones and Oates 2018) and n=1657 (King and Rolland 2023); 1 in an Italian hospital setting, n=23 (Durante 2012)).

11.6.5.1 Change in wound bed: Slough

11.6.5.1.1 Studies that fully met the decision problem

2 single-arm studies that fully met the decision problem reported change in wound slough.

Silver (silver sulphadiazine Allevyn Ag foam dressing, dressing category: foams, absorbent pads(Lantis and Gendics 2011)):

- 1 prospective single-arm study (US, tertiary care; n=24) (Lantis and Gendics 2011) reported a reduction in the percentage of devitalised (yellow slough or black necrotic) tissue from baseline (21.9%) to treatment discontinuation (5.4%), though statistical significance of this difference was not tested.

Silver (Physiotulle Ag (silver sulphadiazine; dressing category: wound contact layer (Jorgensen et al. 2008)):

- 1 prospective single-arm study (Denmark and Canada, outpatients, n=24) evaluating **Physiotulle Ag silver sulphadiazine dressing (dressing type: wound contact layer)** (Jorgensen et al. 2008) reported that slough reduced from 11% to 5% at day 31.

11.6.5.1.2 Studies that partly met the decision problem

4 studies that partly met the decision problem reported change in wound slough.

DACC (dressing category: wound contact layer, gauze (Bruce 2012)):

- A prospective single-arm study (UK and Ireland, community centres and acute hospitals) of **DACC** (hydropolymer gel matrix; n=14 wounds in 13 patients (Bruce 2012)) reported that slough was reduced from 6 wounds at baseline to 4 at end of treatment (28 days).

Enzyme Alginogel (dressing category: ointments, gels, hydrogels(Jones and Oates 2018, King and Rolland 2023)):

- 2 prospective case series (infected wounds in UK primary care) did not report a follow up timepoint, but the wound bed (debridement of slough/necrotic tissue) was described

as improved in 278/331 (84%) and unchanged or worse in 53/331 (16%) in the first study (Jones and Oates 2018) and improved in 1211/1503 (81%) and unchanged or worse in 292/1503 (19%) in the second study (King and Rolland 2023); difference between observed value and the expected value of 50%: $p < 0.0001$ for both studies.

Honey (manuka MediHoney topical or gel, dressing category: ointments, gels, hydrogels (Biglari et al. 2013)):

- 1 prospective single-arm study of honey dressings (n=101 infected general wounds in German and Austrian hospitals) (Biglari et al. 2013) reported a statistically significant change in mean slough/necrosis score (an average of score from 0 meaning presence of slough/necrosis to 1 meaning no slough/necrosis) from baseline to follow-up (0.16 SD 0.37 at baseline vs 0.74 SD 0.44 at mean 4.88 SD 4.4 weeks, $p < 0.05$) at end of study (4.88 weeks, 0.74, SD 0.74) vs baseline (0.16, SD 0.37).

11.6.5.2 Change in wound bed: Exudate

11.6.5.2.1 Studies that fully met the decision problem

2 studies that fully met the decision problem reported change in wound exudate.

Iodine (cadexomer iodine Iodosorb powder, dressing category: ointments, gels, hydrogels (Skog et al. 1983)):

- 1 RCT (location not stated) compared an iodine dry dressing (n=38) with standard treatment (n=36) (Skog et al. 1983). Mean exudate VAS 0 to 100 scores were significantly lower at 6 weeks in the iodine group than standard treatment group (iodine 11 SD 1.5 vs no agent 23 SD 3.6, $p < 0.005$).

Silver (various sub-agents, dressing category: foams, absorbent pads (Humbert et al. 2006, Truchetet et al. 2012, Lantis and Gendics 2011)):

- 1 RCT (France, mainly outpatients) compared **ionic silver complex Biatain Ag foam** (n=40) with calcium alginate fibre dressing (n=40) (Humbert et al. 2006). Little or no exudate was present during 65.0% of dressing removals with silver compared with 50.5% in the comparator group, $p = 0.04$.
- 1 prospective single-arm study assessing silver in a **silver sulphate Mepilex ag foam** (France, outpatients, n=794) (Truchetet et al. 2012) reported a reduction in copious exudate from 55% at baseline to 4.5% at a median of 19 days.
- 1 prospective single-arm study assessing silver (**silver sulphadiazine polyurethane foam**; US, tertiary care; n=24) (Lantis and Gendics 2011)) reported a statistically significant reduction in the level of exudate ($p < 0.001$) between baseline and treatment discontinuation.

Silver (ionic silver DURAFIBRE Ag gelling fibre (dressing category: alginate, gelling fibre, absorbent fibre(Forlee et al. 2014)):

- 1 single-arm study (South Africa; n=14) (Forlee et al. 2014) reported exudate decreased from 64.3% at baseline to 0 at final assessment.

Silver (silver oxysalts KerraContact Ag polyethylene mesh, dressing category: alginate, gelling fibre, absorbent fibre (Woolstencroft 2018)):

- 1 single-arm study (UK, 10 secondary care clinics, n=30) (Woolstencroft 2018) reported levels of exudate were reduced in 83% of patients.

11.6.5.2.2 Studies that partly met the decision problem

5 studies that partly met the decision problem reported change in wound exudate.

Chitosan (chitosan, dressing category: alginate, gelling fibre, absorbent fibre(Mo et al. 2015)):

- A Chinese RCT (hospital setting) (Mo et al. 2015) in patients with any infected wound reported that the mean exudate score (definition NR) at week 4 was lower with chitosan (40.51; n=42) than with the comparator (Vaseline gauze; 50.49; n=37; p=0.008).

DACC (dressing category: wound contact layer, gauze) (Bruce 2012):

- A prospective single-arm study (UK and Ireland, community centres and acute hospitals) of DACC (n=14 wounds in 13 patients (Bruce 2012)) reported that exudate was reduced from 14 wounds at baseline to 10 at end of treatment (28 days).

Enzyme Alginogel (dressing category: ointments, gels, hydrogels(Jones and Oates 2018, King and Rolland 2023)):

- 2 prospective case series (infected wounds in UK primary care) did not report a follow up timepoint, but the moisture balance was described as improved in 294/352 (83.52%) and unchanged or worse in 58/352 (16.48%) in the first study (Jones and Oates 2018); and well-managed in 1321/1599 (82.6%) and unchanged or worse in 278/1599 (17.4%) in the second study (King and Rolland 2023); difference between observed value and the expected value of 50%: p<0.0001 for both studies.

Honey (monofloral honey, dressing category: wound contact layers, gauze (Moghazy et al. 2010)):

- 1 prospective single-arm study of honey dressings (Egypt, outpatients, n=30 (Moghazy et al. 2010)) reported the proportion of patients with foul/purulent exudate reduced from 76.7% at baseline to none at 1 month, while the patients with serosanguinous exudate reduced from 23.3% at baseline to none at 3 months (p<0.01).

11.6.5.3 *Change in wound bed: Granulation*

11.6.5.3.1 Studies that fully met the decision problem

5 studies that fully met the decision problem reported change in wound bed granulation.

Iodine (cadexomer iodine Iodosorb powder, (dressing category: ointments, gels, hydrogels (Skog et al. 1983)):

- 1 RCT (location not stated) compared an iodine dry dressing (n=38) with standard treatment (n=36) (Skog et al. 1983). Mean granulation VAS 0 to 100 scores at 6 weeks were lower in the iodine group than non-antimicrobial dressings group (iodine 76 SD 4.0 vs no agent 60 SD 4.6 $p<0.05$).

Octenidine (octenidineplus foam or alginate compared with gel plus wound contact layer and gauze, dressing category: ointments, gels, hydrogels (Hammerle and Strohal 2016)):

- 1 non-randomised comparative study (Austria, secondary care) compared octenidine gel plus foam or alginate (n=14 patients, 17 venous leg ulcers) with octenidine gel plus wound contact layer and gauze (n=15 patients, 15 venous leg ulcers) (Hammerle and Strohal 2016). There was no statistically significant difference between interventions in the percentage of granulation tissue over time.

Silver (ionic silver DURAFIBRER Ag gelling fibre, dressing category: alginate, gelling fibre, absorbent fibre (Forlee et al. 2014)):

- 1 single-arm study (South Africa; n=14) (Forlee et al. 2014) reported discolouration of granulation tissue decreased from n=2 (14.3%) at baseline to 0 at final assessment.

Silver (silver sulphadiazine Allevyn Ag foam dressing, dressing category: foams, absorbent pads (Lantis and Gendics 2011)):

- 1 prospective single-arm study (US, tertiary care; n=24) (Lantis and Gendics 2011) reported a reduction in the percentage of dull red (unhealthy granulation) tissue in the included ulcers from baseline (39% of ulcer tissue) to treatment discontinuation (15.4% of ulcer tissue).

Silver (Physiotulle Ag, silver sulphadiazine; dressing category: wound contact layer (Jorgensen et al. 2008)):

- 1 prospective single-arm study (Denmark and Canada, outpatients, n=24) (Jorgensen et al. 2008) reported that unhealthy granulation tissue reduced from 19% to 8% at day 31, with healthy granulation tissue 30% and 31%, respectively.

11.6.5.3.2 Studies that partly met the decision problem

6 studies that partly met the decision problem reported change in wound granulation.

Copper (cupric oxide, dressing category: wound contact layer, gauze (Dokic S et al. 2023, Melamed et al. 2021)):

- 1 prospective case series (Slovenia, hospital) (Dokic S et al. 2023) in patients with long-standing wounds (n=12) reported that granulation took place during the 3 months of follow up. The other prospective single-arm study (Israel, outpatients) of a cupric oxide polypropylene dressing (n=13) (Melamed et al. 2021) reported that granulation tissue increased from baseline by 28.5% at 1 week ($p<0.01$) and at 43.37% at 4 weeks ($p<0.001$).

Enzyme Alginogel ((dressing category: Ointments, gels, hydrogels) (Durante 2012, King and Rolland 2023, Jones and Oates 2018)):

1 prospective case series (Italian hospitals) (Durante 2012) of 20 patients with acute or chronic wounds reported that the proportion of the wound composed of granulation tissue increased to day 14, then reduced as the proportion of neo-epithelial tissue increased at day 30 and day 60. The other 2 prospective case series (infected wounds in UK primary care) did not report a follow up timepoint, but the quality of granulation tissue was described as improved in 1230/1587 (77.5%) and unchanged or worse in 357/1587 (22.5%) in 1 study (King and Rolland 2023) and in 276/352 (78.41%) and 76/352 (21.59%) respectively in the other (Jones and Oates 2018) (difference between observed value and the expected value of 50%: $p<0.0001$ in both studies).

Honey (monofloral honey, dressing category: wound contact layers, gauze (Moghazy et al. 2010)):

1 prospective single-arm trial (Egyptian, outpatients) reported that 13/30 (43.3%) participants had wounds showing healthy granulation at 3 months.

11.6.5.4 Change in wound bed: Oedema

Studies fully that fully met the decision problem

3 studies that fully met the decision problem reported change in wound oedema.

Iodine (cadexomer iodine Iodosorb powder, dressing category: ointments, gels, hydrogels (Skog et al. 1983)):

- 1 RCT (location not stated) compared an iodine dry dressing (n=38) with standard treatment (n=36) (Skog et al. 1983). Both treatments statistically significantly reduced mean VAS 0 to 100 oedema scores from baseline (iodine 23 SD 3.2 at baseline to 8 SD

2.0 at week 6, $p < 0.005$; no agent 26 SD 3.9 at baseline to 20 SD 3.0 at week 6, $p < 0.05$).

Silver (ionic silver DURAFIBRER Ag gelling fibre, dressing category: alginate, gelling fibre, absorbent fibre (Forlee et al. 2014)):

- 1 single-arm study (South Africa; $n=14$) (Forlee et al. 2014) reported that the number of patients with oedema decreased from 3/14 (21.4%) at baseline to 0 at final assessment (no test of statistical significance was reported).

Silver (silver sulphadiazine Allevyn Ag foam, dressing category: foams, absorbent pads (Lantis and Gendics 2011)):

- 1 prospective single-arm study (US, tertiary care; $n=24$) (Lantis and Gendics 2011) reported a reduction in oedema from baseline (22/24 91.7%) to treatment discontinuation (5/24 20.8%), though no test of statistical significance was reported.

11.6.5.4.1 Studies that partly met the decision problem

1 study that partly met the decision problem reported change in the number of wounds with oedema.

DACC (dressing category: wound contact layer, gauze (Bruce 2012)):

- A prospective single-arm study (UK and Ireland, community centres and acute hospitals) of DACC ($n=14$ wounds in 13 patients (Bruce 2012)) reported a reduction in the number of wounds with oedema from 8/14 at baseline to 1/14 at end of treatment (28 days). No test of statistical significance was reported.

11.6.5.5 *Change in wound bed: Skin condition*

11.6.5.5.1 Studies that fully met the decision problem

No studies that fully met the decision problem reported change in wound skin condition.

11.6.5.5.2 Studies that partly met the decision problem

5 studies that partly met the decision problem reported change in wound skin condition.

Copper (cupric oxide dressing category: wound contact layer, gauze (Melamed et al. 2021)):

- 1 prospective single-arm study (Israel, outpatients, n=13) (Melamed et al. 2021) reported no peri-wound redness was observed during the 4 weeks of treatment.

DACC (dressing category: wound contact layer, gauze) (Bruce 2012):

- A prospective single-arm study (UK and Ireland, community centres and acute hospitals) of DACC (n=14 wounds in 13 patients (Bruce 2012)) reported that healthy peri-wound skin was increased from 2 wounds at baseline to 7 at end of treatment (28 days).

Enzyme Alginogel (dressing category: ointments, gels, hydrogels (Durante 2012, Jones and Oates 2018, King and Rolland 2023)):

- 1 prospective case series (Italian hospitals) (Durante 2012) of 20 patients with acute or chronic wounds reported that the evolution of the surrounding skin condition was excellent in 45%, good in 50% and poor in 5%. The other 2 prospective case series (infected wounds in UK primary care) did not report a follow up timepoint, but the peri-wound skin was described as improved in 255/356 (71.63%) and unchanged or worse in 101/356 (28.37%) in the first study (Jones and Oates 2018) and improved in 1124/1624 (69.2%) and unchanged or worse in 500/1624 (30.8%) in the second study (King and Rolland 2023); difference between observed value and the expected value of 50%: $p < 0.0001$ for both studies.

11.6.6 Dressing changes

11.6.6.1 Frequency of dressing changes and/or mean dressing wear time across study

11.6.6.1.1 Studies that fully met the decision problem

3 studies that fully met the decision problem reported dressing change outcomes including 1 French mainly outpatient setting RCT (n=80) comparing **ionic silver complex (dressing category: foams, absorbent pads)** to non-antimicrobial dressings (Humbert et al. 2006). The other studies were single-arm, including 1 South African study in a secondary care setting evaluating **ionic silver DURAFIBRER Ag gelling fibre (dressing category: alginate, gelling fibre, absorbent fibre, n=14 (Forlee et al. 2014))** and 1 UK study in a tertiary care setting evaluating **silver oxysalt KerraContact Ag (dressing category: alginate, gelling fibre, absorbent fibre, n=30 (Woolstencroft 2018))**.

Silver (ionic silver complex Contreet Ag/Biatain Ag foam dressing category: foams, absorbent pads (Humbert et al. 2006)):

In 1 French RCT (mainly outpatients) that compared silver polyurethane foam (n=40) with calcium alginate fibre dressing (n=40) (Humbert et al. 2006), the frequency of dressing replacement was similar between the groups (every 2.7 days vs every 2.8 days).

Silver (silver oxysalts KerraContact Ag polyethylene mesh, dressing category: alginate, gelling fibre, absorbent fibre (Woolstencroft 2018)):

1 single-arm study (UK, 10 clinics) (Woolstencroft 2018) reported that among 22/31 patients with available data on dressing wear time the percentage of dressings worn for 5 to 7 days was 42.8% compared with previous dressing types (31.2%), and that the average dressing wear time was 9 days (range 7 to 28 days) (Woolstencroft 2018).

Silver (ionic silver DURAFIBRER Ag gelling fibre, dressing category: alginate, gelling fibre, absorbent fibre (Forlee et al. 2014)):

1 South African single-arm study (secondary care, n=14) (Forlee et al. 2014) reported mean wear time for each patient across all assessments where the new dressing was used was 6.4 days (median 6.9 days, range 4.7 to 7.0 days).

11.6.6.1.2 Studies that partly met the decision problem

No studies that that partly met the decision problem reported dressing change outcomes.

11.6.7 Antibiotics

11.6.7.1 Prescription of antibiotics

11.6.7.1.1 Studies that fully met the decision problem

2 studies that fully met the decision problem reported the use of antibiotics including 1 UK hospital setting RCT (n=99) comparing **metallic silver (dressing category: alginate, gelling fibre, absorbent fibre)** with non-antimicrobial dressings (Meaume et al. 2005) and 1 South African single-arm study in a secondary care setting evaluating **ionic silver DURAFIBRER Ag gelling fibre (dressing category: alginate, gelling fibre, absorbent fibre, n=14 (Forlee et al. 2014))**

Silver (metallic Silvercell hydroalgininate, dressing category: alginate, gelling fibre, absorbent fibre (Meaume et al. 2005)):

In the UK RCT (hospital setting) comparing silver-releasing hydroalgininate (n=51) with no agent (n=48) (Meaume et al. 2005), over the 4-week study period, systemic antibiotics were administered to similar numbers of people in the 2 groups (7.8% vs 10.4%; p=0.736).

Silver (ionic silver DURAFIBRE Ag gelling fibre, dressing category: alginate, gelling fibre, absorbent fibre (Forlee et al. 2014)):

The South African prospective single-arm study (secondary care, n=14) (Forlee et al. 2014) reported that 10/14 (83.3%) patients were prescribed antibiotics.

11.6.7.1.2 Studies that partly met the decision problem

No studies that partly met the decision problem reported antibiotic use.

11.6.8 Recurrence

11.6.8.1 Recurrence of wound or infection

11.6.8.1.1 Studies that fully met the decision problem

1 single-arm study evaluating **silver sulphadiazine Allevyn Ag foam** fully met the decision problem and reported recurrence of wound or infection.

Silver (silver sulphadiazine Allevyn Ag foam, dressing category: foams, absorbent pads (Lantis and Gendics 2011)):

1 US prospective single-arm trial (tertiary care wound practice, n=24) evaluating silver (polyurethane foam dressing) (Lantis and Gendics 2011) reported that in 5 of the 11 patients whose ulcer had closed at treatment discontinuation, the ulcer had re-opened by the week 12 follow-up assessments.

11.6.8.1.2 Studies that partly met the decision problem

1 single-arm study evaluating **monofloral honey** that partly met the decision problem reported recurrence of wound or infection.

Honey (monofloral honey, dressing category: wound contact layers, gauze (Moghazy et al. 2010)):

1 prospective single-arm study of honey dressings (Egypt, outpatients, n=30 (Moghazy et al. 2010)) reported that at 3 months, 26.7% of ulcers had closed, resurfaced and reclosed.

11.6.9 Pain

11.6.9.1 Pain score

11.6.9.1.1 Studies that fully met the decision problem

5 studies that fully met the decision problem reported patient-reported pain scores. This included 3 RCTs, of which 2 compared eligible agents to non-antimicrobial dressings (1 Swedish RCT in a mixed treatment setting comparing **cadexomer iodine Iodosorb powder, dressing category: ointments, gels, hydrogels**, n=74 (Skog et al. 1983); 1 French RCT in secondary care settings evaluating **ionic silver complex Biatain Ag foam (dressing category: foams, absorbent pads**, n=80 (Humbert et al. 2006)) and 1 (UK community nursing setting, n=80) which compared **ionic silver Aquacel Ag Hydrofiber (dressing category: alginate, gelling fibre, absorbent fibre)** to **DACC (dressing category: wound contact layer, gauze)** (Mosti et al. 2015). The remaining 2 studies were single-arm, of which 1 evaluated **silver sulphate (dressing category: foams, absorbent pads, French outpatient setting, n=534)** (Truchetet et al. 2012) and 1 evaluated **Physiotulle Ag (silver sulphadiazine, dressing category: wound contact layer, Canadian and Danish outpatient setting, n=24)** (Jorgensen et al. 2008).

Iodine (cadexomer iodine Iodosorb powder, (dressing category: ointments, gels, hydrogels (Skog et al. 1983)):

1 RCT (Sweden, mixed treatment settings) compared an iodine dry dressing (n=38) with standard treatment (n=36) (Skog et al. 1983). Both treatments statistically significantly reduced mean VAS 0 to 100 ulcer pain score (iodine 32 SD 4.7 at baseline to 10 SD 2.5 at week 6, $p<0.005$; no agent 33 SD 4.3 at baseline to 23 SD 3.7 at week 6, $p<0.05$) but the effect of iodine was observed earlier (score in iodine arm at week 1 was 27 SD 4.6 $p<0.005$ vs baseline; no agent score at week 1 was 29 SD 4.1, p value not reported but stated to be non-significant) and scores at week 6 were statistically significantly lower in the iodine arm compared to non-antimicrobial dressings ($p<0.01$).

Silver (various sub-agents, dressing category: foams, absorbent pads (Humbert et al. 2006, Truchetet et al. 2012)):

1 RCT (France, mainly outpatients) compared **ionic silver complex polyurethane foam** (n=40) with calcium alginate fibre dressing (n=40) (Humbert et al. 2006) and reported that pain (apart from dressing changes) was statistically significantly lower with silver ($p=0.003$).

1 prospective single-arm study in France (private outpatient setting, n=794) evaluating **silver sulphate foam** (Truchetet et al. 2012) reported a fall in mean wound-pain intensity on a 100mm VAS from 50 (SD 24) at baseline to 24.6 (SD 20.9) at follow up (p value NR).

Silver (Physiotulle Ag, unclear agent subtype; dressing category: wound contact layer (Jorgensen et al. 2008))

1 prospective single-arm study (Denmark and Canada, outpatients) evaluating **silver sulphadiazine Physiotulle Ag (dressing type: wound contact layer, n=24)** (Jorgensen et al. 2008) reported that persistent wound pain fell from 6.3 at baseline to 3.0 at 12 hours after the first dressing application and remained low for the first 5 days; pain after dressing removal fell from 2.4 on day 3 to 1.1 on day 31; and pain after cleansing fell from 6.3 on day 3 to 1.8 on day 31 (p value NR).

Silver (ionic silver Aquacel Ag Hydrofiber (Mosti et al. 2015), dressing category: alginate, gelling fibre):

- 1 pilot RCT (UK, community nursing services) comparing silver (**ionic silver Aquacel Ag Hydrofiber, dressing category: alginate, gelling fibre, absorbent fibre, n=20**) with DACC (**dressing category: wound contact layer, gauze, n=20**) (Mosti et al. 2015) reported that pain scores decreased in both groups (–35% and –38%, respectively, no statistically significant difference).

Silver (silver oxysalt KerraContact Ag polyethylene mesh, dressing category: alginate, gelling fibre, absorbent fibre (Woolstencroft 2018)):

1 single-arm study (UK, tertiary care clinic setting, n=30) (Woolstencroft 2018) stated that 52% of patients reported significant or complete reduction in pain.

11.6.9.1.2 Studies that partly met the decision problem

3 studies that partly met the decision problem reported patient-reported pain scores including 1 RCT in an Australian wound care clinic setting comparing **PHMB dressings of various dressing types, n=79** (Vallejo et al. 2022)) and 2 single-arm studies (1 in an Italian hospital setting evaluating **enzyme alginogel (dressing category: ointments, gels, hydrogels, n=23 (Durante 2012)** and 1 German and Austrian study in hospital settings evaluating **manuka MediHoney topical or gel, dressing category: ointments, gels, hydrogels, n=154** (Biglari et al. 2013)).

Enzyme Alginogel (dressing category: ointments, gels, hydrogels (Durante 2012)):

1 prospective case series (Italy, hospital, n=20) (Durante 2012) reported NRS 0 to 11 pain scores between day 0 and day 60 (n=13) for the 3 series of measurements taken during application of the enzyme alginogel from mean 1.0 (SD 1.9) at first application to 0.2 (SD 0.6) at the day 60 application.

Honey (manuka MediHoney topical or gel, dressing category: ointments, gels, hydrogels (Biglari et al. 2013)):

1 prospective single-arm study of honey dressings (n=101 infected general wounds in German and Austrian hospitals) (Biglari et al. 2013) reported reduction in pain score (VAS 0 to 10 scale) from baseline (1.71) to study end (0.55, p<0.05).

PHMB (dressing category: mixed (Vallejo et al. 2022))

1 RCT assessed PHMB (**dressing category: mixed**; n=25) vs no agent (cleansing of the wound after and between treatments with clean water or saline, then non-medicated dressing products, n=25) in a community wound clinic in Australia with a follow up of 12 weeks (Vallejo et al. 2022). When pain levels were compared, lower median NRS 0 to 10 pain scores were observed in the intervention group at 6 weeks (PHMB 0 SD 0, no agent 0 SD 2 p=0.04) but there was no statistically significant difference in pain levels at any other time point (baseline PHMB 1 SD 3, no agent 0 SD 3; week 1 PHMB 1 SD 3, no agent 0 SD 3; week 12 PHMB 0 SD 0, no agent 0 SD 0, p=0.54).

11.6.9.2 Patients reporting being in pain

11.6.9.2.1 Studies that fully met the decision problem

3 studies that fully met the decision problem reported the number and percentage of patients who reported pain. including 1 Greek RCT in an unclear setting evaluating **ionic silver complex Contreet Ag/Biatain Ag foam, dressing category: foams, absorbent pads, n=42** (Dimakakos et al. 2009)). The remaining 2 studies were single-arm, including 1 South African study in a secondary care setting evaluating **ionic silver DURAFIBRER Ag gelling fibre (dressing category: alginate, gelling fibre, absorbent fibre, n=14** (Forlee et al. 2014)) and 1 US study in a tertiary care setting evaluating **silver sulphadiazine Allevyn Ag foam (dressing category: foams, absorbent pads, n=24** (Lantis and Gendics 2011)).

Silver (ionic silver complex Contreet Ag/Biatain Ag foam, dressing category: foams, absorbent pads (Dimakakos et al. 2009) and silver sulphadiazine Allevyn Ag foam, dressing category: Foams, absorbent pads (Lantis and Gendics 2011)):

1 Greek RCT (setting NR) (Dimakakos et al. 2009) reported that all patients (n=21) using the silver dressing were pain free at 8 weeks compared with 13/21 (62%) pain free in the no agent group at the end of Week 9.

1 prospective single-arm study in the US (tertiary care wound practice, n=24) evaluating a polyurethane foam dressing (Lantis and Gendics 2011) reported a reduction in the percentage of patients reporting spontaneous pain between dressing changes from 83.3% at baseline to 30.4% at Week 8.

Silver (ionic silver DURAFIBRER Ag gelling fibre (dressing category: alginate, gelling fibre, absorbent fibre (Forlee et al. 2014)):

The South African prospective single-arm study (n=14) (Forlee et al. 2014) reported pain as an indicator of infection in 35.7% of patients at baseline and none at the final assessment.

11.6.9.2.2 Studies that partly met the decision problem

7 studies that partly met the decision problem reported the number and percentage of patients who reported pain including 1 Chinese hospital setting RCT comparing **chitosan, dressing category: alginate, gelling fibre, absorbent fibre** to non-antimicrobial dressings (n=45 in each arm) (Mo et al. 2015). The other 6 studies were single-arm studies including 2 studies evaluating **cupric oxide (dressing type: wound contact layer**, 1 in a Slovenian hospital setting, n=12 (Dokic S et al. 2023); 1 in Israel in an outpatient treatment setting, n=13 (Melamed et al. 2021)), 1 German and Austrian study in hospital settings evaluating **manuka MediHoney topical or gel, dressing category: ointments, gels, hydrogels, n=154** (Biglari et al. 2013), 1 in the UK and Ireland in mixed community centre and hospital settings evaluating **DACC (dressing category: wound contact layer, gauze, n=23 (Bruce 2012))**, and 2 studies evaluating enzyme alginogel (dressing category: ointments, gels, hydrogels: 2 in UK primary care settings, n=356 (Jones and Oates 2018) and n=1657 (King and Rolland 2023)).

Chitosan (chitosan, dressing category: alginate, gelling fibre, absorbent fibre (Mo et al. 2015):

A Chinese RCT (hospital setting, n=45 in each arm) (Mo et al. 2015) in patients with any infected wound reported that there was less pain following dressing removal in the chitosan group than the no agent group at weeks 2 and 3 (both $p < 0.05$) and at week 4 (scores 1.12 vs 2.30 on an 11-point numerical rating scale [0 no pain to 10 severe pain]; $p < 0.001$).

Copper (cupric oxide, dressing category: wound contact layer, gauze) (Dokic S et al. 2023, Melamed et al. 2021)):

2 prospective single-arm studies evaluating copper (n=12, (Dokic S et al. 2023), n=13 (Melamed et al. 2021)) stated that patients did not report being in pain during treatment.

DACC (dressing category: wound contact layer, gauze (Bruce 2012)):

1 prospective case series of DACC (UK and Ireland; primary and secondary care; n=14 wounds in 13 patients (Bruce 2012)) reported that after 28 days' follow-up (or until infection reduced), of the 11 patients experiencing pain at the start of the evaluation, 2 (18%) patients presented with pain at the end.

Enzyme Alginogel (dressing category: ointments, gels, hydrogels (Jones and Oates 2018, King and Rolland 2023)):

2 studies (infected wounds in UK primary care) did not report a follow up timepoint, but similar numbers of patients in both studies reported that pain improved as stayed the same or worsened (170/344 49.42% vs 174/344 50.58% in 1 study (Jones and Oates 2018) and 830/1571 52.8% vs 741/1571 47.2% in the other study (King and Rolland 2023)). In both studies authors compared the percentage of patients with improved pain to an expected chance value of 50% and reported no statistically significant difference ($p = 0.4358$ (Jones and Oates 2018) and $p = 0.4149$ (King and Rolland 2023)).

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Honey (manuka MediHoney topical or gel, dressing category: ointments, gels, hydrogels (Biglari et al. 2013)):

1 prospective single-arm study of honey dressings (n=101 infected general wounds in German and Austrian hospitals) (Biglari et al. 2013) reported that 42/101 of patients did not have pain at baseline; of the 60 that did, 54 (90%) had reduced pain and 6 (10%) stayed the same.

11.6.9.3 Discomfort

11.6.9.3.1 Studies that fully met the decision problem

2 studies that fully met the decision problem reported patient discomfort including 1 French mainly outpatient setting RCT (n=80) comparing **ionic silver complex (dressing category: foams, absorbent pads)** to non-antimicrobial dressings (Humbert et al. 2006) and 1 single-arm UK secondary care setting study evaluating **silver oxysalt KerraContact Ag (dressing category: alginate, gelling fibre, absorbent fibre n=31)** (Woolstencroft 2018).

Silver (ionic silver complex Biatain AG foam, dressing category: foams, absorbent pads (Humbert et al. 2006)):

1 RCT (France, mainly outpatients, n=40 in each arm) compared silver polyurethane foam with calcium alginate fibre dressing (Humbert et al. 2006) and reported that more patients rated comfort with the dressing in place as “excellent” or “good” with silver (86.8%) than with no agent (70.5%, p<0.001).

Silver (silver oxysalt KerraContact Ag polyethylene mesh, dressing category: alginate, gelling fibre, absorbent fibre (Woolstencroft 2018)):

1 single-arm study (UK, 10 secondary care clinics, n=31) (Woolstencroft 2018) stated that 56% of patients said the silver dressing was better than the previous dressing in terms of comfort.

11.6.9.3.2 Studies that partly met the decision problem

2 single-arm studies that partly met the decision problem reported patient discomfort including 1 Slovenian hospital setting study evaluating **cupric oxide (dressing type: wound contact layer, n=12)** (Dokic S et al. 2023); and 1 UK and Ireland in mixed community centre and hospital settings study evaluating **DACC (dressing category: wound contact layer, gauze, n=23)** (Bruce 2012)).

Copper (cupric oxide, dressing category: wound contact layer, gauze (Melamed et al. 2021)):

1 prospective single-arm study evaluating copper (n=13, (Melamed et al. 2021)) stated that patients did not report discomfort during installation and changing of dressing.

DACC (dressing category: wound contact layer, gauze (Bruce 2012)):

1 prospective case series of DACC (UK and Ireland; primary and secondary care; n=14 wounds in 13 patients (Bruce 2012)) reported that patients who were also receiving compression therapy were asked to rate the comfort of the dressings under compression (score from 1 'not satisfied' to 10 'satisfied'); the mean patient score was 9 (range 6 to 10).

11.6.10 HRQoL

11.6.10.1 Studies that fully met the decision problem

1 single-arm study that fully met the decision problem (evaluating **ionic silver DURAFIBER Ag**) reported HRQoL (Forlee et al. 2014).

Silver (ionic silver DURAFIBER Ag gelling fibre (dressing category: alginate, gelling fibre, absorbent fibre (Forlee et al. 2014)):

1 single-arm study (South Africa, secondary care; n=14) (Forlee et al. 2014) reported that EQ-5D index score improved from 0.55 at baseline to 0.86 at 8 weeks (p=0.031) and the VAS score improved from 65 to 78.9 (p value NR).

11.6.10.2 Studies that partly met the decision problem

1 RCT that partly met the decision problem (comparing **various PHMB** dressings) reported HRQoL (Vallejo et al. 2022).

PHMB (dressing category: mixed (Vallejo et al. 2022):

1 RCT compared PHMB (n=25) vs no agent (cleansing of the wound after and between treatments with clean water or saline, then non-medicated dressing products, n=25) in a community wound clinic in Australia with a follow up of 12 weeks (Vallejo et al. 2022). It reported no difference between the groups on total wound-related quality of life score at 12 weeks.

11.6.11 Adverse Events

11.6.11.1 Overall TRAEs / serious TRAEs

11.6.11.1.1 Studies that fully met the decision problem

8 studies that fully met the decision problem reported overall adverse events. This included 5 RCTs, of which 3 compared silver foam dressings (**all dressing category: foams, absorbent pads**) to non-antimicrobial dressings (1 Greek in an unclear setting evaluating **ionic silver complex, n=42** (Dimakakos et al. 2009); 1 French mainly in outpatient settings evaluating **ionic silver complex, n=80** (Humbert et al. 2006); 1 in various European hospital settings evaluating **silver sulphate, n=201** (NCT01036438 2009)). 1 UK hospital setting RCT compared **metallic silver (dressing category: alginate, gelling fibre, absorbent fibre, n=99)**

to non-antimicrobial dressings (Meaume et al. 2005) and 1 UK community nursing setting (n=80) compared **ionic silver Aquacel Ag Hydrofiber (dressing category: alginate, gelling fibre, absorbent fibre)** to **DACC (dressing category: wound contact layer, gauze)** (Mosti et al. 2015). 1 cohort study in an Austrian secondary care setting (n=16) compared **octenidine (dressing category: ointments, gels, hydrogels)** with different secondary dressings (Hammerle and Strohal 2016). The remaining 2 studies were single-arm, of which 1 evaluated **silver sulphadiazine Allevyn Ag foam dressing (dressing category: foams, absorbent pads; USA tertiary care setting, n=24)** (Lantis and Gendics 2011), 1 evaluated **Physiotulle Ag (silver sulphadiazine, dressing category: wound contact layer, Canadian and Danish outpatient setting, n=24)** (Jorgensen et al. 2008).

Octenidine (dressing category: ointments, gels, hydrogels (Hammerle and Strohal 2016)):

1 non-randomised comparative study (Austria, secondary care) compared **octenidine gel plus foam or alginate** (n=14 patients, 17 venous leg ulcers); with a comparator group: **octenidine gel plus wound contact layer and gauze** (n=15 patients, 15 venous leg ulcers) (Hammerle and Strohal 2016); no treatment-related adverse events or serious adverse events occurred.

Silver (dressing category: foams, absorbent pads (Dimakakos et al. 2009, Humbert et al. 2006, NCT01036438 2009, Lantis and Gendics 2011)):

In the Greek RCT (setting NR, n=21 in each arm), none of the patients experienced systemic or local side effects attributed to the intervention in the **ionic silver complex** or the **no agent** group (Dimakakos et al. 2009).

In the French RCT (mainly outpatients, n=40 in each arm) comparing **ionic silver complex Biatain Ag foam** with calcium alginate fibre dressing (Humbert et al. 2006), there were 3 adverse events in each group including pain/itching (2 in each group), 1 epidermitis in the silver group and 1 redness/maceration in the comparator group; 1 patient in the silver group and 2 in the comparator group discontinued due to these events.

In the European (hospital setting, not including the UK) RCT comparing **silver sulphate Mepilex Ag foam** (n=100) with an absorbent foam dressing without silver (n=101) (NCT01036438 2009), skin/subcutaneous adverse events considered related to the ulcer (not necessarily treatment) were noted in 14% in the silver group and 18.81% in the comparator group (p value NR).

1 prospective single-arm study (US, tertiary care) evaluating **silver sulphadiazine Allevyn Ag foam** (Lantis and Gendics 2011) reported 1 possibly device-related adverse event out of 33 patients in the safety analysis: a report of severe pain on dressing removal at Week 6 (but not at subsequent time points). There were no serious treatment-related adverse events.

Silver (silver sulphadiazine Physiotulle Ag, dressing category: wound contact layer (Jorgensen et al. 2008))

Another single-arm study in Denmark and Canada (outpatients) evaluating **Physiotulle Ag** (Jorgensen et al. 2008) reported 4 treatment-related adverse events: 2 dermatitis and 2 local irritation or maceration.

Silver (metallic Silvercell hydroalgininate, dressing category: alginate, gelling fibre, absorbent fibre (Meaume et al. 2005)):

1 RCT (UK, hospital) comparing a silver-releasing hydroalgininate (n=51) with a pure calcium alginate dressing (n=48) (Meaume et al. 2005) reported adverse events that the investigator was 'certain' had a relationship with the applied dressing: 3/51 patients in the silver group (including peri-wound eczema and extension of slough; dry wound; unclear in the third patient) and 1/48 in the control group (pain during dressing change), so the allocated dressing was discontinued, and a foam dressing was used instead.

Silver (ionic silver Aquacel Ag Hydrofiber, dressing category: alginate, gelling fibre, absorbent fibre) vs DACC (Mosti et al. 2015)):

1 pilot RCT (UK, community nursing services, n=20 in each arm) comparing silver with DACC (Mosti et al. 2015) reported that there were no serious adverse events during the study.

11.6.11.1.2 Studies that partly met the decision problem

Chitosan (chitosan, dressing category: alginate, gelling fibre, absorbent fibre (Mo et al. 2015)):

1 RCT (3 university hospital centres in China, n=45 in each arm) compared **chitosan** vs no agent (vaseline gauze) for 4 weeks (Mo et al. 2015) and reported no adverse events or severe adverse events in either group.

Copper (cupric oxide, dressing category: wound contact layer, gauze (Melamed et al. 2021))

1 prospective single-arm study (Israel, outpatients, n=13) of a cupric oxide polypropylene dressing (Melamed et al. 2021) reported no adverse events.

Enzyme Alginogel (dressing category: ointments, gels, hydrogels (Durante 2012)):

1 prospective case series (Durante 2012) of 20 patients with acute or chronic wounds treated in Italian hospitals reported 2 adverse events: 1 allergic reaction seen in surrounding skin and 1 transient maceration. No serious adverse events were reported.

Honey (manuka MediHoney topical or gel, dressing category: ointments, gels, hydrogels (Biglari et al. 2013)):

1 prospective single-arm study of honey dressings (n=101 infected general wounds in German and Austrian hospitals) (Biglari et al. 2013) reported that 1.3% complained of poor tolerance

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such as skin reactions or pain (an unspecified number of these patients dropped out of the study).

Iodine (cadexomer iodine Iodosorb powder, dressing category: ointments, gels, hydrogels (Skog et al. 1983)):

1 RCT (location and setting not stated) using an iodine dry dressing (n=38) compared with standard treatment (n=36) (Skog et al. 1983) and reported pain on application of the dressing (iodine 4 patients vs no agent 1 patient); 1 patient in the iodine group had a skin rash (not sensitive to iodine but to coal tar derivatives in soap). 1 patient had itching that resolved after 2 weeks, though it is unclear which treatment arm this patient was in. There were no significant changes in routine laboratory tests.

11.6.11.2 Specific AEs

11.6.11.2.1 Studies that fully met the decision problem

3 studies that fully met the decision problem reported specific adverse events including 1 Spanish community health centre cohort study comparing 3 forms of silver dressing with **various sub-agent and dressing types**, n=25 in each arm (Gago et al. 2008), and 2 single-arm Belgian studies evaluating **1% silver sulfadiazine cream (dressing category: ointments, gels, hydrogels**, 1 hospital setting, n=29 (Degreef and Michiels 1984); 1 unclear setting, n=19 (Melotte et al. 1985)),

Silver (1% silver sulfadiazine cream, dressing category: ointments, gels, hydrogels (Degreef and Michiels 1984, Melotte et al. 1985)):

1 prospective case series (Belgium, hospital setting) (Degreef and Michiels 1984) reported that 3/29 patients experienced contact eczema considered related to the ointment vehicle and not the silver agent. Another prospective single-arm study (Belgium, unclear setting, n=19, 17 with non-arterial ulcers) (Melotte et al. 1985) stated that no allergic reactions occurred.

Silver (ionic silver Acticoat polyethylene dressing, dressing category: Wound contact layer; ionic silver complex Comfeel Hydrocolloid or Biatain Ag foam, dressing category: mixed; ionic silver Aquacel Ag gelling hydrofiber; dressing category: Alginate, gelling fibre, absorbent fibre (Gago et al. 2008))

1 prospective cohort study compared 3 groups (each n=25): Acticoat™; Comfeel™ or Biatain™ Ag; or Aquacel Ag (Gago et al. 2008) and reported no pain during dressing changes.

11.6.11.2.2 Studies that partly met the decision problem

2 single-arm studies that partly met the decision problem reported specific adverse events including 1 in the UK and Ireland in mixed community centre and hospital settings evaluating **DACC (dressing category: wound contact layer, gauze, n=23 (Bruce 2012))** and 1 in an

Italian hospital setting evaluating **enzyme alginogel (dressing category: ointments, gels, hydrogels, n=23 (Durante 2012))**.

DACC (dressing category: wound contact layer, gauze) (Bruce 2012):

1 prospective case series of DACC (n=14 wounds in 13 patients (Bruce 2012)) in chronic wounds in UK and Irish community centres and acute hospitals reported that 2 (15%) of patients stated they had 'bearable' pain while the dressing was being removed.

Enzyme Alginogel (dressing category: ointments, gels, hydrogels (Durante 2012)):

1 prospective case series (Durante 2012) of patients with acute or chronic wounds treated in Italian hospitals reported that treatment was stopped in 1/23 patients due to an allergic reaction.

11.7 Appendix G: Efficacy and safety outcome data tables

11.7.1 Wound healing

Study name and location	Technology name	Number of days to heal	Complete healing n (%)	Partial healing n (%)
Chitosan				
Mo 2015 (Mo et al. 2015) Design: RCT Follow-up: 4 weeks Location: China Setting: 3 university hospital centres	Intervention: Chitosan (patients with infected wounds, n=35)	NR	Patients with complete healing: 8/35 (23*)	Patients with ≥80% healing: 7/35 (20*)
	Comparator: Vaseline gauze (patients with infected wounds, n=34)	NR	Patients with complete healing: 1/34 (2.9*)	Patients with ≥50% healing: 3/34 (9*)
Orig et al 2016 (Orig and Singleton 2016) Design: Prospective single-arm trial Follow-up: Mean evaluation time 8.18 days Location: NR Setting: Acute hospital ward	Intervention: Chitosan (Kytocel dressing).	NR	Patients with healed wounds at discharge (mean 8.18): 4/20 (20)	Improvement in quality of granulation tissue at discharge (mean 8.18): 11/20 (55)
Copper				
Dokic 2023 (Dokic S et al. 2023) Design: Prospective case series Follow-up: 3 months Location: Slovenia	Intervention: Copper wound dressings (n=12)	NR	Patients with complete healing: 12 (100)	NR

Study name and location	Technology name	Number of days to heal	Complete healing n (%)	Partial healing n (%)
Setting: Hospital Melamed 2021 (Melamed et al. 2021) Design: Single-arm trial Follow-up: 4 weeks of treatment and 2 weeks of follow up using unspecified “standard of care” dressings. Location: Israel Setting: Outpatient hospital clinic	Intervention: Cupric oxide dressing	NR	NR	NR
Treadwell 2022 (Treadwell T et al. 2022) Design: Prospective case series Follow-up: NR Location: Alabama, USA Setting: Medical centre	Intervention: Cupric oxide wound dressing (n=25)	NR	Patients with complete healing during course of therapy: 8*/25 (31)	Patients with healing >50% during course of therapy: 17*/34 (68)
DACC				
Bruce 2012 (Bruce 2012) Study design: Prospective case series Follow-up: 28 days (or until infection reduced) Location: UK and Ireland Setting: 4 community centres and 2 acute hospitals	Intervention: Cutimed Sorbact Hydroactive dressing (n=13 patients, 14 wounds)	NR	NR	Number of wounds with granulation tissue: Start of treatment: 10 End of treatment: 11 Number of wounds with epithelialisation: Start of treatment: 3 End of treatment: 8

Study name and location	Technology name	Number of days to heal	Complete healing n (%)	Partial healing n (%)
				Number of wounds with inflammation: Start of treatment: 11 End of treatment: 4 These are reported to be signs of progression towards healing
Enzyme Alginogel				
Durante 2012 (Durante 2012) Design: Prospective case series Follow-up: 60 days Location: Italy Setting: Hospital, with continuation in home setting	Intervention: Enzyme Alginogel (Flaminal - composed of hydrated alginate polymers in a polyethylene glycol matrix embedded with a patented antimicrobial enzymatic complex).	NR	Complete healing (n=23): Day 14: 1/23 Day 30: 7/23 Day 60: 12/23	Patients with significant decrease in wound area and volume (p<0.001): Day 60: 20/20 (100%)
Jones et al 2018 (Jones and Oates 2018) Design: Prospective case series Follow-up: Unclear Location: UK Setting: Primary care (forms completed by district nurses)	Intervention: Enzyme Alginogel (Flaminal, - a hydro-active, broad-spectrum Enzyme Alginogel, n=352).	NR	NR	NR
King et al 2023 (King and Rolland 2023) Design: Prospective case series	Intervention: Enzyme Alginogel (Flaminal, - a hydro-active, broad-spectrum Enzyme Alginogel, n= 1587)	NR	NR	NR

Study name and location	Technology name	Number of days to heal	Complete healing n (%)	Partial healing n (%)
Follow-up: Unclear Location: UK Setting: Primary care (forms completed by district nurses)				
Honey				
Biglari et al 2013 (Biglari et al. 2013) Design: Prospective case series Follow-up: 4.88 (SD 4.4) weeks Location: 9 sites in Germany and 1 in Austria Setting: Hospital	Intervention: Honey (various Medihoney™ dressing products, n=104)	Study duration for patients with healed wounds (weeks, mean SD): 4.46 (3.83)	Patients with complete healing: 32/101 (31.4)	Patients (%) with improved wounds (improvement defined as wound area reducing): 53.3 Patients (%) with stagnant (+/- 10% size of wound area) wounds: 9.2 Patients (%) with deteriorating wounds (wound area growing >10%): 6.1
Yang et al 2015 (Yang K et al. 2015) Design: Prospective single-arm study Follow-up: 4 weeks Location: USA Setting: Hospital	Intervention: Topical medical grade honey	NR	NR	NR
Moghazy et al 2010 (Moghazy et al. 2010)	Intervention: Honey (Medium-pored non-sterile gauze saturated with honey, n=30).	Mean duration of healing (weeks, mean SD): 2.3 (0.94)	Patients with closed wounds: Baseline: 0/30 (0) 1 month: 4/30 (13.3) 2 months: 4/30 (13.3)	Patients whose wounds decreased in size from baseline to 3 months: 28/30 (93.3)

Study name and location	Technology name	Number of days to heal	Complete healing n (%)	Partial healing n (%)
Design: Prospective single-arm trial Follow-up: 3 months Location: Egypt Setting: Referred to outpatient care from hospital admission			3 months: 5/30 (16.7) p=0.0089	Patients with partial healing: 1 month: 0/30 (0) 2 months: 0/30 (0) 3 months: 13/30 (43.3) 2 (6.7) patients were candidates for amputation and 2 (6.7) received grafts.
Iodine				
Skog 1983 (Skog et al. 1983) Design: RCT Follow-up: 6 weeks Location: Sweden Setting: Mixed; at home (visiting nurse) or hospital clinic	Intervention: Cadexomer iodine (Iodosorb [^] , Perstorp AB) (n=38)	NR	NR	NR
	Comparator: Standard treatment (n=36)	NR	NR	NR
Octenidine				
Hammerle and Strohal, 2016 (Hammerle and Strohal 2016) Study design: Non-randomised trial Follow-up: 42 days Location: Austria Setting: Secondary care (single centre)	Intervention: Octenidine + foam or alginate (n=14 patients, 17 venous leg ulcers)	NR	Number of healed wounds: Day 26: 2/17 (11)	NR
	Comparator: Octenidine gel alone with wound contact layer and suction gauze (n=15 patients, 15 venous leg ulcers)	NR	Number of healed wounds: Day 26: 3/15 (20*) Day 42: 7/15 (47)	NR
PHMB				

Study name and location	Technology name	Number of days to heal	Complete healing n (%)	Partial healing n (%)
Vallejo et al 2022 (Vallejo et al. 2022) Associated records: Protocol: Vallejo et al 2021 (Vallejo 2021) Design: RCT Follow-up: 12 weeks Location: Australia Setting: 1 community wound clinic.	Intervention: PHMB (topical PHMB as a soak in plain gauze for 15 minutes after debridement and at each dressing change, and then in a sustained dressing (AMD foam, or gel with PHMB, or Kerlix AMD gauze, H&R Healthcare, UK; ITT, n=25).	NR	Patients with healed wounds at 12 weeks: 4/25 (16) Difference vs no agent at 12 weeks: p=0.47 Patients with deteriorated wounds at 12 weeks: 2/25 (8) Difference vs no agent at 12 weeks: p=0.001	Pressure Ulcer Scale for Healing (PUSH) Tool (mean, SD): Baseline: 11.9 (2.2) Week 1: 11.7 (2.2) Week 12: 7.8 (4.3) Difference vs no agent: at 12 weeks p=0.53
	Comparator: No agent (cleansing of the wound after and between treatments with clean water or saline, then non-medicated dressing products; ITT, n=25).	NR	Patients with healed wounds at 12 weeks: 6/25 (24) Difference vs PHMB at 12 weeks : p=0.47 Patients with deteriorated wounds at 12 weeks: 2/25 (8) Difference vs PHMB at 12 weeks: p=0.003	PUSH (mean, SD): Baseline: 11.4 (2.3) Week 12: 8.4 (5.8) Difference vs PHMB at 12 weeks : p=0.53
Koullias 2022 (Koullias et al. 2022)	Intervention: Type 1 collagen matrix plus polyhexamethylene	NR	Frequency of wound closure, % 4 weeks: 9 8 weeks: 33.14	NR

Study name and location	Technology name	Number of days to heal	Complete healing n (%)	Partial healing n (%)
Study design: Prospective case series Follow-up: 32 weeks Location: USA Setting: Unclear (dressings applied by physicians in unclear settings)	biguanide antimicrobial (PCMP) barrier (n=67)		12 weeks: 41.76 16 weeks: 45.35 24 weeks: 53.1 32 weeks: 72.64	
Silver				
Degreef et al 1984 (Degreef and Michiels 1984) Study Design: Prospective case series Follow up: 4 weeks Location: Belgium Setting: Hospital	Intervention: Silver (1% silver sulfadiazine cream applied once a day in a thin layer of 2 to 3 mm and covered by a sterile bandage) (n=29)	NR	Patients with healed ulcers at 2 weeks: 1/29 (3.4)	NR
Dimakakos et al 2009 (Dimakakos et al. 2009) Study Design: RCT Follow up: 9 weeks Location: Greece Setting: NR	Intervention: Silver releasing foam dressing (n=21)	NR	Patients with complete healing at week 9: 17 (81), p v. comparator = 0.02, 95% CI (χ^2 test). CI are not reported. Shallow (<0.5cm) ulcer complete healing by week 9: 13 (93) Deep (>0.5cm) ulcer complete healing by week 9: 4 (57) Patients n (%) with complete healing by week: Week 3: 2 (9.5*)	NR

Study name and location	Technology name	Number of days to heal	Complete healing n (%)	Partial healing n (%)
			Week 4: 3 (14.3*) Week 5: 3 (14.3*) Week 6: 2 (9.5*) Week 7: 1 (4.8*) Week 8: 2 (9.5*) Week 9: 4 (19*) 6 highly exuding ulcers, 10 ulcers with moderate exudation, and 1 ulcer with low exudation had completely healed after 9 weeks of treatment	
	Comparator: No agent (non-adhesive foam dressing) (n=21)	NR	Patients with complete healing at week 9: 10 (48), p v. silver = 0.02, 95% CI (χ^2 test). CI are not reported. Shallow (<0.5cm) ulcer complete healing by week 9: 9 (56) Deep (>0.5cm) ulcer complete healing by week 9: 1 (20) Patients (n) with complete healing by week: Week 3: 2 Week 4: 1 Week 5: 1 Week 6: 1 Week 7: 0 Week 8: 2 Week 9: 3	NR

Study name and location	Technology name	Number of days to heal	Complete healing n (%)	Partial healing n (%)
Forlee 2014 (Forlee et al. 2014) Study design: Single-arm trial Follow-up: 8 weeks (The wound was swabbed every 7 days) Location: South Africa Setting: Three secondary care centres	Intervention: Gelling fibre dressing containing silver (DURAFIBER™ Ag) (complete case analysis, n=14)	NR	Cumulative number of healed wounds: Week 1: 0 (0) Week 2: 0 (0) Week 3: 1 (7.1) Week 4: 3 (21.4) Week 5: 4 (28.6) Week 6: 4 (28.6) Week 7: 5 (35.7) Week 8: 7 (50)	NR
Humbert 2006 (Humbert et al. 2006) Study Design: RCT Follow up: 6 weeks Location: France Setting: 17 sites that included dermatology, vascular, angiophlebology and dermatology practices; 85% of silver arm and 72.5% of no agent arm were outpatients.	Intervention: Silver (Biatain AG, a hydrophilic polyurethane foam dressing with silver ions and bonded onto a semipermeable polyurethane film) Comparator: No agent (calcium alginate fibre dressing, Algosteril Brothier Laboratories)	NR	NR	NR
Manning et al 2020 (Manning et al. 2020) Associated Records: Conference abstract: Manning 2019 (Manning et al. 2019)	Intervention: Bioabsorbable polymeric matrix containing ionic and metallic silver (n=16)	NR	NR	Patients with improved wounds (definition NR) at 3 weeks: 11/16 (68.75*)

Study name and location	Technology name	Number of days to heal	Complete healing n (%)	Partial healing n (%)
Study Design: Single-arm trial Follow up: 12 weeks Location: USA Setting: Wound care clinic within a secondary care setting				
Meaume et al, 2005 (Meaume et al. 2005) Study design: RCT Follow-up: 4 weeks Location: UK Setting: 13 hospital centres	Intervention: Silver-releasing hydroalginate dressing (Silvercel) (ITT, n=51)	NR	Wound closure at 4 weeks: 1/51	Wound considered “improved”: 33/51 Wounds closed or considered “improved”: 34/51 (67) Difference vs no agent: p=0.425
	Comparator: No agent (pure calcium alginate dressing, Algosteril) (ITT, n=48)	NR	Wound closure at 4 weeks: 1/48	Wound considered “improved”: 25/48 Wounds closed or considered “improved”: 26/48 (54) Difference vs silver: p=0.425
Melotte 1985 (Melotte et al. 1985) Study design: Prospective case series Follow-up: 6 weeks Location: Belgium Setting: NR	Intervention: 1% silver sulfadiazine cream (n=19)	NR	Number of patients with healed wounds: 11/19 patients healed within an average of 19 days (7 to 39 days)	NR

Study name and location	Technology name	Number of days to heal	Complete healing n (%)	Partial healing n (%)
Molnlycke Health Care AB 2014 (NCT01036438) (NCT01036438 2009) Study design: RCT Follow-up: 8 weeks Location: Czech Republic, France, Germany and the Netherlands Setting: Unclear, appears to be hospital	Intervention: Silver (absorbent foam silver dressing, Mepilex Ag, ITT n=100)	NR	NR	NR
	Comparator: No agent (absorbent foam silver dressing, Mepilex without silver, ITT n=101)	NR	NR	NR
Truchetet 2012 (Truchetet et al. 2012) Study design: Prospective case series Follow up: Median 19 days (7 to 97) Location: France Setting: Private outpatient	Intervention: Mepilex Ag (venous leg ulcer subgroup, n=534)	NR	Patients with healed wounds (%): 9.8	Patients with wounds considered “improved” (%): 77
Woolstencroft 2018 (Woolstencroft 2018)	Intervention: KerraContactTM Ag	NR	Wounds fully healed (n=30): 2/30 (7)	Significant wound improvement (%): 60

Study name and location	Technology name	Number of days to heal	Complete healing n (%)	Partial healing n (%)
Study design: Single-arm trial Follow-up: 4 weeks Location: UK Setting: Secondary care (10 tissue viability clinics)	dressing with Ag Oxysalts TM (n=31)			Wound improvement (%): 30 No change in wound (%): 10
Harding 2016 (Harding et al. 2016) Study design: Prospective single-arm trial Follow-up: 8 weeks Location: UK and Poland Setting: 6 study centres, unclear setting	Intervention: AQUACEL Ag+ hydrofiber dressing Week 1-4, AQUACEL wound dressings Week 5-8 (patients with clinically infected wounds, n=10)	NR	Patients with healed wounds: Healed: 1/10 (10)	Marked improvement: 8/10 (80) Mild improvement: 1/10 (10) No change or deterioration: 0/10 (0)
Lantis 2011 (Lantis and Gendics 2011) Study design: Prospective single-arm trial Follow-up: 12 weeks Location: USA Setting: Tertiary care wound practice	Intervention: a non-adhesive silver sulphadiazine, polyurethane foam dressing (Allevyn Ag Non-Adhesive) (n=24)	Median time to wound closure in patients whose wounds fully healed: 91 days	Patients achieving ulcer closure by treatment discontinuation (median duration of 80.5 days, mean treatment duration 57.3 days, SD NR) 11/24 (45.8) Percentage of patients who achieved ulcer closure at 2, 4 and 8 weeks following baseline assessment 2 weeks: 0 4 weeks: 4.2 (1/24) 8 weeks: 29.2 (7/24)	NR

Study name and location	Technology name	Number of days to heal	Complete healing n (%)	Partial healing n (%)
Vanscheidt 2003 (Vanscheidt et al. 2003) Study design: Prospective single-arm trial Follow-up: 28 days Location: France and Germany Setting: NR	Intervention: Aquacel Ag (n=11 patients with infected wounds)	NR	NR	NR
Jorgensen 2008 (Jorgensen et al. 2008) Study design: Prospective single-arm trial Follow-up: 31 days (± 2 days) Location: Denmark and Canada Setting: Outpatient clinics at 4 centres	Intervention: Silver and ibuprofen releasing foam dressing (Physiotulle Ag) n=24	NR	NR	NR
Comparative studies of eligible agents				
Gago 2008 (Gago et al. 2008) Study design: Prospective cohort study Follow-up: 8 weeks Location: Spain Setting: Community health centre	Intervention 1: Acticoat™ (n=25)	NR	Number of wounds healed: Week 5: 1 (4) Week 6: 4 (16) Week 7: 9 (36) Week 8: 14 (56) Time to complete healing was faster in group 1 compared to group 2 and 3 (p < 0.05), after	NR

Study name and location	Technology name	Number of days to heal	Complete healing n (%)	Partial healing n (%)
			adjusting for baseline wound area Hazard ratio vs Comfeel/Biatin Ag: 2.73 (p=0.042, 95% CI 1.04 to 7.27) Hazard ratio vs Aquacel Ag: 2.8 (p=0.027, 95% CI 1.13 to 6.94)	
	Intervention 2: Comfeel™ or Biatain™ Ag (Comfeel n = 9) Biatin n = 16)	NR	Number of wounds healed: Week 5: 0 (0) Week 6: 2 (8) Week 7: 3 (12) Week 8: 6 (24)	NR
	Intervention 3: Aquacel Ag (n=25)	NR	Number of wounds healed: Week 5: 1 (4) Week 6: 2 (8) Week 7: 4 (16) Week 8: 7 (28)	NR
Miller et al 2010 (Miller et al. 2010) Associated records: Trial registration: (ACTRN12606000094572 2006) and two papers (Miller et al. 2011a, Miller et al. 2011b) Study design: RCT Follow-up: 12 weeks Location: UK Setting: Community nursing services	Intervention: Nanocrystalline silver dressing (complete case analysis, n=133)	Survival analysis for total number of days to heal: No significant difference between groups, log-rank p=0.7, wilcoxon p=0.8.	Patients with healed wounds (100% closure): 85/133 (64), difference vs comparator p=>0.05 Subgroup analysis found no difference between the treatment groups in the number of wounds healed overall for young (χ^2 (1) 50.07, p > 0.05) and old wounds (χ^2 (1) 50.17, p > 0.05) as well as for small (χ^2 (1) 50.10, p > 0.05) and big wounds (χ^2 (1) 50.02, p > 0.05)	NR

Study name and location	Technology name	Number of days to heal	Complete healing n (%)	Partial healing n (%)
			Proportion of patients with healed wounds (100% closure): Week 2: 10 (8), $X^2=0.02$ Week 4: 20 (17), $X^2=0.54$ Week 6: 17 (17), $X^2=0.01$ Week 8: 16 (20), $X^2=0.01$ Week 10: 13 (20), $X^2=0.37$ Week 12: 9 (17), $X^2=0.01$	
	Comparator: Cadexomer iodine dressing (complete case analysis, n=133)		Patients with healed wounds (100% closure): 84/133 (63), difference vs silver $p \geq 0.05$ Subgroup analysis found no difference between the treatment groups in the number of wounds healed overall for young (χ^2 (1) 50.07, $p > 0.05$) and old wounds (χ^2 (1) 50.17, $p > 0.05$) as well as for small (χ^2 (1) 50.10, $p > 0.05$) and big wounds (χ^2 (1) 50.02, $p > 0.05$). Proportion of patients with healed wounds (100% closure): Week 2: 7 (5) $X^2=0.02$ Week 4: 28 (22) $X^2=0.54$ Week 6: 16 (21) $X^2=0.01$ Week 8: 16 (21) $X^2=0.01$ Week 10: 9 (16) $X^2=0.37$ Week 12: 8 (17) $X^2=0.01$	NR

Study name and location	Technology name	Number of days to heal	Complete healing n (%)	Partial healing n (%)
Molle 2023 (Molle et al. 2023) Design: Non-randomised clinical trial Follow-up: 30 days Location: NR Setting: NR	Intervention: Manuka honey (n=25 ulcers)	NR	Ulcers healed at day 30 (%): 13.6 Difference vs baseline: p=0.001	NR
	Comparator: Silver dressing (n=25 ulcers)	NR	Ulcers healed at day 30 (%): 64 Difference vs baseline: p=0.000 ²	NR
Mosti et al, 2015 (Mosti et al. 2015) Study design: Pilot RCT Follow-up: 4 days Location: UK Setting: Community nursing services	Intervention: Silver (Silver-containing hydrofiber Aquacel Ag)	NR	NR	NR
	Comparator: DACC (microorganism-binding, Cutimed Sorbact)	NR	NR	NR

Key: AMD – Antimicrobial dressing, CI – Confidence interval, DACC – Dialkylcarbamoyl chloride, HA – Hyaluronic acid, ITT – Intention-to-treat, NR – Not reported, OHP – Octenidine dihydrochloride/phenoxyethanol, PCMP – Polyhexamethylene biguanide antimicrobial, PHMB – Polyhexamethylene biguanide, PUSH – Pressure ulcer scale for healing, RCT – Randomised controlled trial, SD – Standard deviation, UK – United Kingdom, USA – United States of America

² P value as reported in the paper, presumed to be p<0.001

11.7.2 Infection

Study name and location	Technology name	Local infection n (%)	Wound severity score Mean (SD)
Chitosan			
Mo 2015 (Mo et al. 2015)	Intervention: Chitosan (n=45)	NR	NR
Design: RCT Follow-up: 4 weeks Location: China Setting: 3 university hospital centres	Comparator: Vaseline gauze (n=45)	NR	NR
Orig et al 2016 (Orig and Singleton 2016)	Intervention: Chitosan (Kytocel dressing). Wear time ranged from 2 to 7 days. Variety of secondary dressings used including super absorbent dressings, surgical pads and foams.	NR	NR
Design: Prospective single-arm trial Follow-up: Mean evaluation time 8.18 days. Location: NR Setting: Acute hospital ward			
Copper			
Dokic 2023 (Dokic S et al. 2023)	Intervention: Copper wound dressings (n=12)	Patients with successful resolution of infection: 12 (100)	NR
Design: Prospective case series Follow-up: 3 months Location: Slovenia Setting: Hospital			
Melamed 2021 (Melamed et al. 2021)	Intervention: Cupric oxide dressing	NR	NR
Design: Single-arm trial			

Study name and location	Technology name	Local infection n (%)	Wound severity score Mean (SD)
Follow-up: 4 weeks of treatment and 2 weeks of follow up using unspecified "standard of care" dressings. Location: Israel Setting: Outpatient hospital clinic			
Treadwell 2022 (Treadwell T et al. 2022) Design: Prospective case series Follow-up: NR Location: Alabama, USA Setting: Medical centre	Intervention: Cupric oxide wound dressing (n=25)	NR	NR
DACC			
Bruce 2012 (Bruce 2012) Study design: Prospective case series Follow-up: 28 days (or until infection reduced) Location: UK and Ireland Setting: 4 community centres and 2 acute hospitals	Intervention: Cutimed Sorbact Hydroactive dressing (n=13 patients, 14 wounds)	Wounds with decreased signs of infection at 4 weeks (n=14): 2 (14)	NR
Enzyme Alginogel			
Durante 2012 (Durante 2012) Design: Prospective case series Follow-up: 60 days Location: Italy	Intervention: Enzyme Alginogel, Flaminal (patients with infected wounds, n=3)	Resolution of infection (n=3, patients with infected wounds at baseline): Day 14: 2/3 (66.66*) Day 30:3/3 (100)	NR

Study name and location	Technology name	Local infection n (%)	Wound severity score Mean (SD)
Setting: Hospital, with continuation in home setting Jones et al 2018 (Jones and Oates 2018) Design: Prospective case series Follow-up: Unclear Location: UK Setting: Primary care (forms completed by district nurses)	Intervention: Enzyme Alginogel (Flaminal, - a hydro-active, broad-spectrum Enzyme Alginogel, n=340).	Clinician reported improvement in signs of infection/critical colonisation (n=340 respondents): Improvement: 253/340 (74.41) No change or worsening: 87 (25.59) Difference between observed value and the expected value of 50%: $p < 0.0001$, (95% CI 69.52 78.76)	NR
King et al 2023 (King and Rolland 2023) Design: Prospective case series Follow-up: Unclear Location: UK Setting: Primary care (forms completed by district nurses)	Intervention: Enzyme Alginogel (Flaminal, - a hydro-active, broad-spectrum Enzyme Alginogel, n=1528)	Clinician reported improvement in signs of infection/critical colonisation (n=1528 respondents): Improvement: 1114/1528 (72.9) No change or worsening: 414/1528 (27.1) Difference between observed value and the expected value of 50%: $p < 0.0001$ (95% CI 70.22 to 75.45)	NR
Honey			
Biglari et al 2013 (Biglari et al. 2013) Design: Prospective case series Follow-up: 4.88 (SD 4.4) weeks	Intervention: Honey (various Medihoney™ dressing products, n=104)	NR	NR

Study name and location	Technology name	Local infection n (%)	Wound severity score Mean (SD)
Location: 9 sites in Germany and 1 in Austria Setting: Hospital			
Yang et al 2015 (Yang K et al. 2015) Design: Prospective single-arm study Follow-up: 4 weeks Location: USA Setting: Hospital	Intervention: Topical medical grade honey	NR	NR
Moghazy et al 2010 (Moghazy et al. 2010) Design: Prospective single-arm trial Follow-up: 3 months Location: Egypt Setting: Referred to outpatient care from hospital admission	Intervention: Honey (Medium-pored non-sterile gauze saturated with honey).	NR	NR
Iodine			
Skog 1983 (Skog et al. 1983) Design: RCT Follow-up: 6 weeks Location: Sweden Setting: Mixed; at home (visiting nurse) or hospital clinic	Intervention: Cadexomer iodine (Iodosorb^, Perstorp AB) (complete case, n=26)	Patients with staphylococcus aureus infection before treatment All study patients: 77% S. aureus reduced or eliminated during treatment Iodine group: 17 (1 reduced, 16 cleared) S. aureus persisted or new infection occurred during treatment Iodine group: 7	NR

Study name and location	Technology name	Local infection n (%)	Wound severity score Mean (SD)
	Comparator: Standard treatment (complete case, n=27)	Patients with staphylococcus aureus infection before treatment All study patients: 77% S. aureus reduced or eliminated during treatment Standard group: 2 (2 reduced, 0 cleared) (P<0.001 Chi-square test with Yates' correction) S. aureus persisted or new infection occurred during treatment Standard group: 18 (P < 0001, chi-square test with Yates' correction)	NR
Octenidine			

Study name and location	Technology name	Local infection n (%)	Wound severity score Mean (SD)
Hammerle and Strohal, 2016 (Hammerle and Strohal 2016) Study design: Non-randomised trial Follow-up: 42 days Location: Austria Setting: Secondary care (single centre)	Intervention: Octenidine + foam or alginate (subgroup patients with infected wounds n=5 wounds)	Change in signs of local infection: 3 days: no change 3/5; less infection 2/5 5 days: no change 1/5; less infection 4/5 12 days: no change 1/5; less infection 2/5; increased infection 1/5 26 days: no change 1/5; less infection 2/5; increased infection 1/5 42 days: no change 1/4; less infection 1/4; increased infection 1/4 Number infected wounds at 42 days: 3/4 (vs octenidine alone p=0.038) Patients with no sign of infection (among subgroup of 5 patients with infected wounds at baseline, n %): 3 days: 0/5 (0*) 5 days: 0/5 (0*) 12 days: 0/5 (0*) 26 days: 1/5 (20*) 42 days: 1/4 (25*) Significant differences in number of patients with infected wounds at the end of treatment favouring octenidine alone, p=0.038	NR
	Comparator: Octenidine gel alone with wound contact layer and suction gauze (n=15 patients, 15 venous leg ulcers)	Change in signs of local infection: 3 days: no change 4/6; less infection 2/6. 5 days: no change 3/6; less infection 3/6. 12 days: no change 1/6; less infection 2/6. 26 days: no change 2/6 42 days: no change 1/6; increased infection 1/6.	NR

Study name and location	Technology name	Local infection n (%)	Wound severity score Mean (SD)
		Number infected wounds at 42 days: 0/4 Patients with no sign of infection (among subgroup of 5 patients with infected wounds at baseline, n %): 3 days: 0/5 (0*) 5 days: 0/5 (0*) 12 days: 2/5 (40*) 26 days: 3/5 (60*) 42 days: 4/4 (100*) Significant differences in number of patients with infected wounds at the end of treatment favouring octenidine alone, p=0.038	
PHMB			
Vallejo et al 2022 (Vallejo et al. 2022) Associated records: Protocol: Vallejo et al 2021 (Vallejo 2021) Design: RCT Follow-up: 12 weeks Location: Australia Setting: 1 community wound clinic.	Intervention: PHMB (topical PHMB as a soak in plain gauze for 15 minutes after debridement and at each dressing change, and then in a sustained dressing (AMD foam, or gel with PHMB, or Kerlix AMD gauze, H&R Healthcare, UK; ITT, n=25).	NR	NR
	Comparator: No agent (cleansing of the wound after and between treatments with clean water or saline, then non-medicated dressing products; ITT, n=25).	NR	NR
Koullias 2022 (Koullias et al. 2022) Study design: Prospective case series	Intervention: Type 1 collagen matrix plus polyhexamethylene biguanide antimicrobial (PCMP) barrier (n=67)	NR	NR

Study name and location	Technology name	Local infection n (%)	Wound severity score Mean (SD)
Follow-up: 32 weeks Location: USA Setting: Unclear (dressings applied by physicians in unclear settings)			
Silver			
Degreef et al 1984 (Degreef and Michiels 1984) Study Design: Prospective case series Follow up: 4 weeks Location: Belgium Setting: Hospital	Intervention: Silver (n=29)	Patients with negative ulcer swab cultures: Week 2: 14 (48.2) Week 4: 19 (65.5) (at week 4 the remaining 10 patients included 5 with continuing positive swabs (including 2 suffering necrosis), 2 with renewed positive swabs after initial sterilisation and 3 drop-outs due to contact eczema not considered agent-related).	NR
Dimakakos et al 2009 (Dimakakos et al. 2009) Study design: RCT Follow-up: 9 weeks Location: Greece Setting: NR	Intervention: Silver releasing foam dressing (n=21)	NR	NR
	Comparator: No agent (non-adhesive foam dressing (n=21)	NR	NR
Forlee 2014 (Forlee et al. 2014) Study design: Single-arm trial Follow-up: 8 weeks (The wound was swabbed every 7 days) Location: South Africa	Intervention: Gelling fibre dressing containing silver (DURAFIBER™ Ag) (n=14)	Number of patients with at least one sign of infection: Baseline: 14 (100) Week 4: 4 (28.6) p=0.002 Week 8: 1 (7.1) p<0.001 Number of infected wounds: Baseline: 12 (85.7)	NR

Study name and location	Technology name	Local infection n (%)	Wound severity score Mean (SD)
Setting: Three secondary care centres		Week 4: 0 (0) p <0.001 Week 8: 1 (7.1) p<0.001 Median time to complete resolution of clinical signs of infection: 29.5 days (95% CI 14 to 49 days)	
Humbert 2006 (Humbert et al. 2006) Study Design: RCT Follow up: 6 weeks Location: France Setting: 17 sites that included dermatology, vascular, angiophlebology and dermatology practices; 85% of silver arm and 72.5% of no agent arm were outpatients.	Intervention: Silver (Biatain AG, n=40)	NR	NR
	Comparator: No agent (calcium alginate fibre dressing, n=40)	NR	NR
Manning et al 2020 (Manning et al. 2020) Associated Records: Conference abstract: Manning 2019 (Manning et al. 2019) Study Design: Single-arm trial Follow up: 12 weeks Location: USA Setting: Wound care clinic within a secondary care setting	Intervention: Silver (Bioabsorbable polymeric matrix containing ionic and metallic silver)	NR	NR
Meaume et al, 2005 (Meaume et al. 2005)	Intervention: Silver-releasing hydroalginate dressing (Silvercel) (ITT, n=51)	NR	Modified ASEPSIS score at 14 days (mean SD, ITT n=51): 104.2 (72.8), P=0.791

Study name and location	Technology name	Local infection n (%)	Wound severity score Mean (SD)
Study design: RCT Follow-up: 4 weeks (daily assessment in first 14 days, weekly thereafter) Location: UK Setting: 13 hospital centres			Subgroup leg ulcers: (n=38): 111.8 (79.1) Modified ASEPSIS score at 14 days (mean SD, PP n=41) 98.2 (63.2), P=0.963 Subgroup Leg ulcers only: (n=29) 102.7 (70.3) Wound severity score: <u>Mean (SD):</u> Baseline: 17.5 (2.5) P vs comparator = 0.289 Week 4: 11.9 (3.5), P vs comparator =0.171 Subgroup Leg ulcer only: (n=38): 11.8 (3.4) <u>Absolute decrease at week 4 (mean SD):</u> -5.6 (3.2), P v. comparator =0.063 Subgroup Leg ulcer only: (n=38): -5.7 (2.8) <u>% decrease in score:</u> -32.1% (17.4%), P v. comparator =0.034 Subgroup Leg ulcer only (n=38): -32.6% (15.4%)

Study name and location	Technology name	Local infection n (%)	Wound severity score Mean (SD)
	Comparator: No agent (pure calcium alginate dressing, Algosteril) (ITT, n=48)	NR	Modified ASEPIS score at 14 days: 95.4 (62.2), P=0.791 Subgroup Leg ulcers only: (n=33) 86.3 (51.0) PP analysis (mean, SD): (n=39) 87.8 (58.7), P=0.963 Subgroup Leg ulcers only: (n=27): 77.4 (48.4) Wound severity score: <u>Mean score:</u> Baseline: 16.9 (3.0) P vs silver = 0.289 Week 4: 12.8 (3.7), P v. silver =0.171 Subgroup Leg ulcer only: (n=33) 12.3 (3.3) <u>Absolute decrease at week 4 (mean SD):</u> -4.1 (4.3), P v. silver =0.063 Subgroup Leg ulcer only: (n=33) - 4.4 (4.3) <u>% decrease in score:</u> -22.6% (25.4%), P v. silver =0.034 Subgroup Leg ulcer only: (n=33) - 25% (21.8%)

Study name and location	Technology name	Local infection n (%)	Wound severity score Mean (SD)
Melotte 1985 (Melotte et al. 1985) Study design: Prospective case series Follow-up: 6 weeks Location: Belgium Setting: NR	Intervention: 1% silver sulfadiazine cream (n=19) Comparator: None	Time to negative swab cultures in days (n=4 patients with resolved infections; mean, range): 14 (7 to 33)	NR
Mölnlycke Health Care AB 2014 (NCT01036438) (NCT01036438 2009) Study design: RCT Follow-up: 8 weeks Location: Czech Republic, France, Germany and the Netherlands Setting: Unclear, appears to be hospital	Intervention: Silver (absorbent foam silver dressing, Mepilex Ag, ITT n=100)	NR	NR
	Comparator: No agent (absorbent foam silver dressing, Mepilex without silver, ITT n=101)	NR	NR
Truchetet 2012 (Truchetet et al. 2012) Study design: Prospective case series Follow up: Median 19 days (7 to 97) Location: France Setting: Private outpatient	Intervention: Mepilex Ag (Mölnlycke Health Care)(n=794)	Change in number of signs of infection in venous leg ulcer wounds (mean, SD): -2.2 (1.5), p<0.001	NR
Woolstencroft 2018 (Woolstencroft 2018) Study design: Single-arm trial Follow-up: 4 weeks	Intervention: KerraContactTM Ag dressing with Ag OxysaltsTM (Silver wound dressing with 2 non-adherent polyethylene mesh contact layers and a polyester core)	NR	NR

Study name and location	Technology name	Local infection n (%)	Wound severity score Mean (SD)
Location: UK Setting: Secondary care (10 tissue viability clinics)			
Harding 2016 (Harding et al. 2016) Study design: Prospective single-arm trial Follow-up: 8 weeks Location: UK and Poland Setting: 6 study centres, unclear setting	Intervention: AQUACEL Ag+ hydrofiber dressing Week 1-4, AQUACEL wound dressings Week 5-8 Clinically infected (n=10)	NR	NR
Lantis 2011 (Lantis and Gendics 2011) Study design: Prospective single-arm trial Follow-up: 12 weeks Location: USA Setting: Tertiary care wound practice	Intervention: non-adhesive silver sulphadiazine, polyurethane foam dressing (Allevyn Ag Non-Adhesive) (n=24)	Patients with any clinical signs of infection: Baseline (Week 0): 24 (100) Week 2: 22 (91.7), p=0.219 Week 4 (n=23): 18 (78.3), p=0.033 Week 8 (n=23): 14 (60.9), p=0.002 Treatment Discontinuation: 12 (50), p<0.001 Patients with no progression towards healing: Baseline (Week 0): 24 (100) Week 2: 3 (12.5) Week 4 (n=23): 5 (21.7) Week 8 (n=23): 4 (17.4) Treatment Discontinuation: 7 (29.2)	NR

Study name and location	Technology name	Local infection n (%)	Wound severity score Mean (SD)
		Number of clinical signs of infection, mean (median; range): Baseline (Week 0): 5.5 (5; 3-9) Week 2: 3.5 (4; 0-6) p<0.001 Week 4 (n=23): 2.6 (3; 0 to 6) p<0.001 Week 8 (n=23): 1.6 (1; 0 to 6) p<0.001 Treatment Discontinuation: 1.6 (0.5; 0 to 7) p<0.001	
Vanscheidt 2003 (Vanscheidt et al. 2003) Study design: Prospective single-arm trial Follow-up: 28 days Location: France and Germany Setting: NR	Intervention: Aquacel Ag (n=11 patients with infected wounds)	Resolution of infection 28 days: 2/11 (18*)	NR
Jorgensen 2008 (Jorgensen et al. 2008) Study design: Prospective single-arm trial Follow-up: 31 days ($\pm$ 2 days) Location: Denmark and Canada Setting: Outpatient clinics at 4 centres	Intervention: Silver and ibuprofen releasing foam dressing (Physiotulle Ag) n=24	NR	NR
Comparative studies of eligible agents			
Gago 2008 (Gago et al. 2008)	Intervention 1: Acticoat™	Number of wounds with no clinical signs of infection:	NR

Study name and location	Technology name	Local infection n (%)	Wound severity score Mean (SD)
Study design: Prospective cohort study Follow-up: 8 weeks Location: Spain Setting: Community health centre	(n=25)	Week 1: 7 (28) Week 2: 15 (60) Week 3: 15 (60) Week 4: 25 (100) Weeks to resolution of infection (mean, SD): 2.52 (1.29) Infections resolved significantly faster in group 1 than groups 2 and 3 ($p < 0.05$) Number of treatments (mean, SD): 7.56 (3.88) Infection resolution (hazard ratios): Hazard ratio vs Comfeel/Biatin Ag: 1.96 ($p=0.018$; 95% CI 1.12 to 3.43) Hazard ratio vs Aquacel Ag: 1.89 ($p=0.025$; 95% CI 1.08 to 3.31)	
	Intervention 2: Comfeel™ or Biatain™ Ag (Comfeel n = 9) Biatin n = 16)	Number of wounds with no clinical signs of infection: Week 1: 0 (0) Week 2: 1 (4) Week 3: 2 (8) Week 4: 25 (100) Weeks to resolution of infection (mean, SD): 3.88 (.44) Number of treatments (mean, SD): 11.64 (1.32)	NR
	Intervention 3: Aquacel Ag (n=25)	Number of wounds with no clinical signs of infection:	NR

Study name and location	Technology name	Local infection n (%)	Wound severity score Mean (SD)
		Week 1: 0 (0) Week 2: 2 (8) Week 3: 3 (12) Week 4: 25 (100) Weeks to resolution of infection (mean, SD): 3.80 (0.58) Number of treatments (mean, SD): 11.40 (1.73)	
Miller et al, 2010 (Miller et al. 2010) Associated records: Trial registration: (ACTRN12606000094572 2006) and two papers (Miller et al. 2011a, Miller et al. 2011b) Study design: RCT Follow-up: 12 weeks (data collected at 2 week intervals up to 12 weeks or wound closure) Location: UK Setting: Community nursing services	Intervention: Nanocrystalline silver dressing (complete case analysis, n=133)	NR	NR
	Comparator: Cadexomer iodine dressing (complete case analysis, n=133)	NR	NR
Molle 2023 (Molle et al. 2023) Design: Non-randomised clinical trial Follow-up: 30 days Location: NR	Intervention: Manuka honey (n=25 ulcers)	Number of ulcers with negative bacterial swab tests at day 15 (%): 84	NR
	Comparator: Silver dressing (n=25 ulcers)	Number of ulcers with negative bacterial swab tests at day 15 (%): 44	NR

Study name and location	Technology name	Local infection n (%)	Wound severity score Mean (SD)
Setting: NR			
Mosti et al, 2005 (Mosti et al. 2015) Study design: Pilot RCT Follow-up: 4 days Location: UK Setting: Community nursing services	Intervention: Silver (Silver-containing hydrofiber Aquacel Ag)	NR	NR
	Comparator: DACC (microorganism-binding, Cutimed Sorbact)	NR	NR

Key: AMD – Antimicrobial dressing, CI – Confidence interval, DACC – Dialkylcarbamoyl chloride, ITT – Intention-to-treat, NR –Not reported, OHP – Octenidine dihydrochloride/phenoxyethanol, PCMP – Polyhexamethylene biguanide antimicrobial, PHMB – Polyhexamethylene biguanide, PP – Per protocol, RCT – Randomised controlled trial, SD – Standard deviation, UK – United Kingdom, USA – United States of America

11.7.3 Clinical signs of infection

Study name and location	Technology name	Covert, n (%)			Overt signs, n (%)				
		Pocketing / tunneling/ undermining	Epithelial bridging	Hyper/Friable granulation	Local erythema	Inc temp around wound	Swelling	Purulent drainage/ discharge	Malodour
Chitosan									
Mo 2015 (Mo et al. 2015) Design: RCT Follow-up: 4 weeks Location: China Setting: 3 university hospital centres	Intervention: Chitosan (n=45)	NR	NR	NR	NR	NR	NR	NR	NR
	Comparator: Vaseline gauze (n=45)	NR	NR	NR	NR	NR	NR	NR	NR
Orig et al 2016 (Orig and Singleton 2016) Design: Prospective single-arm trial Follow-up: Mean evaluation time 8.18 days. Location: NR Setting: Acute hospital ward	Intervention: Chitosan (KytoCel dressing). Wear time ranged from 2 to 7 days. Variety of secondary dressings used including super absorbent dressings, surgical pads and foams.	NR	NR	NR	NR	NR	NR	NR	NR

Study name and location	Technology name	Covert, n (%)			Overt signs, n (%)				
		Pocketing / tunneling/ undermining	Epithelial bridging	Hyper/Friable granulation	Local erythema	Inc temp around wound	Swelling	Purulent drainage/ discharge	Malodour
Copper									
Dokic 2023 (Dokic S et al. 2023) Design: Prospective case series Follow-up: 3 months Location: Slovenia Setting: Hospital	Intervention: Copper wound dressings (n=12)	NR	NR	NR	NR	NR	NR	NR	NR
Melamed 2021 (Melamed et al. 2021) Design: Single-arm trial Follow-up: 4 weeks of treatment and 2 weeks of follow up using unspecified “standard of care” dressings. Location: Israel Setting: Outpatient hospital clinic	Intervention: Cupric oxide dressing	NR	NR	NR	NR	NR	NR	NR	NR

Study name and location	Technology name	Covert, n (%)			Overt signs, n (%)				
		Pocketing / tunneling / undermining	Epithelial bridging	Hyper/Friable granulation	Local erythema	Inc temp around wound	Swelling	Purulent drainage/ discharge	Malodour
Treadwell 2022 (Treadwell T et al. 2022) Design: Prospective case series Follow-up: NR Location: Alabama, USA Setting: Medical centre	Intervention: Cupric oxide wound dressing (n=25)	NR	NR	NR	NR	NR	NR	NR	NR
DACC									
Bruce 2012 (Bruce 2012) Study design: Prospective case series Follow-up: 28 days (or until infection reduced) Location: UK and Ireland Setting: 4 community centres	Intervention: Cutimed Sorbact Hydroactive dressing (n=13 patients, 14 wounds)	NR	NR	NR	Wounds with erythema: Start of treatment: 9 End of treatment: 0	Wounds with heat: Start of treatment: 6 End of treatment: 0	NR	NR	Wounds with odour: Start of treatment: 12 End of treatment: 3

Study name and location	Technology name	Covert, n (%)			Overt signs, n (%)				
		Pocketing / tunneling/ undermining	Epithelial bridging	Hyper/Friable granulation	Local erythema	Inc temp around wound	Swelling	Purulent drainage/ discharge	Malodour
and 2 acute hospitals									
Enzyme Alginogel									
Durante 2012 (Durante 2012) Design: Prospective case series Follow-up: 60 days Location: Italy Setting: Hospital, with continuation in home setting	Intervention: Enzyme Alginogel (Flaminal - composed of hydrated alginate polymers in a polyethylene glycol matrix embedded with a patented antimicrobial enzymatic complex).	NR	NR	NR	NR	NR	NR	NR	NR
Jones et al 2018 (Jones and Oates 2018)	Intervention: Enzyme Alginogel (Flaminal - a hydro-active, broad-spectrum	NR	NR	NR	NR	NR	NR	NR	NR

Study name and location	Technology name	Covert, n (%)			Overt signs, n (%)				
		Pocketing / tunneling/ undermining	Epithelial bridging	Hyper/Friable granulation	Local erythema	Inc temp around wound	Swelling	Purulent drainage/ discharge	Malodour
Design: Prospective case series Follow-up: Unclear Location: UK Setting: Primary care (forms completed by district nurses)	Enzyme Alginogel).								
King et al 2023 (King and Rolland 2023) Design: Prospective case series Follow-up: Unclear Location: UK Setting: Primary care (forms completed by district nurses)	Intervention: Enzyme Alginogel (Flaminal - a hydro-active, broad-spectrum Enzyme Alginogel)	NR	NR	NR	NR	NR	NR	NR	NR
Honey									

Study name and location	Technology name	Covert, n (%)			Overt signs, n (%)				
		Pocketing / tunneling/ undermining	Epithelial bridging	Hyper/Friable granulation	Local erythema	Inc temp around wound	Swelling	Purulent drainage/ discharge	Malodour
Biglari et al 2013 (Biglari et al. 2013) Design: Prospective case series Follow-up: 4.88 (SD 4.4) weeks Location: 9 sites in Germany and 1 in Austria Setting: Hospital	Intervention: Honey (various Medihoney™ dressing products, n=101)	NR	NR	NR	NR	NR	NR	NR	NR
Yang et al 2015 (Yang K et al. 2015) Design: Prospective single-arm study Follow-up: 4 weeks Location: USA Setting: Hospital	Intervention: Topical medical grade honey	NR	NR	NR	NR	NR	NR	NR	NR
Moghazy et al 2010 (Moghazy et al. 2010) Design: Prospective single-arm trial Follow-up: 3 months	Intervention: Honey (Medium-pored non-sterile gauze saturated with honey, n=30).	NR	NR	NR	NR	NR	Patients with inflammation: Baseline: 30/30 (100%)	Patients with foul/purulent exudate: Baseline: 23 (76.7) 1 month: 0 2 month: 0	NR

Study name and location	Technology name	Covert, n (%)			Overt signs, n (%)				
		Pocketing / tunneling/ undermining	Epithelial bridging	Hyper/Friable granulation	Local erythema	Inc temp around wound	Swelling	Purulent drainage/ discharge	Malodour
Location: Egypt Setting: Referred to outpatient care from hospital admission							1 month: 1/30 (3/3) 2 months: 0/30 (0) 3 months: 0/30 (0) p<0.001	3 month: 0	
Iodine									
Skog 1983 (Skog et al. 1983) Design: RCT Follow-up: 6 weeks Location: Sweden Setting: Mixed; at home (visiting nurse) or hospital clinic	Intervention: Cadexomer iodine (Iodosorb, Perstorp AB) (n=38)	NR	NR	NR	Erythema VAS scale (mean, SEM): Pre-treatment: 28 (2.9) Week 1: 27 (2.7) Week 6: 13 (2) p vs. comparator <0.005	NR	NR	Pus and debris VAS scale (mean, SEM) Pre-treatment: 31 (3.1) Week 1: 23 (2.8) Week 6: 8 (1.6) p vs comparator <0.005	NR
	Comparator: Standard treatment (n=36)	NR	NR	NR	Erythema VAS scale (mean, SEM):	NR	NR	Pus and debris VAS scale	NR

Study name and location	Technology name	Covert, n (%)			Overt signs, n (%)				
		Pocketing / tunneling/ undermining	Epithelial bridging	Hyper/Friable granulation	Local erythema	Inc temp around wound	Swelling	Purulent drainage/ discharge	Malodour
					Pre-treatment: 27 (2.7) Week 1: 26 (2.7) Week 6: 23 (2.9), p vs. iodine <0.005			(mean, SEM): Pre-treatment: 33 (4.4) Week 1: 30 (3.9) Week 6: 22(3.4) p vs iodine <0.005	
Octenidine									
Hammerle and Strohal, 2016 (Hammerle and Strohal 2016) Study design: Non-randomised trial Follow-up: 42 days Location: Austria Setting: Secondary care (single centre)	Intervention: Octenidine + foam or alginate (n=14 patients, 17 venous leg ulcers)	NR	NR	NR	NR	NR	NR	NR	NR
	Comparator: Octenidine gel alone with wound contact layer and suction gauze (n=15 patients,	NR	NR	NR	NR	NR	NR	NR	NR

Study name and location	Technology name	Covert, n (%)			Overt signs, n (%)				
		Pocketing / tunneling/ undermining	Epithelial bridging	Hyper/Friable granulation	Local erythema	Inc temp around wound	Swelling	Purulent drainage/ discharge	Malodour
	15 venous leg ulcers)								
PHMB									
Vallejo et al 2022 (Vallejo et al. 2022) Associated records: Protocol: Vallejo et al 2021 (Vallejo 2021) Design: RCT Follow-up: 12 weeks Location: Australia Setting: 1 community wound clinic.	Intervention: PHMB (topical PHMB as a soak in plain gauze for 15 minutes after debridement and at each dressing change, and then in a sustained dressing (AMD foam, or gel with PHMB, or Kerlix AMD gauze, H&R Healthcare, UK; ITT, n=25).	NR	NR	NR	NR	NR	NR	NR	NR
	Comparator: No agent (cleansing of the wound after and between	NR	NR	NR	NR	NR	NR	NR	NR

Study name and location	Technology name	Covert, n (%)			Overt signs, n (%)				
		Pocketing / tunneling/ undermining	Epithelial bridging	Hyper/Friable granulation	Local erythema	Inc temp around wound	Swelling	Purulent drainage/ discharge	Malodour
	treatments with clean water or saline, then non-medicated dressing products; ITT, n=25).								
Koullias 2022 (Koullias et al. 2022) Study design: Prospective case series Follow-up: 32 weeks Location: USA Setting: Unclear (dressings applied by physicians in unclear settings)	Intervention: Type 1 collagen matrix plus polyhexamethylene biguanide antimicrobial (PCMP) barrier (n=67)	NR	NR	NR	NR	NR	NR	NR	NR
Silver									
Degreef et al 1984 (Degreef and Michiels 1984)	Intervention: Silver (1% silver sulfadiazine cream applied once a day in a	NR	NR	NR	NR	NR	NR	NR	NR

Study name and location	Technology name	Covert, n (%)			Overt signs, n (%)				
		Pocketing / tunneling/ undermining	Epithelial bridging	Hyper/Friable granulation	Local erythema	Inc temp around wound	Swelling	Purulent drainage/ discharge	Malodour
Study Design: Prospective case series Follow up: 4 weeks Location: Belgium Setting: Hospital	thin layer of 2 to 3 mm and covered by a sterile bandage)								
Dimakakos et al 2009 (Dimakakos et al. 2009)	Intervention: Silver releasing foam dressing (n=21)	NR	NR	NR	NR	NR	NR	NR	NR
Study design: RCT Follow-up: 9 weeks Location: Greece Setting: NR	Comparator: No agent (non-adhesive foam dressing (n=21)	NR	NR	NR	NR	NR	NR	NR	NR
Forlee 2014 (Forlee et al. 2014)	Intervention: Gelling fibre dressing containing silver (DURAFIBER™ Ag) (n=14)	NR	NR	Patients with wound granulation: Baseline: 2 (14.3) Week 8: 0 (0)	Patients with wound erythema: Baseline 6 (42.9) Week 8 1(7.1)	Patients with wound increased peri-wound temperature: Baseline: 5 (35.7) Week 8: 0 (0)	NR	Patients with wound purulent discharge: Baseline: 3 (21.4) Week 8: 0 (0)	Patients with wound malodour: Baseline 6 (42.9) Week 8: 0 (0)

Study name and location	Technology name	Covert, n (%)			Overt signs, n (%)				
		Pocketing / tunneling/ undermining	Epithelial bridging	Hyper/Friable granulation	Local erythema	Inc temp around wound	Swelling	Purulent drainage/ discharge	Malodour
Setting: Three secondary care centres									
Humbert 2006 (Humbert et al. 2006) Study Design: RCT Follow up: 6 weeks Location: France Setting: 17 sites that included dermatology, vascular, angiophlebology and dermatology practices; 85% of silver arm and 72.5% of no agent arm were outpatients.	Intervention: Silver (Biatain AG, n=40)	NR	NR	NR	NR	NR	NR	NR	Patients with wound malodour (%): Baseline: 87.5 Day 14: 28.2 Change from baseline: - 59.3
	Comparator: No agent (calcium alginate fibre dressing, n=40)	NR	NR	NR	NR	NR	NR	NR	Patients with wound malodour (%): Baseline: 82.5 Day 14: 47.2 Change from baseline: - 35.3
Manning et al 2020	Intervention: Bioabsorbable	NR	NR	NR	NR	NR	NR	NR	NR

Study name and location	Technology name	Covert, n (%)			Overt signs, n (%)				
		Pocketing / tunneling/ undermining	Epithelial bridging	Hyper/Friable granulation	Local erythema	Inc temp around wound	Swelling	Purulent drainage/ discharge	Malodour
(Manning et al. 2020) Associated Records: Conference abstract: Manning 2019 (Manning et al. 2019) Study Design: Single-arm trial Follow up: 12 weeks Location: USA Setting: Wound care clinic within a secondary care setting	polymeric matrix containing ionic and metallic silver								
Meaume et al, 2005 (Meaume et al. 2005) Study design: RCT Follow-up: 4 weeks (daily assessment in first 14 days, weekly thereafter) Location: UK	Intervention: Silver-releasing hydroalginate dressing (Silvercel) (ITT, n=51)	NR	NR	NR	NR	NR	NR	NR	NR
	Comparator: No agent (pure calcium)	NR	NR	NR	NR	NR	NR	NR	NR

Study name and location	Technology name	Covert, n (%)			Overt signs, n (%)				
		Pocketing / tunneling/ undermining	Epithelial bridging	Hyper/Friable granulation	Local erythema	Inc temp around wound	Swelling	Purulent drainage/ discharge	Malodour
Setting: 13 hospital centres	alginate dressing, Algosteril) (ITT, n=48)								
Melotte 1985 (Melotte et al. 1985) Study design: Prospective case series Follow-up: 6 weeks Location: Belgium Setting: NR	Intervention: 1% silver sulfadiazine cream Comparator: None	NR	NR	NR	NR	NR	NR	NR	NR
Molnlycke Health Care AB 2014 (NCT01036438) (NCT01036438 2009) Study design: RCT Follow-up: 8 weeks	Intervention: Silver (absorbent foam silver dressing, Mepilex Ag, ITT n=100)	NR	NR	NR	NR	NR	NR	NR	NR

Study name and location	Technology name	Covert, n (%)			Overt signs, n (%)				
		Pocketing / tunneling/ undermining	Epithelial bridging	Hyper/Friable granulation	Local erythema	Inc temp around wound	Swelling	Purulent drainage/ discharge	Malodour
Location: Czech Republic, France, Germany and the Netherlands Setting: Unclear, appears to be hospital	Comparator: No agent (absorbent foam silver dressing, Mepilex without silver, ITT n=101)	NR	NR	NR	NR	NR	NR	NR	NR
Truchetet 2012 (Truchetet et al. 2012) Study design: Prospective case series Follow up: Median 19 days (7 to 97) Location: France Setting: Private outpatient	Intervention: Mepilex Ag (Mölnlycke Health Care)(n=794)	NR	NR	NR	Overall erythematous peri-wound skin (%): Baseline: 74% Follow up (mean 19 days): 52	NR	NR	NR	Wounds with malodour (%): Follow up: 1%
Woolstencroft 2018 (Woolstencroft 2018) Study design: Single-arm trial Follow-up: 4 weeks Location: UK	Intervention: KerraContactTM Ag dressing with Ag OxysaltsTM (Silver wound dressing with 2	NR	NR	NR	NR	NR	NR	NR	Reduction in wound odour: 77% of wounds

Study name and location	Technology name	Covert, n (%)			Overt signs, n (%)				
		Pocketing / tunneling/ undermining	Epithelial bridging	Hyper/Friable granulation	Local erythema	Inc temp around wound	Swelling	Purulent drainage/ discharge	Malodour
Setting: Secondary care (10 tissue viability clinics)	non-adherent polyethene mesh contact layers and a polyester core) (n=31)								64.4% (n=20) of these reduced significantly
Harding 2016 (Harding et al. 2016) Study design: Prospective single-arm trial Follow-up: 8 weeks Location: UK and Poland Setting: 6 study centres, unclear setting	Intervention: AQUACEL Ag+ hydrofiber dressing Week 1-4, AQUACEL wound dressings Week 5-8 Clinically infected (n=10)	NR	NR	NR	NR	NR	NR	NR	NR
Lantis 2011 (Lantis and Gendics 2011) Study design: Prospective single-arm trial	Intervention: a non-adhesive silver sulphadiazine, polyurethane foam dressing (Allevyn Ag)	NR	NR	Friable granulation tissue: Baseline (Week 0): 5 (20.8)	Local peri-ulcer erythema: Baseline (Week 0): 18 (75)	Increased temperature around ulcer: Baseline (Week 0): 4 (16.7)	NR	Purulent exudate: Baseline (Week 0): 4 (16.7) Week 2: 6 (25)	Malodour: Baseline (Week 0): 10 (41.7) Week 2: 9 (37.5)

Study name and location	Technology name	Covert, n (%)			Overt signs, n (%)				
		Pocketing / tunneling/ undermining	Epithelial bridging	Hyper/Friable granulation	Local erythema	Inc temp around wound	Swelling	Purulent drainage/ discharge	Malodour
Follow-up: 12 weeks Location: USA Setting: Tertiary care wound practice	Non-Adhesive) (n=24)			Week 2: 4 (16.7) Week 4 (n=23): 5 (21.7) Week 8 (n=23): 4 (17.4) Treatment Discontinuation: 3 (12.5)	Week 2: 16 (66.7) Week 4 (n=23): 10 (43.5) Week 8 (n=23): 8 (34.8) Treatment Discontinuation: 5 (20.8)	Week 2: 1 (4.2) Week 4 (n=23): 0 Week 8 (n=23): 0 Treatment discontinuation: 0		Week 4 (n=23): 4 (17.4) Week 8 (n=23): 2 (8.7) Treatment Discontinuation: 1 (4.2)	Week 4 (n=23): 8 (34.8) Week 8 (n=23): 4 (17.4) Treatment Discontinuation: 5 (20.8)
Vanscheidt 2003 (Vanscheidt et al. 2003) Study design: Prospective single-arm trial Follow-up: 28 days Location: France and Germany Setting: NR	Intervention: Aquacel Ag (n=11 patients with infected wounds)	NR	NR	NR	Patients with redness and inflammation: 3/11 27%	NR	NR	NR	NR
Jorgensen 2008 (Jorgensen et al. 2008)	Intervention: Silver and ibuprofen	NR	NR	NR	NR	NR	NR	NR	Patients with wound

Study name and location	Technology name	Covert, n (%)			Overt signs, n (%)				
		Pocketing / tunneling/ undermining	Epithelial bridging	Hyper/Friable granulation	Local erythema	Inc temp around wound	Swelling	Purulent drainage/ discharge	Malodour
Study design: Prospective single-arm trial Follow-up: 31 days (± 2 days) Location: Denmark and Canada Setting: Outpatient clinics at 4 centres	releasing foam dressing (Physiotulle Ag) n=24								malodour (%) Baseline: 37 Day 9: 8 Day 31: 4
Comparative studies of eligible agents									
Gago 2008 (Gago et al. 2008) Study design: Prospective cohort study Follow-up: 8 weeks Location: Spain Setting: Community health centre	Intervention 1: Acticoat™ (n=25)	NR	NR	NR	NR	NR	NR	NR	NR
	Intervention 2: Comfeel™ or Biatain™ Ag (Comfeel n = 9) Biatin n = 16)	NR	NR	NR	NR	NR	NR	NR	NR
	Intervention 3: Aquacel Ag (n=25)	NR	NR	NR	NR	NR	NR	NR	NR
Miller et al, 2010 (Miller et al. 2010)	Intervention: Nanocrystalline silver dressing (complete case	NR	NR	NR	NR	NR	NR	NR	NR

Study name and location	Technology name	Covert, n (%)			Overt signs, n (%)				
		Pocketing / tunneling/ undermining	Epithelial bridging	Hyper/Friable granulation	Local erythema	Inc temp around wound	Swelling	Purulent drainage/ discharge	Malodour
Associated records: Trial registration: (ACTRN1260600009 4572 2006) and two papers (Miller et al. 2011a, Miller et al. 2011b) Study design: RCT Follow-up: 12 weeks (data collected at 2 week intervals up to 12 weeks or wound closure) Location: UK Setting: Community nursing services	analysis, n=133)								
	Comparator: Cadexomer iodine dressing (complete case analysis, n=133)	NR	NR	NR	NR	NR	NR	NR	NR
Molle 2023 (Molle et al. 2023) Design: Non-randomised clinical trial Follow-up: 30 days Location: NR Setting: NR	Intervention: Manuka honey	NR	NR	NR	NR	NR	NR	NR	NR
	Comparator: Silver dressing	NR	NR	NR	NR	NR	NR	NR	NR

Study name and location	Technology name	Covert, n (%)			Overt signs, n (%)				
		Pocketing / tunneling/ undermining	Epithelial bridging	Hyper/Friable granulation	Local erythema	Inc temp around wound	Swelling	Purulent drainage/ discharge	Malodour
Mosti et al, 2005 (Mosti et al. 2015) Study design: Pilot RCT Follow-up: 4 days Location: UK Setting: Community nursing services	Intervention: Silver (Silver-containing hydrofiber Aquacel Ag)	NR	NR	NR	NR	NR	NR	NR	NR
	Comparator: DACC (microorganism-binding, Cutimed Sorbact)	NR	NR	NR	NR	NR	NR	NR	NR

Key: AMD – Antimicrobial dressing, DACC – Dialkylcarbamoyl chloride, ITT – Intention-to-treat, NR – Not reported, OHP – Octenidine dihydrochloride/phenoxyethanol, PCMP – Polyhexamethylene biguanide antimicrobial, PHMB – Polyhexamethylene biguanide, RCT – Randomised controlled trial, SD – Standard deviation, SEM – standard error of the mean, UK – United Kingdom, USA – United States of America, VAS - visual analogue scales.

11.7.4 Wound size/area

Study name and location	Technology name	Change in wound size or area	Rate of change in wound size or area
Chitosan			
Mo 2015 (Mo et al. 2015) Design: RCT Follow-up: 4 weeks Location: China Setting: 3 university hospital centres	Intervention: Chitosan (ITT, n=45)	Percentage change in mean wound area in from baseline cm² (mean, SD): Week 1: -14%, no significant difference vs no agent p>0.05 Week 2: -36.01% significantly greater than no agent p<0.033 Week 3: -53.77% significantly greater than no agent p<0.033 Week 4: -65.97% (4.48%) significantly greater than no agent p<0.001	NR
	Comparator: No agent, Vaseline gauze (ITT, n=45)	Percentage change in mean wound area from baseline in cm² (mean, SD): Week 1: -14.88%, no significant difference vs chitosan p>0.05 Week 2: -24.32%, significantly lesser than no agent p<0.033 Week 3: -36.02%, significantly lesser than no agent p<0.033 Week 4: -39.95 (4.48%), significantly less than chitosan p<0.001	NR
Orig et al 2016 (Orig and Singleton 2016) Design: Prospective single-arm trial	Intervention: Chitosan (Kytocel dressing). Wear time ranged from 2 to 7 days. Variety	NR	NR

Study name and location	Technology name	Change in wound size or area	Rate of change in wound size or area
Follow-up: Mean evaluation time 8.18 days. Location: NR Setting: Acute hospital ward	of secondary dressings used including super absorbent dressings, surgical pads and foams.		
Copper			
Dokic 2023 (Dokic S et al. 2023) Design: Prospective case series Follow-up: 3 months Location: Slovenia Setting: Hospital	Intervention: Copper wound dressings (n=12)	NR	NR
Melamed 2021 (Melamed et al. 2021) Design: Single-arm trial Follow-up: 4 weeks of treatment and 2 weeks of follow up using unspecified “standard of care” dressings. Location: Israel Setting: Outpatient hospital clinic	Intervention: Cupric oxide dressing (n=13)	Mean change in wound size at end of treatment (weeks 1 to 4 with copper dressing): -53.2%, p = 0.003 Mean change in wound size at final follow up (after 4 weeks with copper dressing and 6 weeks with unspecified “standard care” dressings): -65%, p < 0.001	NR
Treadwell 2022 (Treadwell T et al. 2022) Design: Prospective case series Follow-up: NR Location: Alabama, USA	Intervention: Cupric oxide wound dressing (n=25)	NR	NR

Study name and location	Technology name	Change in wound size or area	Rate of change in wound size or area
Setting: Medical centre			
DACC			
Bruce 2012 (Bruce 2012) Study design: Prospective case series Follow-up: 28 days (or until infection reduced) Location: UK and Ireland Setting: 4 community centres and 2 acute hospitals	Intervention: Cutimed Sorbact Hydroactive dressing (n=13 patients, 14 wounds)	Wounds reduced in size (n %) 11/14 (79) Wounds reduced >25, <49% in size (n %); 1/14 (7) Wounds reduced >75% in size (n %) 6/14 (43)	NR
Enzyme Alginogel			
Durante 2012 (Durate 2012) Design: Prospective case series Follow-up: 60 days Location: Italy Setting: Hospital, with continuation in home setting	Intervention: Enzyme Alginogel (Flaminal - composed of hydrated alginate polymers in a polyethylene glycol matrix embedded with a patented antimicrobial enzymatic complex). (n=23)	Wound surface area (cm², mean SD): Baseline (n=23): 2.6 (3.8) Day 14 (n=22): 1.9 (2.6) Day 30 (n=21): 0.6 (0.8) Day 60 (n=13): 0.4 (0.8) Difference at day 60 vs baseline: p=0.001 Wound volume (cm³, mean SD): Baseline (n=23): 2.8 (5.6) Day 14 (n=22): 1.6 (2.6) Day 30 (n=21): 0.3 (0.5) Day 60 (n=13): 0.1 (0.3) Difference at day 60 vs baseline: p=0.001	NR
Jones et al 2018 (Jones and Oates 2018) Design: Prospective case series Follow-up: Unclear	Intervention: Enzyme Alginogel (Flaminal - a hydro-active, broad-spectrum Enzyme Alginogel).	NR	NR

Study name and location	Technology name	Change in wound size or area	Rate of change in wound size or area
Location: UK Setting: Primary care (forms completed by district nurses)			
King et al 2023 (King and Rolland 2023) Design: Prospective case series Follow-up: Unclear Location: UK Setting: Primary care (forms completed by district nurses)	Intervention: Enzyme Alginogel (Flaminal - a hydro-active, broad-spectrum Enzyme Alginogel)	NR	NR
Honey			
Biglari et al 2013 (Biglari et al. 2013) Design: Prospective case series Follow-up: 4.88 (SD 4.4) weeks Location: 9 sites in Germany and 1 in Austria Setting: Hospital	Intervention: Honey (various Medihoney™ dressing products, n=101)	Wound area (cm², mean SD): Baseline: 29.66 (57.57) End of study (mean 4.8, SD 4.4 weeks): 11.32 (33.3) Difference at end of study vs baseline: p=0.05	NR
Yang et al 2015 (Yang K et al. 2015) Design: Prospective single-arm study Follow-up: 4 weeks Location: USA	Intervention: Topical medical grade honey (n=20)	Overall change in wound area (%) from baseline to 4 weeks: -21 Difference at 4 weeks vs baseline: p<0.05	NR

Study name and location	Technology name	Change in wound size or area	Rate of change in wound size or area
Setting: Hospital Moghazy et al 2010 (Moghazy et al. 2010) Design: Prospective single-arm trial Follow-up: 3 months Location: Egypt Setting: Referred to outpatient care from hospital admission	Intervention: Honey (Medium-pored non-sterile gauze saturated with honey, n=30).	Proportion of patients by range of wound size (cm²) over time: <u>Baseline:</u> 1 to 5: 8/30 (26.8) 6 to 10: 13/30 (43.3) 11 to 15: 1/30 (3.3) 16 to 20: 1/30 (3.3) 21 to 105: 7/30 (23.3) Chi-squared test: 0.0002 (p<0.01) <u>1 month:</u> 0 4/30 (13.3) 1 to 5: 9/30 (30) 6 to 10: 8/30 (26.8) 11 to 15: 2/30 (6.7) 16 to 20: 1/30 (3.3) 21 to 105: 4/30 (13.3) <u>2 months:</u> 0: 8/30 (includes 4 resurfaced ulcers, 26.8) 1 to 5: 10/30 (33.3) 6 to 10: 4 (13.3) 11 to 15: 1/30 (3.3) 16 to 20: 1/30 (3.3) 21 to 75: 3/30 (10) Chi-squared test: <0.0001 (p<0.01) <u>3 months:</u> 0: 13/30 (includes 8 resurfaced ulcers, 43.3) 1 to 5: 10/30 (33.3) 6 to 10: 0/30 (0) 11 to 15: 1/30 (3.3) 16 to 20: 1/30 (3.3)	NR

Study name and location	Technology name	Change in wound size or area	Rate of change in wound size or area
		21 to 24: 1/30 (3.3) Chi-squared test: <0.0001 (p<0.01)	
Iodine			
Skog 1983 (Skog et al. 1983) Design: RCT Follow-up: 6 weeks Location: Sweden Setting: Mixed; at home (visiting nurse) or hospital clinic	Intervention: Cadexomer iodine (Iodosorb [^] , Perstorp AB) (n=38)	Percentage change in ulcer size Week 6: -34 Difference vs comparator, p<0.02	NR
	Comparator: Standard treatment (n=36)	Percentage change in ulcer size Week 6: 5 Difference vs comparator, p<0.02	NR
Octenidine			
Hammerle and Strohal, 2016 (Hammerle and Strohal 2016) Study design: Non-randomised trial Follow-up: 42 days Location: Austria Setting: Secondary care (single centre)	Intervention: Octenidine gel + foam or alginate (n=14 patients, 17 venous leg ulcers)	Wound area cm² (median, range): Baseline: 10.3 (1.3 to 91.5) Day 3: 9.6 (1.0 to 91.4) Day 12: 6.7 (0.2 to 27.1) Day 42: 3.7 (0.0 to 11.7) Percentage wound area change from baseline to day 42: -64.1%, difference vs octenidine with contact layer, gauze p = 0.845	NR
	Comparator: Octenidine gel alone with wound contact layer and suction gauze (n=15 patients, 15 venous leg ulcers)	Wound area cm² (median, range): Baseline: 5.3 (0.8 to 24.9) Day 3: 3.6 (0.8 to 22.8) Day 12: 2.3 (0.0 to 29.6) Day 42: 0.2 (0.0 to 17.7) Percentage wound area change from baseline to day 42: -96.2, difference vs octenidine with foam/alginate p = 0.845	NR

Study name and location	Technology name	Change in wound size or area	Rate of change in wound size or area
PHMB			
Vallejo et al 2022 (Vallejo et al. 2022) Associated records: Protocol: Vallejo et al 2021 (Vallejo 2021) Design: RCT Follow-up: 12 weeks Location: Australia Setting: 1 community wound clinic.	Intervention: PHMB (topical PHMB as a soak in plain gauze for 15 minutes after debridement and at each dressing change, and then in a sustained dressing (AMD foam, or gel with PHMB, or Kerlix AMD gauze, H&R Healthcare, UK; ITT, n=25).	Proportion of wounds reduced in size at 12 weeks (%): 61 Difference vs no agent at 12 weeks: p= 0.019	NR
	Comparator: No agent (cleansing of the wound after and between treatments with clean water or saline, then non-medicated dressing products; ITT, n=25).	Proportion of wounds reduced in size at 12 weeks (%): 12.7 Difference vs PHMB at 12 weeks: p= 0.019	NR
Koullias 2022 (Koullias et al. 2022) Study design: Prospective case series Follow-up: 32 weeks Location: US	Intervention: Type 1 collagen matrix plus polyhexamethylene biguanide antimicrobial (PCMP) barrier (n=67)	Incidence of reduction from baseline ulcer area, depth and volume (%) >60% reduction in area: 77.61 >60% reduction in depth: 70.15 >75% reduction in volume: 86.57	NR

Study name and location	Technology name	Change in wound size or area	Rate of change in wound size or area
Setting: Unclear (dressings applied by physicians in unclear settings)			
Silver			
Degreef et al 1984 (Degreef and Michiels 1984) Study Design: Prospective case series Follow up: 4 weeks Location: Belgium Setting: Hospital	Intervention: Silver (1% silver sulfadiazine cream applied once a day in a thin layer of 2 to 3 mm and covered by a sterile bandage)	NR	NR
Dimakakos et al 2009 (Dimakakos et al. 2009) Study design: RCT Follow-up: 9 weeks Location: Greece Setting: NR	Intervention: Silver releasing foam dressing (n=21)	NR	NR
	Comparator: No agent (non-adhesive foam dressing (n=21))	NR	NR
Forlee 2014 (Forlee et al. 2014) Study design: Single-arm trial Follow-up: 8 weeks (The wound was swabbed every 7 days) Location: South Africa Setting: Three secondary care centres	Intervention: Gelling fibre dressing containing silver (DURAFIBER™ Ag) (n=14)	Median percentage change in wound area from baseline: Week 1 (n=13): 4.7% Week 2 (n=13): -28.0% Week 3 (n=13): -38.9% Week 4 (n=13): -43.5% Week 5 (n=14): -56.9% Week 6 (n=14): -73.8% Week 7 (n=14): -91.1% Week 8 (n=14): -98.2% (mean 78.3, range 30.2 to 100)	NR

Study name and location	Technology name	Change in wound size or area	Rate of change in wound size or area
Humbert 2006 (Humbert et al. 2006) Study Design: RCT Follow up: 6 weeks Location: France Setting: 17 sites that included dermatology, vascular, angiophlebology and dermatology practices; 85% of silver arm and 72.5% of no agent arm were outpatients.	Intervention: Silver (Biatain AG, n=40)	Change in wound surface area in cm² from baseline to week 6 (cm² mean, SD): -4.65 (6.41) % change (SD): -37.3 (44.4) Between-group difference in change from baseline to 6 weeks: 2.6 times greater in silver group p=0.04	NR
	Comparator: No agent (calcium alginate fibre dressing, n=40)	Change in wound surface area in cm² and % from baseline to week 6 (cm² mean, SD): -1.85 (7.16) % change (SD): -14.2 (54.2) Between-group difference in change from baseline to 6 weeks: 2.6 times greater in silver group p=0.04	NR
Manning et al 2020 (Manning et al. 2020) Associated Records: Conference abstract: Manning 2019 (Manning et al. 2019) Study Design: Single-arm trial Follow up: 12 weeks Location: USA Setting: Wound care clinic within a secondary care setting	Intervention: Bioabsorbable polymeric matrix containing ionic and metallic silver (n=16)	Mean percentage change in wound area from baseline at 3 weeks (n=11 patients with improved ulcers): -60 Average percentage change in wound area from baseline at 12 weeks (n=16): Reduction >75	NR
Meaume et al, 2005 (Meaume et al. 2005) Study design: RCT	Intervention: Silver-releasing hydroalginate dressing (Silvercel) (ITT, n=51)	Wound area change at week 4 (cm², mean SD): -8.9 (16.0) Between-group difference: p=0.117 Subgroup Leg ulcer only: (n=38): -9.5 (17.9)	Healing rate (cm²/day) Week 1: -0.79 (1.65) Week 2: -0.55 (1.32) Week 3: -0.14 (1.81) Week 4: -0.32 (0.57)

Study name and location	Technology name	Change in wound size or area	Rate of change in wound size or area
Follow-up: 4 weeks (daily assessment in first 14 days, weekly thereafter) Location: UK Setting: 13 hospital centres		Wound area change at week 4 (% reduction, mean SD): -23.7 (43.6) Between-group difference: p=0.923 Subgroup Leg ulcer only: (n=38): -21.0 (45.4)	Between group comparison at week 4: p=0.024 (ANOVA on log-transformed data) Subgroup Leg ulcers only (week 4, n=38): 0.34 (0.64)
	Comparator: No agent (pure calcium alginate dressing, Algosteril) (ITT, n=48)	Wound area change at week 4 (cm², mean SD) -4.4 (11.3) Between-group difference: p=0.117 Subgroup Leg ulcer only: (n=33) -6.0 (11.7) Wound area change at week 4 (% reduction, mean SD) -24.0 (41.6) Between-group difference: p=0.923 Subgroup Leg ulcer only: (n=33) -28.5 (37)	Healing rate (cm²/day) Week 1: 0.16 (0.9) Week 2: -0.23 (0.86) Week 3: 0.14 (0.86) Week 4: -0.16 (0.4) Between group comparison at week 4: p=0.024 (ANOVA on log-transformed data) Subgroup Leg ulcers only (week 4, n=33): 0.21 (0.42)
Melotte 1985 (Melotte et al. 1985) Study design: Prospective case series Follow-up: 6 weeks Location: Belgium Setting: NR	Intervention: 1% silver sulfadiazine cream Comparator: None	NR	NR
Molnlycke Health Care AB 2014 (NCT01036438) (NCT01036438 2009) Study design: RCT Follow-up: 8 weeks Location: Czech Republic, France,	Intervention: Silver (absorbent foam silver dressing, Mepilex Ag, ITT n=100)	Change in wound area at 8 weeks (cm², mean SD): -5.09 (14.23)	NR
	Comparator: No agent (absorbent	Change in wound area at 8 weeks (cm², mean SD): -4.65 (15.43)	NR

Study name and location	Technology name	Change in wound size or area	Rate of change in wound size or area
Germany and the Netherlands Setting: Unclear, appears to be hospital	foam silver dressing, Mepilex without silver, ITT n=101)		
Truchetet 2012 (Truchetet et al. 2012) Study design: Prospective case series Follow up: Median 19 days (7 to 97) Location: France Setting: Private outpatient	Intervention: Mepilex Ag (Mölnlycke Health Care)	NR	NR
Woolstencroft 2018 (Woolstencroft 2018) Study design: Single-arm trial Follow-up: 4 weeks Location: UK Setting: Secondary care (10 tissue viability clinics)	Intervention: KerraContactTM Ag dressing with Ag OxysaltsTM (Silver wound dressing with 2 non-adherent polyethylene mesh contact layers and a polyester core)	NR	NR
Harding 2016 (Harding et al. 2016) Study design: Prospective single-arm trial Follow-up: 8 weeks Location: UK and Poland Setting: 6 study centres, unclear setting	Intervention: AQUACEL Ag+ hydrofiber dressing Week 1-4, AQUACEL wound dressings Week 5-8 (clinically infected n = 10)	Mean wound area reduction in patients with clinically infected ulcers (%): 8 weeks: 70.2 (SD 24.7%, range 13.6 to 100%).	NR

Study name and location	Technology name	Change in wound size or area	Rate of change in wound size or area
Lantis 2011 (Lantis and Gendics 2011) Study design: Prospective single-arm trial Follow-up: 12 weeks Location: USA Setting: Tertiary care wound practice	Intervention: a non-adhesive silver sulphadiazine, polyurethane foam dressing (Allevyn Ag, non-Adhesive) (n=24)	Patients achieving at least a 75% reduction in ulcer area from baseline, n (%): 8 weeks: 19/24 (79.2) Median percentage change after: 2 weeks (n=24): -28.1 4 weeks (n=23): -56.4 8 weeks (n=23): -93.4 12 weeks (n=24): -96.9 (mean 81.5%, range -72.3 to 100%, p<0.001)	NR
Vanscheidt 2003 (Vanscheidt et al. 2003) Study design: Prospective single-arm trial Follow-up: 28 days Location: France and Germany Setting: NR	Intervention: Aquacel Ag (n=11 patients with infected wounds)	Mean percentage change in wound area: Day 28: -32.5	NR
Jorgensen 2008 (Jorgensen et al. 2008) Study design: Prospective single-arm trial Follow-up: 31 days ($\pm$ 2 days) Location: Denmark and Canada Setting: Outpatient clinics at 4 centres	Intervention: Silver and ibuprofen releasing foam dressing (Physiotulle Ag) n=24	Wound area cm², mean (SD): Baseline: 14.4 (17.7) Day 31: 9.2 (12.8) Mean % relative wound area change: -42	Linear healing rate over the four-week study period (reduction in area divided by mean of wound circumference, cm): 0.32
Comparative studies of eligible agents			

Study name and location	Technology name	Change in wound size or area	Rate of change in wound size or area
Gago 2008 (Gago et al. 2008) Study design: Prospective cohort study Follow-up: 8 weeks Location: Spain Setting: Community health centre	Intervention 1: Acticoat™ (n=25)	NR	NR
	Intervention 2: Comfeel™ or Biatain™ Ag (Comfeel n = 9) Biatin n = 16)	NR	NR
	Intervention 3: Aquacel Ag (n=25)	NR	NR
Miller et al, 2010 (Miller et al. 2010) Associated records: Trial registration: (ACTRN12606000094572 2006) and two papers (Miller et al. 2011a, Miller et al. 2011b) Study design: RCT Follow-up: 12 weeks (data collected at 2 week intervals up to 12 weeks or wound closure) Location: UK Setting: Community nursing services	Intervention: Nanocrystalline silver dressing (complete case analysis, n=133)	NR	Healing rate (% reduction in wound size divided by the number of days between measurement; mean, SD) (n=133): Week 2: (n=129): 2.12 (2.94), significantly faster healing vs iodine overall and in subgroup analyses for old wounds (p<0.01), small wounds (p < 0.01), and large wounds (p<0.05) at week 2. Week 4: (n=115): 2.99 (4.53) Week 6:(n=92): 1.63 (11.34) Week 8: (n=72): 2.82 (4.84) Week 10: (n=58): 0.35 (11.68) Week 12: (n=48): 1.26 (4.79) Overall healing rate: 2.1 (1.89), between-group comparison: not significant, p>0.05.
	Comparator: Cadexomer iodine dressing (complete case analysis, n=133)	NR	Healing rate (% reduction in wound size divided by the number of days between measurement; mean, SD) (n=133) Week 2: (n=127): -0.22 (8.18), significantly slower healing vs silver overall and in subgroup analyses for old wounds (p<0.01), small wounds (p < 0.01), and large wounds (p<0.05) at week 2.

Study name and location	Technology name	Change in wound size or area	Rate of change in wound size or area
			Week 4: (n=117): 3.15 (4.97) Week 6: (n=91): 1.94 (5.18) Week 8: (n=70): 1.32 (10.19) Week 10: (n=51): 1.64 (4.91) Week 12: (n=41): 1.29 (6.09) Overall healing rate: 1.69 (2.46), between-group comparison: not significant, p>0.05
Molle 2023 (Molle et al. 2023) Design: Non-randomised clinical trial Follow-up: Baseline then 15 and 30 days from baseline Location: NR Setting: NR	Intervention: Manuka honey	NR	NR
	Comparator: Silver dressing	NR	NR
Mosti et al, 2005 (Mosti et al. 2015) Study design: Pilot RCT Follow-up: 4 days Location: UK Setting: Community nursing services	Intervention: Silver (Silver-containing hydrofiber Aquacel Ag)	NR	NR
	Comparator: DACC (microorganism-binding, Cutimed Sorbact)	NR	NR

Key: AMD – Antimicrobial dressing, ANOVA – Analysis of variance, DACC – Dialkylcarbamoyl chloride, ITT –Intention-to-treat, NR – Not reported, OHP – Octenidine dihydrochloride/phenoxyethanol, PCMP – Polyhexamethylene biguanide antimicrobial, PHMB – Polyhexamethylene biguanide, RCT – Randomised controlled trial, SD – Standard deviation, UK – United Kingdom, USA – United States of America

11.7.5 Wound bed/ peri-wound skin condition

Study name and location	Technology name	Change in slough, n (%)	Change in exudate, n (%)	Change in granulation, n (%)	Change in oedema, n (%)	Condition of peri-wound skin
Chitosan						
Mo 2015 (Mo et al. 2015) Design: RCT Follow-up: 4 weeks Location: China Setting: 3 university hospital centres	Intervention: Chitosan (n=45)	NR	Number of patients with 'saturated' exudate: Baseline: 12/45 Week 4: 2/45 Mean exudate score (definition NR) at week 4: 40.51, p v. comparator = 0.008	NR	NR	NR
	Comparator: Vaseline gauze (n=45)	NR	Number of patients with 'saturated' exudate: Baseline: 12/45 Week 4: 6/45 Mean exudate score (definition NR) at week 4: 50.49	NR	NR	NR
Orig et al 2016 (Orig and Singleton 2016) Design: Prospective single-arm trial	Intervention: Chitosan (KytoCel dressing).	NR	NR	NR	NR	NR

Study name and location	Technology name	Change in slough, n (%)	Change in exudate, n (%)	Change in granulation, n (%)	Change in oedema, n (%)	Condition of peri-wound skin
Follow-up: Mean evaluation time 8.18 days. Location: NR Setting: Acute hospital ward						
Copper						
Dokic 2023 (Dokic S et al. 2023) Design: Prospective case series Follow-up: 3 months Location: Slovenia Setting: Hospital	Intervention: Copper wound dressings (n=12)	NR	NR	Reported that granulation occurred faster. NR what this is in comparison to.	NR	NR
Melamed 2021 (Melamed et al. 2021) Design: Single-arm trial Follow-up: 4 weeks of treatment and 2 weeks of follow up using unspecified "standard of care" dressings. Location: Israel Setting: Outpatient hospital clinic	Intervention: Cupric oxide dressing (n=13)	NR	NR	Percentage change in granulation tissue after treatment: Week 1: 28.5%, p<0.01 Duration of treatment: 43.37%, p < 0.001	NR	No peri-wound redness observed
Treadwell 2022 (Treadwell T et al. 2022) Design: Prospective case series	Intervention: Cupric oxide wound dressing (n=25)	NR	NR	NR	NR	NR

Study name and location	Technology name	Change in slough, n (%)	Change in exudate, n (%)	Change in granulation, n (%)	Change in oedema, n (%)	Condition of peri-wound skin
Follow-up: NR Location: Alabama, USA Setting: Medical centre						
DACC						
Bruce 2012 (Bruce 2012) Study design: Prospective case series Follow-up: 28 days (or until infection reduced) Location: UK and Ireland Setting: 4 community centres and 2 acute hospitals	Intervention: Cutimed Sorbact Hydroactive dressing (n=13 patients, 14 wounds)	Wounds with slough: Baseline: 6 End of treatment: 4	Wounds with exudate: Baseline: 14 End of treatment: 10	NR	Wounds with oedema: Baseline: 8 End of treatment: 1	Wounds with healthy peri-wound skin: Baseline: 2 End of treatment: 7
Enzyme Alginogel						
Durante 2012 (Durante 2012) Design: Prospective case series Follow-up: 60 days Location: Italy Setting: Hospital, with continuation in home setting	Intervention: Enzyme Alginogel (Flaminal) (n=23)	NR	NR	Percentage of wound area covered by granulation (% mean, SD): Baseline (n=23): 32 (29) Day 14 (n=22): 53 (29) Day 30 (n=21): 30 (31) Day 60 (n=13): 28 (37) Difference at day 60 vs baseline: p=0.001	NR	Surrounding skin evolution as assessed by care team (n=20): Excellent: 9 (45%) Good: 10 (50%) Poor: 1 (5%)

Study name and location	Technology name	Change in slough, n (%)	Change in exudate, n (%)	Change in granulation, n (%)	Change in oedema, n (%)	Condition of peri-wound skin
Jones et al 2018 (Jones and Oates 2018) Design: Prospective case series Follow-up: Unclear Location: UK Setting: Primary care (forms completed by district nurses)	Intervention: Enzyme Alginogel (Flaminal - a hydro-active, broad-spectrum Enzyme Alginogel) (n=356)	Change in wound bed (debridement of slough/necrotic tissue) per clinician assessment (n=331 respondents): Improved: 278/331 (84) No change or worsening: 53/331 (16) Difference between observed value and the expected value of 50%: p<0.0001 (95% CI 79.65 to 87.55)	Change in moisture balance per clinician assessment (n=352 respondents): Improved: 294/352 (83.52) No change/worsening : 58/352 (16.48) Difference between observed value and the expected value of 50%: p<0.0001 (95% score CI 79.29 to 87.03)	Improvement in quality of granulation tissue (n=352 respondents): Improved: 276/352 (78.41) No change or worsening: 76/352 (21.59) Difference between observed value and the expected value of 50%: p<0.0001 (95% score CI 73.82 to 82.39)	NR	Change in condition of peri-wound skin per clinician assessment (n= full response, 356 respondents): Improved: 255/356 (71.63) No change or worsening: 101/356 (28.37) Difference between observed value and the expected value of 50%: p<0.0001 (95% CI 66.73 to 76.06)
King et al 2023 (King and Rolland 2023) Design: Prospective case series Follow-up: Unclear Location: UK	Intervention: Enzyme Alginogel (Flaminal - a hydro-active, broad-spectrum Enzyme Alginogel) (n=1657)	Change in wound bed (debridement of slough/necrotic tissue) per clinician assessment	Management of moisture balance per clinician assessment (n=1599 respondents): Well-managed: 1321/1599 (82.6)	Improvement in quality of granulation tissue (n=1587 respondents): Improved: 1230/1587 (77.5)	NR	Change in condition of peri-wound skin per clinician assessment (n= full response,

Study name and location	Technology name	Change in slough, n (%)	Change in exudate, n (%)	Change in granulation, n (%)	Change in oedema, n (%)	Condition of peri-wound skin
Setting: Primary care (forms completed by district nurses)		(n=1503 respondents): Improved: 1211/1503 (81) No change or worsening: 292/1503 (19) Difference between observed value and the expected value of 50%: p<0.0001 (95% CI 78.24 to 82.71)	No change/not managed: 278/1599 (17.4) Difference between observed value and the expected value of 50%: p<0.0001 (95% score CI 80.47 to 84.56)	No change or worsening: 357/1587 (22.5) Difference between observed value and the expected value of 50%: p<0.0001 (95% CI 75.08 to 79.75%)		1624 respondents): Improved: 1124/1624 (69.2) No change or worsening: 500/1624 (30.8) Difference between observed value and the expected value of 50%: p<0.0001 (95% CI 66.66 to 71.85)
Honey						
Biglari et al 2013 (Biglari et al. 2013) Design: Prospective case series Follow-up: 4.88 (SD 4.4) weeks Location: 9 sites in Germany and 1 in Austria Setting: Hospital	Intervention: Honey (various Medihoney™ dressing products, n=104)	Mean slough/necrosis score (average of scores from grade 0 (presence of slough/necrosis) to grade 1 (no slough/necrosis): Baseline: 0.16 (0.37) End of study (mean 4.88 weeks,	NR	NR	NR	NR

Study name and location	Technology name	Change in slough, n (%)	Change in exudate, n (%)	Change in granulation, n (%)	Change in oedema, n (%)	Condition of peri-wound skin
		SD 4.4): 0.74 (0.44) Difference at end of study vs baseline: p<0.05				
Yang et al 2015 (Yang K et al. 2015) Design: Prospective single-arm study Follow-up: 4 weeks Location: USA Setting: Hospital	Intervention: Topical medical grade honey	NR	NR	NR	NR	NR
Moghazy et al 2010 (Moghazy et al. 2010) Design: Prospective single-arm trial Follow-up: 3 months Location: Egypt Setting: Referred to outpatient care from hospital admission	Intervention: Honey (Medium-pored non-sterile gauze saturated with honey, n=30).	NR	Patients with foul/purulent exudate: Baseline: 23/30 (76.7) 1 month: 0 2 month: 0 3 month: 0 Patients with serosanguinous exudate: Baseline: 7/30 (23.3) 1 month: 24/30 (84%) 2 month: 8/30 (26.8)	Wounds showing healthy granulation: 3 months: 13/30 (43.3%)	NR	NR

Study name and location	Technology name	Change in slough, n (%)	Change in exudate, n (%)	Change in granulation, n (%)	Change in oedema, n (%)	Condition of peri-wound skin
			3 month: 0 Patients with non-characteristic (scanty, serous) exudate: Baseline: 0 1 month: 0 2 month: 11/30 (36.7%) 3 month: 12/30 (40%) Chi-squared test for difference in proportion of patients with each type of exudate at all timepoints: <0.001 (p<0.01)			
Iodine						
Skog 1983 (Skog et al. 1983) Design: RCT Follow-up: 6 weeks Location: Sweden Setting: Mixed; at home (visiting nurse) or hospital clinic	Intervention: Cadexomer iodine (Iodosorb [^] , Perstorp AB) (n=38)	NR	Exudate VAS scale (mean, SEM): Pre-treatment: 37 (3.5) Week 1: 27 (3.1) Week 6: 11 (1.5), p vs. comparator <0.005	Granulation VAS scale (mean, SEM): Pre-treatment: 39 (5.4) Week 1: 47 (5.0) Week 6: 76 (4.0), p vs. comparator <0.05	Oedema VAS scale (mean, SEM): Pre-treatment: 23 (3.2) Week 1: 21 (3.0) Week 6: 8 (2.0), vs baseline p<0.005	NR

Study name and location	Technology name	Change in slough, n (%)	Change in exudate, n (%)	Change in granulation, n (%)	Change in oedema, n (%)	Condition of peri-wound skin
	Comparator: Standard treatment (n=36)	NR	Exudate VAS scale (mean, SEM): Pre-treatment: 35 (4) Week 1: 32 (3.5) Week 6: 23 (3.6), p vs. iodine <0.005	Granulation VAS scale (mean, SEM): Pre-treatment: 47 (4.2) Week 1: 51 (3.9) Week 6: 60 (4.6), p vs. iodine <0.05	Oedema VAS scale (mean, SEM): Pre-treatment: 26 (3.9) Week 1: 22 (3.2) Week 6: 20 (3.0), p vs baseline p<0.05	NR
Octenidine						
Hammerle and Strohal, 2016 (Hammerle and Strohal 2016) Study design: Non-randomised trial Follow-up: 42 days Location: Austria Setting: Secondary care (single centre)	Intervention: Octenidine + foam or alginate (n=14 patients, 17 venous leg ulcers)	NR	NR	Granulation tissue present (%) Baseline: 62 Visit 1: 65 Visit 2: 70 Visit 3: 78 Visit 4: 77 Visit 5: 79 p=n.s.	NR	NR
	Comparator: Octenidine gel alone with wound contact layer and suction gauze (n=15 patients, 15 venous leg ulcers)	NR	NR	Granulation tissue present (%) Baseline: 52 Visit 1: 63 Visit 2: 74 Visit 3: 80 Visit 4: 86 Visit 5: 97 p=n.s.	NR	NR
PHMB						
Vallejo et al 2022 (Vallejo et al. 2022)	Intervention: PHMB (AMD foam,	NR	NR	NR	NR	NR

Study name and location	Technology name	Change in slough, n (%)	Change in exudate, n (%)	Change in granulation, n (%)	Change in oedema, n (%)	Condition of peri-wound skin
Associated records: Protocol: Vallejo et al 2021 (Vallejo 2021) Design: RCT Follow-up: 12 weeks Location: Australia Setting: 1 community wound clinic.	or gel with PHMB, or Kerlix AMD gauze, H&R Healthcare, UK; (ITT, n=25).					
	Comparator: No agent (ITT, n=25).	NR	NR	NR	NR	NR
Koullias 2022 (Koullias et al. 2022) Study design: Prospective case series Follow-up: 32 weeks Location: US Setting: Unclear (dressings applied by physicians in unclear settings)	Intervention: Type 1 collagen matrix plus polyhexamethylene biguanide antimicrobial (PCMP) barrier (n=67)	NR	NR	NR	NR	NR
Silver						
Degreef et al 1984 (Degreef and Michiels 1984) Study Design: Prospective case series Follow up: 4 weeks Location: Belgium Setting: Hospital	Intervention: Silver (1% silver sulfadiazine cream applied once a day in a thin layer of 2 to 3 mm and covered by a sterile bandage)	NR	NR	NR	NR	NR

Study name and location	Technology name	Change in slough, n (%)	Change in exudate, n (%)	Change in granulation, n (%)	Change in oedema, n (%)	Condition of peri-wound skin
Dimakakos et al 2009 (Dimakakos et al. 2009) Study design: RCT Follow-up: 9 weeks Location: Greece Setting: NR	Silver releasing foam dressing (n=21)	NR	NR	NR	NR	NR
	No agent (non-adhesive foam dressing (n=21))	NR	NR	NR	NR	NR
Forlee 2014 (Forlee et al. 2014) Study design: Single-arm trial Follow-up: 8 weeks (The wound was swabbed every 7 days) Location: South Africa Setting: Three secondary care centres	Gelling fibre dressing containing silver (DURAFIBER™ Ag) (n=14)	NR	Patients with increased exudate/secretion levels: Baseline 9 (64.3) Week 8: 0 (0)	Patients with discolouration of granulation tissue: Baseline: 2 (14.3) Week 8: 0 (0)	Patients with signs of oedema: Baseline 3 (21.4) Week 8: 0 (0)	NR
Humbert 2006 (Humbert et al. 2006) Study Design: RCT Follow up: 6 weeks Location: France Setting: 17 sites that included dermatology, vascular, angiophlebology and dermatology practices; 85% of silver arm and 72.5% of no agent arm were outpatients.	Intervention: Silver (Biatain AG, n=40)	NR	Proportion of wounds with little or no exudate during dressing removal: 65.0 Difference vs no agent: significantly greater, p=0.04	NR	NR	NR
	Comparator: No agent (calcium	NR	Proportion of wounds with little or no	NR	NR	NR

Study name and location	Technology name	Change in slough, n (%)	Change in exudate, n (%)	Change in granulation, n (%)	Change in oedema, n (%)	Condition of peri-wound skin
	alginate fibre dressing, n=40)		exudate during dressing removal: 50.5 Difference vs silver: significantly lesser, p=0.04			
Manning et al 2020 (Manning et al. 2020) Associated Records: Conference abstract: Manning 2019 (Manning et al. 2019) Study Design: Single-arm trial Follow up: 12 weeks Location: USA Setting: Wound care clinic within a secondary care setting	Intervention: Bioabsorbable polymeric matrix containing ionic and metallic silver Comparator: None	NR	NR	NR	NR	NR
Meaume et al, 2005 (Meaume et al. 2005) Study design: RCT Follow-up: 4 weeks (daily assessment in first 14 days, weekly thereafter) Location: UK Setting: 13 hospital centres	Silver-releasing hydroalginate dressing (Silvercel) (ITT, n=51)	NR	NR	NR	NR	NR
	No agent (pure calcium alginate dressing, Algosteril) (ITT, n=48)	NR	NR	NR	NR	NR

Study name and location	Technology name	Change in slough, n (%)	Change in exudate, n (%)	Change in granulation, n (%)	Change in oedema, n (%)	Condition of peri-wound skin
Melotte 1985 (Melotte et al. 1985) Study design: Prospective case series Follow-up: 6 weeks Location: Belgium Setting: NR	Intervention: 1% silver sulfadiazine cream Comparator: None	NR	NR	NR	NR	NR
Molnlycke Health Care AB 2014 (NCT01036438) (NCT01036438 2009) Study design: RCT Follow-up: 8 weeks Location: Czech Republic, France, Germany and the Netherlands Setting: Unclear, appears to be hospital	Intervention: Silver (absorbent foam silver dressing, Mepilex Ag, ITT n=100)	NR	NR	NR	NR	NR
	Comparator: No agent (absorbent foam silver dressing, Mepilex without silver, ITT n=101)	NR	NR	NR	NR	NR
Truchetet 2012 (Truchetet et al. 2012) Study design: Prospective case series Follow up: Median 19 days (7 to 97)	Intervention: Mepilex Ag (Mölnlycke Health Care) (n=794)	NR	Wounds highly exudative: Baseline: 55% Follow-up (median 19 days): 4.5%	NR	NR	NR

Study name and location	Technology name	Change in slough, n (%)	Change in exudate, n (%)	Change in granulation, n (%)	Change in oedema, n (%)	Condition of peri-wound skin
Location: France Setting: Private outpatient						
Woolstencroft 2018 (Woolstencroft 2018) Study design: Single-arm trial Follow-up: 4 weeks Location: UK Setting: Secondary care (10 tissue viability clinics)	Intervention: KerraContactTM Ag dressing with Ag OxysaltsTM (n= 30 of total 30 patients)	NR	Significant reduction, n (%): 23/30 (33) Reduction (%): 42 Slight reduction (%): 10 No difference (%): 3 Increase (%): 10 Overall patients with reduced exudate (%): 83	NR	NR	NR
Harding 2016 (Harding et al. 2016) Study design: Prospective single-arm trial Follow-up: 8 weeks Location: UK and Poland Setting: 6 study centres, unclear setting	Intervention: AQUACEL Ag+ hydrofiber dressing Week 1-4, AQUACEL wound dressings Week 5-8 Clinically infected (n=10)	NR	NR	NR	NR	NR

Study name and location	Technology name	Change in slough, n (%)	Change in exudate, n (%)	Change in granulation, n (%)	Change in oedema, n (%)	Condition of peri-wound skin
Lantis 2011 (Lantis and Gendics 2011) Study design: Prospective single-arm trial Follow-up: 12 weeks Location: USA Setting: Tertiary care wound practice	Intervention: a non-adhesive silver sulphadiazine, polyurethane foam dressing (Allevyn Ag Non-Adhesive (n=24)	Reduction in the percentage of devitalised (yellow slough or black necrotic) tissue: Baseline: 21.9% Treatment discontinuation: 5.4%	Patients with increased exudate: Baseline (Week 0): 19 (79.2) Week 2: 9 (37.5) Week 4 (n=23): 3 (13) Week 8 (n=23): 0 Treatment discontinuation: 3 (12.5) There was a significant reduction in the level of exudate (p<0.001) between baseline and treatment discontinuation	Patients with discoloration of granulation tissue: Baseline (Week 0): 6 (25) Week 2: 2 (8.3) Week 4 (n=23): 1 (4.3) Week 8 (n=23): 3 (13.0) Treatment discontinuation: 1 (4.2) Percentage of dull red unhealthy granulation tissue (% of ulcer tissue) Baseline: 39% to treatment discontinuation (15.4)	Patients with oedema: Baseline (Week 0): 22 (91.7) Week 2: 16 (66.7) Week 4 (n=23): 13 (56.5) Week 8 (n=23): 5 (21.7) Treatment Discontinuation: 5 (20.8)	NR
Vanscheidt 2003 (Vanscheidt et al. 2003) Study design: Prospective single-arm trial Follow-up: 28 days Location: France and Germany Setting: NR	Intervention: Aquacel Ag (n=11 patients with infected wounds)	NR	NR	NR	NR	NR

Study name and location	Technology name	Change in slough, n (%)	Change in exudate, n (%)	Change in granulation, n (%)	Change in oedema, n (%)	Condition of peri-wound skin
Jorgensen 2008 (Jorgensen et al. 2008) Study design: Prospective single-arm trial Follow-up: 31 days ($\pm$ 2 days) Location: Denmark and Canada Setting: Outpatient clinics at 4 centres	Intervention: Silver and ibuprofen releasing foam dressing (Physiotulle Ag) n=24	Wound bed covered by slough %, mean (SD): Baseline: 5 (11) Day 31: 1 (5)	NR	Wound bed covered by unhealthy granulation tissue %, mean (SD): Baseline: 10 (19) Day 31: 3 (8) Wound bed covered by healthy granulation tissue%, mean (SD): Baseline: 32 (30) Day 31: 59 (31)	NR	NR
Comparative studies of eligible agents						
Gago 2008 (Gago et al. 2008) Study design: Prospective cohort study Follow-up: 8 weeks Location: Spain Setting: Community health centre	Intervention 1: Acticoat™ (n=25)	NR	NR	NR	NR	NR
	Intervention 2: Comfeel™ or Biatain™ Ag (Comfeel n = 9) Biatin n = 16)	NR	NR	NR	NR	NR
	Intervention 3: Aquacel Ag (n=25)	NR	NR	NR	NR	NR
Miller et al, 2010 (Miller et al. 2010) Associated records: Trial registration:	Nanocrystalline silver dressing (complete case analysis, n=133)	NR	NR	NR	NR	NR

Study name and location	Technology name	Change in slough, n (%)	Change in exudate, n (%)	Change in granulation, n (%)	Change in oedema, n (%)	Condition of peri-wound skin
(ACTRN12606000094572 2006) and two papers (Miller et al. 2011a, Miller et al. 2011b) Study design: RCT Follow-up: 12 weeks (data collected at 2 week intervals up to 12 weeks or wound closure) Location: UK Setting: Community nursing services	Cadexomer iodine dressing (complete case analysis, n=133)	NR	NR	NR	NR	NR
Molle 2023 (Molle et al. 2023) Design: Non-randomised clinical trial Follow-up: 30 days Location: NR Setting: NR	Intervention: Manuka honey	NR	NR	NR	NR	NR
	Comparator: Silver dressing	NR	NR	NR	NR	NR
Mosti et al, 2005 (Mosti et al. 2015) Study design: Pilot RCT Follow-up: 4 days Location: UK Setting: Community nursing services	Silver (Silver-containing hydrofiber Aquacel Ag)	NR	NR	NR	NR	NR
	DACC (microorganism-binding, Cutimed Sorbact)	NR	NR	NR	NR	NR

Key: AMD – Antimicrobial dressing, CI – Confidence interval, DACC – Dialkylcarbamoyl chloride, ITT – Intention-to-treat, NR – Not reported, OHP – Octenidine dihydrochloride/phenoxyethanol, PCMP – Polyhexamethylene biguanide antimicrobial, PHMB – Polyhexamethylene biguanide, RCT – Randomised controlled trial, SD – Standard deviation, UK – United Kingdom, USA – United States of America

11.7.6 Frequency of dressing changes and antibiotic use

Study name and location	Technology name	Frequency of dressing changes across study period	Mean wear time across dressing changes	Prescription of antibiotics
Chitosan				
Mo 2015 (Mo et al. 2015)	Intervention: Chitosan (n=45)	NR	NR	NR
Design: RCT Follow-up: 4 weeks Location: China Setting: 3 university hospital centres	Comparator: Vaseline gauze (n=45)	NR	NR	NR
Orig et al 2016 (Orig and Singleton 2016) Design: Prospective single-arm trial Follow-up: Mean evaluation time 8.18 days. Location: NR Setting: Acute hospital ward	Intervention: Chitosan (KytoCel dressing). Wear time ranged from 2 to 7 days. Variety of secondary dressings used including super absorbent dressings, surgical pads and foams.	NR	NR	NR
Copper				
Dokic 2023 (Dokic S et al. 2023) Design: Prospective case series Follow-up: 3 months Location: Slovenia Setting: Hospital	Intervention: Copper wound dressings (n=12)	NR	NR	NR

Study name and location	Technology name	Frequency of dressing changes across study period	Mean wear time across dressing changes	Prescription of antibiotics
Melamed 2021 (Melamed et al. 2021) Design: Single-arm trial Follow-up: 4 weeks of treatment and 2 weeks of follow up using unspecified “standard of care” dressings. Location: Israel Setting: Outpatient hospital clinic	Intervention: Cupricoxide dressing	NR	NR	NR
Treadwell 2022 (Treadwell T et al. 2022) Design: Prospective case series Follow-up: NR Location: Alabama, USA Setting: Medical centre	Intervention: Cupric oxide wound dressing (n=25)	NR	NR	NR
DACC				
Bruce 2012 (Bruce 2012) Study design: Prospective case series Follow-up: 28 days (or until infection reduced) Location: UK and Ireland Setting: 4 community centres and 2 acute hospitals	Intervention: Cutimed Sorbact Hydroactive dressing (n=13 patients, 14 wounds)	NR	NR	NR
Enzyme Alginogel				

Study name and location	Technology name	Frequency of dressing changes across study period	Mean wear time across dressing changes	Prescription of antibiotics
Durante 2012 (Durante 2012) Design: Prospective case series Follow-up: 60 days Location: Italy Setting: Hospital, with continuation in home setting	Intervention: Enzyme Alginogel (Flaminal - composed of hydrated alginate polymers in a polyethylene glycol matrix embedded with a patented antimicrobial enzymatic complex)	NR	NR	NR
Jones et al 2018 (Jones and Oates 2018) Design: Prospective case series Follow-up: Unclear Location: UK Setting: Primary care (forms completed by district nurses)	Intervention: Enzyme Alginogel (Flaminal - a hydro-active, broad-spectrum Enzyme Alginogel)	NR	NR	NR
King et al 2023 (King and Rolland 2023) Design: Prospective case series Follow-up: Unclear Location: UK Setting: Primary care (forms completed by district nurses)	Intervention: Enzyme Alginogel (Flaminal - a hydro-active, broad-spectrum Enzyme Alginogel)	NR	NR	NR
Honey				

Study name and location	Technology name	Frequency of dressing changes across study period	Mean wear time across dressing changes	Prescription of antibiotics
Biglari et al 2013 (Biglari et al. 2013) Design: Prospective case series Follow-up: 4.88 (SD 4.4) weeks Location: 9 sites in Germany and 1 in Austria Setting: Hospital	Intervention: Honey (various Medihoney™ dressing products, n=101)	NR	NR	NR
Yang et al 2015 (Yang K et al. 2015) Design: Prospective single-arm study Follow-up: 4 weeks Location: USA Setting: Hospital	Intervention: Topical medical grade honey	NR	NR	NR
Moghazy et al 2010 (Moghazy et al. 2010) Design: Prospective single-arm trial Follow-up: 3 months Location: Egypt Setting: Referred to outpatient care from hospital admission	Intervention: Honey (Medium-pored non-sterile gauze saturated with honey).	NR	NR	NR
Iodine				
Skog 1983 (Skog et al. 1983) Design: RCT Follow-up: 6 weeks Location: Sweden	Intervention: Cadexomer iodine (Iodosorb^, Perstorp AB) (n=38)	NR	NR	NR

Study name and location	Technology name	Frequency of dressing changes across study period	Mean wear time across dressing changes	Prescription of antibiotics
Setting: Mixed; at home (visiting nurse) or hospital clinic	Comparator: Standard treatment (n=36)	NR	NR	NR
Octenidine				
Hammerle and Strohal, 2016 (Hammerle and Strohal 2016) Study design: Non-randomised trial Follow-up: 42 days Location: Austria Setting: Secondary care (single centre)	Intervention: Octenidine + foam or alginate (n=14 patients, 17 venous leg ulcers)	NR	NR	NR
	Comparator: Octenidine gel alone with wound contact layer and suction gauze (n=15 patients, 15 venous leg ulcers)	NR	NR	NR
PHMB				
Vallejo et al 2022 (Vallejo et al. 2022) Associated records: Protocol: Vallejo et al 2021 (Vallejo 2021) Design: RCT Follow-up: 12 weeks Location: Australia Setting: 1 community wound clinic.	Intervention: PHMB (topical PHMB as a soak in plain gauze for 15 minutes after debridement and at each dressing change, and then in a sustained dressing (AMD foam, or gel with PHMB, or Kerlix AMD gauze, H&R Healthcare, UK; ITT, n=25).	NR	NR	NR

Study name and location	Technology name	Frequency of dressing changes across study period	Mean wear time across dressing changes	Prescription of antibiotics
	Comparator: No agent (cleansing of the wound after and between treatments with clean water or saline, then non-medicated dressing products; ITT, n=25).	NR	NR	NR
Koullias 2022 (Koullias et al. 2022) Study design: Prospective case series Follow-up: 32 weeks Location: US Setting: Unclear (dressings applied by physicians in unclear settings)	Intervention: Type 1 collagen matrix plus polyhexamethylene biguanide antimicrobial (PCMP) barrier (n=67)	NR	NR	NR
Silver				
Degreef et al 1984 (Degreef and Michiels 1984) Study Design: Prospective case series Follow up: 4 weeks Location: Belgium Setting: Hospital	Intervention: Silver (1% silver sulfadiazine cream applied once a day in a thin layer of 2 to 3 mm and covered by a sterile bandage)	NR	NR	NR
Dimakakos et al 2009 (Dimakakos et al. 2009)	Silver releasing foam dressing (n=21)	NR	NR	NR

Study name and location	Technology name	Frequency of dressing changes across study period	Mean wear time across dressing changes	Prescription of antibiotics
Study design: RCT Follow-up: 9 weeks Location: Greece Setting: NR	No agent (non-adhesive foam dressing (n=21))	NR	NR	NR
Forlee 2014 (Forlee et al. 2014) Study design: Single-arm trial Follow-up: 8 weeks (The wound was swabbed every 7 days) Location: South Africa Setting: Three secondary care centres	Gelling fibre dressing containing silver (DURAFIBER™ Ag) (complete case analysis, n=14)	NR	Mean wear time across dressing changes: 6.4 days Mean wear time for each patient across all assessments where the new dressing was used 6.4 days (median 6.9 days, range 4.7 to 7.0 days)	Patients prescribed antibiotics, n (%): 10/14 (83.3)
Humbert 2006 (Humbert et al. 2006) Study Design: RCT Follow up: 6 weeks Location: France Setting: 17 sites that included dermatology, vascular, angiophlebology and dermatology practices; 85% of silver arm and 72.5% of no agent arm were outpatients.	Intervention: Silver (Biatain AG, n=40)	Frequency of dressing replacements (days, mean SD): 2.7 (1.3) Total n of dressing changes: 206	NR	Antibiotic therapy was not permitted during the trial
	Comparator: No agent (calcium alginate fibre dressing, n=40)	Frequency of dressing replacements (days, mean SD): 2.8 (1.4) Total n of dressing changes: 184	NR	

Study name and location	Technology name	Frequency of dressing changes across study period	Mean wear time across dressing changes	Prescription of antibiotics
Manning 2020 (Manning et al. 2020) Associated Records: Conference abstract: Manning 2019 (Manning et al. 2019) Study Design: Single-arm trial Follow up: 12 weeks Location: USA Setting: Wound care clinic within a secondary care setting	Intervention: Bioabsorbable polymeric matrix containing ionic and metallic silver	NR	NR	NR
Meaume et al, 2005 (Meaume et al. 2005) Study design: RCT Follow-up: 4 weeks Location: UK Setting: 13 hospital centres	Intervention: Silver-releasing hydroalginate dressing (Silvercel) (ITT, n=51)	NR	NR	Use of systemic antibiotics: 5/51 (10.4%), vs comparator p=0.736 PP analysis: 0/40 (0%), vs comparator p=0.053
	Comparator: No agent (pure calcium alginate dressing, Algosteril) (ITT, n=48)			Use of systemic antibiotics: 4/48 (7.8%), vs silver p=0.736 PP analysis: 4/38 (10.5%), vs silver p=0.053

Study name and location	Technology name	Frequency of dressing changes across study period	Mean wear time across dressing changes	Prescription of antibiotics
Melotte 1985 (Melotte et al. 1985) Study design: Prospective case series Follow-up: 6 weeks Location: Belgium Setting: NR	Intervention: 1% silver sulfadiazine cream Comparator: None	NR	NR	NR
Mölnlycke Health Care AB 2014 (NCT01036438) (NCT01036438 2009) Study design: RCT Follow-up: 8 weeks Location: Czech Republic, France, Germany and the Netherlands Setting: Unclear, appears to be hospital	Intervention: Silver (absorbent foam silver dressing, Mepilex Ag, ITT n=100)	NR	NR	NR
	Comparator: No agent (absorbent foam silver dressing, Mepilex without silver, ITT n=101)	NR	NR	NR
Truchetet 2012 (Truchetet et al. 2012) Study design: Prospective case series Follow up: Median 19 days (7 to 97) Location: France Setting: Private outpatient	Intervention: Mepilex Ag (Mölnlycke Health Care)	NR	NR	NR
Woolstencroft 2018 (Woolstencroft 2018)	Intervention: KerraContact TM Ag	Number of dressings worn for 5 to 7 days compared to	Average wear time, days (n=22):	NR

Study name and location	Technology name	Frequency of dressing changes across study period	Mean wear time across dressing changes	Prescription of antibiotics
Study design: Single-arm trial Follow-up: 4 weeks Location: UK Setting: Secondary care (10 tissue viability clinics)	dressing with Ag Oxysalts™ (Silver wound dressing with 2 non-adherent polyethylene mesh contact layers and a polyester core) (n=31)	previous dressings used (n,%): Previous: 5 (31.2) KeeraContact™ AG: 12 (42.8)	19 (range 7 to 28)	
Harding 2016 (Harding et al. 2016) Study design: Prospective single-arm trial Follow-up: 8 weeks Location: UK and Poland Setting: 6 study centres, unclear setting	Intervention: AQUACEL Ag+ hydrofiber dressing Week 1-4, AQUACEL wound dressings Week 5-8 Clinically infected (n=10)	NR	NR	NR
Lantis 2011 (Lantis and Gendics 2011) Study design: Prospective single-arm trial Follow-up: 12 weeks Location: USA Setting: Tertiary care wound practice	Intervention: a non-adhesive silver sulphadiazine, polyurethane foam dressing (Allevyn Ag Non-Adhesive) (n=24)	NR	NR	NR
Vanscheidt 2003 (Vanscheidt et al. 2003)	Intervention: Aquacel Ag	NR	NR	NR

Study name and location	Technology name	Frequency of dressing changes across study period	Mean wear time across dressing changes	Prescription of antibiotics
Study design: Prospective single-arm trial Follow-up: 28 days Location: France and Germany Setting: NR	(n=11 patients with infected wounds)			
Jorgensen 2008 (Jorgensen et al. 2008) Study design: Prospective single-arm trial Follow-up: 31 days (± 2 days) Location: Denmark and Canada Setting: Outpatient clinics at 4 centres	Intervention: Silver and ibuprofen releasing foam dressing (Physiotulle Ag) n=24	NR	NR	NR
Comparative studies of eligible agents				
Gago 2008 (Gago et al. 2008) Study design: Prospective cohort study Follow-up: 8 weeks Location: Spain Setting: Community health centre	Intervention 1: Acticoat™ (n=25)	NR	NR	NR
	Intervention 2: Comfeel™ or Biatain™ Ag (Comfeel n = 9) Biatin n = 16)	NR	NR	NR
	Intervention 3: Aquacel Ag (n=25)	NR	NR	NR
Miller et al 2010 (Miller et al. 2010) Associated records: Trial registration	Intervention: Nanocrystalline silver dressing (complete case analysis, n=133)	NR	NR	NR

Study name and location	Technology name	Frequency of dressing changes across study period	Mean wear time across dressing changes	Prescription of antibiotics
(ACTRN12606000094572 2006) and two papers (Miller et al. 2011a, Miller et al. 2011b) Study design: RCT Follow-up: 12 weeks Location: UK Setting: Community nursing services	Comparator: Cadexomer iodine dressing (complete case analysis, n=133)	NR	NR	NR
Molle 2023 (Molle et al. 2023) Design: Non-randomised clinical trial Follow-up: 30 days Location: NR Setting: NR	Intervention: Manuka honey	NR	NR	NR
	Comparator: Silver dressing	NR	NR	NR
Mosti et al, 2005 (Mosti et al. 2015) Study design: Pilot RCT Follow-up: 4 days Location: UK Setting: Community nursing services	Intervention: Silver (Silver-containing hydrofiber Aquacel Ag)	NR	NR	NR
	Comparator: DACC (microorganism-binding, Cutimed Sorbact)	NR	NR	NR

Key: AMD – Antimicrobial dressing, DACC – Dialkylcarbamoyl chloride, HA – Hyaluronic acid, ITT – Intention-to-treat, NR – Not reported, OHP – Octenidine dihydrochloride/phenoxyethanol, PCMP – Polyhexamethylene biguanide antimicrobial, PHMB – Polyhexamethylene biguanide, PP – Per protocol, RCT – Randomised controlled trial, SD – Standard deviation, UK – United Kingdom, USA – United States of America.

11.7.7 Recurrence of wound or infection

Study name and location	Technology name	Infection recurrence, n (%)	Wound recurrence, n (%)
Chitosan			
Mo 2015 (Mo et al. 2015) Design: RCT Follow-up: 4 weeks Location: China Setting: 3 university hospital centres	Intervention: Chitosan (n=45)	NR	NR
	Comparator: Vaseline gauze (n=45)	NR	NR
Orig et al 2016 (Orig and Singleton 2016) Design: Prospective single-arm trial Follow-up: Mean evaluation time 8.18 days. Location: NR Setting: Acute hospital ward	Intervention: Chitosan (KytoCel dressing). Wear time ranged from 2 to 7 days. Variety of secondary dressings used including super absorbent dressings, surgical pads and foams.	NR	NR
Copper			
Dokic 2023 (Dokic S et al. 2023) Design: Prospective case series Follow-up: 3 months Location: Slovenia Setting: Hospital	Intervention: Copper wound dressings (n=12)	NR	NR
Melamed 2021 (Melamed et al. 2021) Design: Single-arm trial	Intervention: Cupric oxide dressing	NR	NR

Study name and location	Technology name	Infection recurrence, n (%)	Wound recurrence, n (%)
Follow-up: 4 weeks of treatment and 2 weeks of follow up using unspecified “standard of care” dressings. Location: Israel Setting: Outpatient hospital clinic			
Treadwell 2022 (Treadwell T et al. 2022) Design: Prospective case series Follow-up: NR Location: Alabama, USA Setting: Medical centre	Intervention: Cupric oxide wound dressing (n=25)	NR	NR
DACC			
Bruce 2012 (Bruce 2012) Study design: Prospective case series Follow-up: 28 days (or until infection reduced) Location: UK and Ireland Setting: 4 community centres and 2 acute hospitals	Intervention: Cutimed Sorbact Hydroactive dressing (n=13 patients, 14 wounds)	NR	NR
Enzyme Alginogel			
Durante 2012 (Durante 2012) Design: Prospective case series Follow-up: 60 days	Intervention: Enzyme Alginogel (Flaminal - composed of hydrated alginate)	NR	NR

Study name and location	Technology name	Infection recurrence, n (%)	Wound recurrence, n (%)
Location: Italy Setting: Hospital, with continuation in home setting	polymers in a polyethylene glycol matrix embedded with a patented antimicrobial enzymatic complex).		
Jones et al 2018 (Jones and Oates 2018) Design: Prospective case series Follow-up: Unclear Location: UK Setting: Primary care (forms completed by district nurses)	Intervention: Enzyme Alginogel (Flaminal - a hydro-active, broad-spectrum Enzyme Alginogel).	NR	NR
King et al 2023 (King and Rolland 2023) Design: Prospective case series Follow-up: Unclear Location: UK Setting: Primary care (forms completed by district nurses)	Intervention: Enzyme Alginogel (Flaminal - a hydro-active, broad-spectrum Enzyme Alginogel)	NR	NR
Honey			
Biglari et al 2013 (Biglari et al. 2013) Design: Prospective case series Follow-up: 4.88 (SD 4.4) weeks	Intervention: Honey (various Medihoney™ dressing products, n=101)	NR	NR

Study name and location	Technology name	Infection recurrence, n (%)	Wound recurrence, n (%)
Location: 9 sites in Germany and 1 in Austria Setting: Hospital			
Yang et al 2015 (Yang K et al. 2015) Design: Prospective single-arm study Follow-up: 4 weeks Location: USA Setting: Hospital	Intervention: Topical medical grade honey	NR	NR
Moghazy et al 2010 (Moghazy et al. 2010) Design: Prospective single-arm trial Follow-up: 3 months Location: Egypt Setting: Referred to outpatient care from hospital admission	Intervention: Honey (Medium-pored non-sterile gauze saturated with honey, n=30).	NR	Patients with ulcers that closed, resurfaced and reclosed: 1 month: 0/30 (0) 2 months: 4/30 (13.3*) 3 months: 8/30 (26.6*)
Iodine			
Skog 1983 (Skog et al. 1983) Design: RCT Follow-up: 6 weeks Location: Sweden Setting: Mixed; at home (visiting nurse) or hospital clinic	Intervention: Cadexomer iodine (Iodosorb^, Perstorp AB) (n=38)	NR	NR
	Comparator: Standard treatment (n=36)	NR	NR
Octenidine			

Study name and location	Technology name	Infection recurrence, n (%)	Wound recurrence, n (%)
Hammerle and Strohal, 2016 (Hammerle and Strohal 2016) Study design: Non-randomised trial Follow-up: 42 days Location: Austria Setting: Secondary care (single centre)	Intervention: Octenidine + foam or alginate (n=14 patients, 17 venous leg ulcers)	NR	NR
	Comparator: Octenidine gel alone with wound contact layer and suction gauze (n=15 patients, 15 venous leg ulcers)	NR	NR
PHMB			
Vallejo et al 2022 (Vallejo et al. 2022) Associated records: Protocol: Vallejo et al 2021 (Vallejo 2021) Design: RCT Follow-up: 12 weeks Location: Australia Setting: 1 community wound clinic.	Intervention: PHMB (topical PHMB as a soak in plain gauze for 15 minutes after debridement and at each dressing change, and then in a sustained dressing (AMD foam, or gel with PHMB, or Kerlix AMD gauze, H&R Healthcare, UK; ITT, n=25).	NR	NR
	Comparator: No agent (cleansing of the wound after and between treatments with clean water or saline, then non-	NR	NR

Study name and location	Technology name	Infection recurrence, n (%)	Wound recurrence, n (%)
	medicated dressing products; ITT, n=25).		
Koullias 2022 (Koullias et al. 2022) Study design: Prospective case series Follow-up: 32 weeks Location: US Setting: Unclear (dressings applied by physicians in unclear settings)	Intervention: Type 1 collagen matrix plus polyhexamethylene biguanide antimicrobial (PCMP) barrier (n=67)	NR	NR
Silver			
Degreef et al 1984 (Degreef and Michiels 1984) Study Design: Prospective case series Follow up: 4 weeks Location: Belgium Setting: Hospital	Intervention: Silver (1% silver sulfadiazine cream applied once a day in a thin layer of 2 to 3 mm and covered by a sterile bandage) (n=29)	NR	NR
Dimakakos et al 2009 (Dimakakos et al. 2009) Study Design: RCT Follow-up: 9 weeks Location: Greece Setting: NR	Intervention: Silver releasing foam dressing (n=21)	NR	NR
	Comparator: No agent (non-adhesive foam dressing) (n=21)	NR	NR
Forlee 2014 (Forlee et al. 2014) Study design: Single-arm trial	Intervention: Gelling fibre dressing containing silver	NR	NR

Study name and location	Technology name	Infection recurrence, n (%)	Wound recurrence, n (%)
Follow-up: 8 weeks (The wound was swabbed every 7 days) Associated Records: N/A currently Location: South Africa Setting: Three secondary care centres	(DURAFIBER™ Ag) (n=14)		
Humbert 2006 (Humbert et al. 2006)	Intervention: Silver (Biatain AG, n=40)	NR	NR
Study Design: RCT Follow up: 6 weeks Location: France Setting: 17 sites that included dermatology, vascular, angiophlebology and dermatology practices; 85% of silver arm and 72.5% of no agent arm were outpatients.	Comparator: No agent (calcium alginate fibre dressing, n=40)	NR	NR
Manning 2020 (Manning et al. 2020) Associated Records: Conference abstract: Manning 2019 (Manning et al. 2019) Study Design: Single-arm trial Follow up: 12 weeks Location: USA	Intervention: Bioabsorbable polymeric matrix containing ionic and metallic silver	NR	NR

Study name and location	Technology name	Infection recurrence, n (%)	Wound recurrence, n (%)
Setting: Wound care clinic within a secondary care setting			
Meaume et al, 2005 (Meaume et al. 2005) Study design: RCT Follow-up: 4 weeks Location: UK Setting: 13 hospital centres	Intervention: Silver-releasing hydroalginate dressing (Silvercel) (ITT, n=51)	Development of clinical infection (as observed by investigators): 33%, vs comparator p=0.223	NR
	Comparator: No agent (pure calcium alginate dressing, Algosteril) (ITT, n=48)	Development of clinical infection (as observed by investigators): 46%, vs silver p=0.223	NR
Melotte 1985 (Melotte et al. 1985) Study design: Prospective case series Follow-up: 6 weeks Location: Belgium Setting: NR	Intervention: 1% silver sulfadiazine cream	NR	NR
Molnlycke Health Care AB 2014 (NCT01036438) (NCT01036438 2009) Study design: RCT Follow-up: 8 weeks Location: Czech Republic, France, Germany and the Netherlands Setting: Unclear, appears to be hospital	Intervention: Silver (absorbent foam silver dressing, Mepilex Ag, ITT n=100)	NR	NR
	Comparator: No agent (absorbent foam silver dressing, Mepilex without silver, ITT n=101)	NR	NR

Study name and location	Technology name	Infection recurrence, n (%)	Wound recurrence, n (%)
Truchetet 2012 (Truchetet et al. 2012) Study design: Prospective case series Follow up: Median 19 days (7 to 97) Location: France Setting: Private outpatient	Intervention: Mepilex Ag (Mölnlycke Health Care)	NR	NR
Woolstencroft 2018 (Woolstencroft 2018) Study design: Single-arm trial Follow-up: 4 weeks Location: UK Setting: Secondary care (10 tissue viability clinics)	Intervention: KerraContactTM Ag dressing with Ag OxysaltsTM	NR	NR
Harding 2016 (Harding et al. 2016) Study design: Prospective single-arm trial Follow-up: 8 weeks Location: UK and Poland Setting: 6 study centres, unclear setting	Intervention: AQUACEL Ag+ hydrofiber dressing Week 1-4, AQUACEL wound dressings Week 5-8 Clinically infected (n=10)	NR	NR
Lantis 2011 (Lantis and Gendics 2011)	Intervention: a non-adhesive silver sulphadiazine, polyurethane foam dressing (n=24)	NR	Patients with complete healing (n=11) whose ulcers had re-opened by week 12: 5/11

Study name and location	Technology name	Infection recurrence, n (%)	Wound recurrence, n (%)
Study design: Prospective single-arm trial Follow-up: 12 weeks Location: USA Setting: Tertiary care wound practice			
Vanscheidt 2003 (Vanscheidt et al. 2003) Study design: Prospective single-arm trial Follow-up: 28 days Location: France and Germany Setting: NR	Intervention: Aquacel Ag (n=11 patients with infected wounds)	NR	NR
Jorgensen 2008 (Jorgensen et al. 2008) Study design: Prospective single-arm trial Follow-up: 31 days ($\pm$ 2 days) Location: Denmark and Canada Setting: Outpatient clinics at 4 centres	Intervention: Silver and ibuprofen releasing foam dressing (Physiotulle Ag) n=24	NR	NR
Comparative studies of eligible agents			
Gago 2008 (Gago et al. 2008)	Intervention 1: Acticoat™ (n=25)	NR	NR

Study name and location	Technology name	Infection recurrence, n (%)	Wound recurrence, n (%)
Study design: Prospective cohort study Follow-up: 8 weeks Location: Spain Setting: Community health centre	Intervention 2: Comfeel™ or Biatain™ Ag (Comfeel n = 9) Biatin n = 16)	NR	NR
	Intervention 3: Aquacel Ag (n=25)	NR	NR
Miller et al 2010 (Miller et al. 2010) Associated records: Trial registration: (ACTRN12606000094572 2006) and two papers (Miller et al. 2011a, Miller et al. 2011b) Study design: RCT Follow-up: 12 weeks Location: UK Setting: Community nursing services	Intervention: Nanocrystalline silver dressing (complete case analysis, n=133)	NR	NR
	Comparator: Cadexomer iodine dressing (complete case analysis, n=133)	NR	NR
Molle 2023 (Molle et al. 2023) Design: Non-randomised clinical trial Follow-up: 30 days Location: NR Setting: NR	Intervention: Manuka honey	NR	NR
	Comparator: Silver dressing	NR	NR
Mosti et al, 2015 (Mosti et al. 2015) Study design: Pilot RCT	Intervention: Silver (Silver-containing hydrofiber Aquacel Ag)	NR	NR

Study name and location	Technology name	Infection recurrence, n (%)	Wound recurrence, n (%)
Follow-up: 4 days Location: UK Setting: Community nursing services	Comparator: DACC (microorganism-binding, Cutimed Sorbact)	NR	NR

Key: AMD – Antimicrobial dressing, DACC – Dialkylcarbamoyl chloride, HA – Hyaluronic acid, ITT – Intention-to-treat, NR – Not reported, OHP – Octenidine dihydrochloride/phenoxyethanol, PCMP – Polyhexamethylene biguanide antimicrobial, PHMB – Polyhexamethylene biguanide, RCT – Randomised controlled trial, SD – Standard deviation, UK – United Kingdom, USA – United States of America

11.7.8 Pain and discomfort

Study name and location	Technology name	Pain score	Patients reporting being in pain, n (%)	Discomfort, n (%)
Chitosan				
Mo 2015 (Mo et al. 2015) Design: RCT Follow-up: 4 weeks Location: China Setting: 3 university hospital centres	Intervention: Chitosan (n=45)	Pain score (NRS 0 to 11) following dressing removal (mean, SD): Week 0: 4.51 Week 1: 3.35 Week 2: 2.35, vs comparator p=0.05 Week 3: 1.66, vs comparator p=0.05 Week 4: 1.12 (0.2), vs comparator p<0.001	NR	NR
	Comparator: Vaseline gauze (n=45)	Pain score (NRS 0 to 11) following dressing removal (mean, SD): Week 0: 4.53 Week 1: 3.63 Week 2: 2.93, vs chitosan p=0.05 Week 3: 2.33, vs chitosan p=0.05 Week 4: 2.30 (0.23), vs chitosan p<0.001	NR	NR
Orig et al 2016 (Orig and Singleton 2016) Design: Prospective single-arm trial Follow-up: Mean evaluation time 8.18 days.	Intervention: Chitosan (KytoCel dressing). Wear time ranged from 2 to 7 days. Variety of secondary dressings used including super absorbent dressings,	NR	NR	NR

Study name and location	Technology name	Pain score	Patients reporting being in pain, n (%)	Discomfort, n (%)
Location: NR Setting: Acute hospital ward	surgical pads and foams.			
Copper				
Dokic 2023 (Dokic S et al. 2023) Design: Prospective case series Follow-up: 3 months Location: Slovenia Setting: Hospital	Intervention: Copper wound dressings (n=12)	NR	Patients did not report pain during installation and changing of dressing.	NR
Melamed 2021 (Melamed et al. 2021) Design: Single-arm trial Follow-up: 4 weeks of treatment and 2 weeks of follow up using unspecified "standard of care" dressings. Location: Israel Setting: Outpatient hospital clinic	Intervention: Cupric oxide dressing	NR	No pain reported	No discomfort reported
Treadwell 2022 (Treadwell T et al. 2022) Design: Prospective case series	Intervention: Cupric oxide wound dressing (n=25)	NR	NR	NR

Study name and location	Technology name	Pain score	Patients reporting being in pain, n (%)	Discomfort, n (%)
Follow-up: NR Location: Alabama, USA Setting: Medical centre				
DACC				
Bruce 2012 (Bruce 2012) Study design: Prospective case series Follow-up: 28 days (or until infection reduced) Location: UK and Ireland Setting: 4 community centres and 2 acute hospitals	Intervention: Cutimed Sorbact Hydroactive dressing (n=13 patients, 14 wounds)	NR	Patients reporting pain: Baseline: 11/13 (85*) Day 28 (among patients with pain at baseline, n=11): 2/11 (18)	Patient-rated comfort of dressing under compression, score of 1 to 10 with 1 being not satisfied with comfort (mean): 9 (range 6 to 10)
Enzyme Alginogel				
Durante 2012 (Durante 2012) Design: Prospective case series Follow-up: 60 days Location: Italy Setting: Hospital, with continuation in home setting	Intervention: Enzyme Alginogel (Flaminal - composed of hydrated alginate polymers in a polyethylene glycol matrix embedded with a patented antimicrobial	VAS pain score (0 to 10; scores taken during dressing application at each timepoint), mean (SD): Baseline (n=23): 1.0 (1.9) Day 14 (n=22): 0.9 (1.7) Day 30 (n=21): 0.6 (1.02) Day 60 (n=13): 0.2 (0.6)	NR	NR

Study name and location	Technology name	Pain score	Patients reporting being in pain, n (%)	Discomfort, n (%)
	enzymatic complex) (n=23)			
Jones et al 2018 (Jones and Oates 2018) Design: Prospective case series Follow-up: Unclear Location: UK Setting: Primary care (forms completed by district nurses)	Intervention: Enzyme Alginogel (Flaminal - a hydro-active, broad-spectrum Enzyme Alginogel, n=344).	NR	Patient-reported change in pain (n=344 respondents): Improvement: 170/344 (49.42) No change or worsening: 174/344 (50.58%) Difference between observed value and the expected value of 50%: p=0.4358 (95% CI 44.17 to 54.68)	NR
King et al 2023 (King and Rolland 2023) Design: Prospective case series Follow-up: Unclear Location: UK Setting: Primary care (forms completed by district nurses)	Intervention: Enzyme Alginogel (Flaminal - a hydro-active, broad-spectrum Enzyme Alginogel n=1571)	NR	Patient-reported change in pain (n=1571 respondents): Improvement: 830/1571 (52.8) No change or worsening: 741/1571 (47.2) Difference between observed value and the expected value of 50%: p=0.4149 (95% CI 49.41 to 56.22)	NR
Honey				
Biglari et al 2013 (Biglari et al. 2013) Design: Prospective case series	Intervention: Honey (various Medihoney™ dressing products, n=102)	Pain score (adults graded 0 (no pain) to 10 (excruciating pain, paediatric patients used VAS 0 to 10), mean (SD): Baseline: 1.71 (1.89)	Patients reporting pain compared to baseline at study end (mean 4.88 weeks, SD 4.4, n %):	NR

Study name and location	Technology name	Pain score	Patients reporting being in pain, n (%)	Discomfort, n (%)
Follow-up: 4.88 (SD 4.4) weeks Location: 9 sites in Germany and 1 in Austria Setting: Hospital		Study end (mean 4.88, SD 4.4 weeks): 0.55 (1.22) Difference at study end vs baseline: p<0.05	Improved (decrease in initial pain levels): 54/102 (55) ³ No change in pain: 6/102 (5.8*) No wound pain at start of study: 42/102 (43)	
Yang et al 2015 (Yang K et al. 2015) Design: Prospective single-arm study Follow-up: 4 weeks Location: USA Setting: Hospital	Intervention: Topical medical grade honey	NR	NR	NR
Moghazy et al 2010 (Moghazy et al. 2010) Design: Prospective single-arm trial Follow-up: 3 months Location: Egypt Setting: Referred to outpatient care from hospital admission	Intervention: Honey (Medium-pored non-sterile gauze saturated with honey).	NR	NR	NR
Iodine				
Skog 1983 (Skog et al. 1983) Design: RCT	Intervention: Cadexomer iodine (Iodosorb^, Perstorp AB)	Pain VAS scale, mean (SEM): Pre-treatment: 32 (4.7) Week 1: 27 (4.6), vs baseline p<0.005	NR	NR

³ Percentages reported in text do not align with numbers data tables; these have been extracted as-reported.

Study name and location	Technology name	Pain score	Patients reporting being in pain, n (%)	Discomfort, n (%)
Follow-up: 6 weeks Location: Sweden Setting: Mixed; at home (visiting nurse) or hospital clinic	(n=38)	Week 6: 10 (2.5), vs baseline p<0.005; vs no agent p<0.01		
	Comparator: Standard treatment (n=36)	Pain VAS scale, mean (SE): Pre-treatment: 33 (4.3) Week 1: 29 (4.1) vs baseline p=not significant Week 6: 23 (3.7), vs baseline p<0.05; vs iodine p<0.01	NR	NR
Octenidine				
Hammerle and Strohal, 2016 (Hammerle and Strohal 2016)	Intervention: Octenidine + foam or alginate (n=14 patients, 17 venous leg ulcers)	NR	NR	NR
Study design: Non-randomised trial Follow-up: 42 days Location: Austria Setting: Secondary care (single centre)	Comparator: Octenidine gel alone with wound contact layer and suction gauze (n=15 patients, 15 venous leg ulcers)	NR	NR	NR
PHMB				
Vallejo et al 2022 (Vallejo et al. 2022) Associated records: Protocol: Vallejo et al 2021 (Vallejo 2021) Design: RCT Follow-up: 12 weeks	Intervention: PHMB (topical PHMB as a soak in plain gauze for 15 minutes after debridement and at each dressing change, and then in a sustained dressing (AMD foam, or gel with PHMB, or Kerlix	Pain score (NRS 0 to 10, median, IQR): Baseline: 1 (3) Week 1: 1 (3) Week 6: 0 (0), difference vs no agent p=0.04 Week 12: 0 (0), difference vs no agent p=0.54	NR	NR

Study name and location	Technology name	Pain score	Patients reporting being in pain, n (%)	Discomfort, n (%)
Location: Australia Setting: 1 community wound clinic.	AMD gauze, H&R Healthcare, UK; ITT, n=25).			
	Comparator: No agent (cleansing of the wound after and between treatments with clean water or saline, then non-medicated dressing products; ITT, n=25).	Pain score (NRS 0 to 10, median, IQR): Baseline: 0 (3) Week 1: 0 (3) Week 6: 0 (2), difference vs PHMB p=0.04 Week 12: 0 (0), difference vs PHMB p=0.54	NR	NR
Koullias 2022 (Koullias et al. 2022) Study design: Prospective case series Follow-up: 32 weeks Location: US Setting: Unclear (dressings applied by physicians in unclear settings)	Intervention: Type 1 collagen matrix plus polyhexamethylene biguanide antimicrobial (PCMP) barrier (n=67)	NR	NR	NR
Silver				
Degreef et al 1984 (Degreef and Michiels 1984) Study Design: Prospective case series Follow up: 4 weeks Location: Belgium	Intervention: Silver (1% silver sulfadiazine cream applied once a day in a thin layer of 2 to 3 mm and covered by a sterile bandage)	NR	NR	NR

Study name and location	Technology name	Pain score	Patients reporting being in pain, n (%)	Discomfort, n (%)
Setting: Hospital				
Dimakakos et al 2009 (Dimakakos et al. 2009) Study Design: RCT Follow-up: 9 weeks Location: Greece Setting: NR	Intervention: Silver releasing foam dressing (n=21)	N patients by VAS pain score category (0 to 10), n (%): <u>Baseline:</u> Mild: 5 Moderate: 11 Severe: 5 <u>Week 3:</u> Mild: 15 Moderate: 3 Severe: 3 <u>Week 8:</u> Mild: 21 (all pain-free) Moderate: 0 Severe: 0 Pain intensity was significantly less in patients vs. comparator at several time points (no p-value reported).	Patients reported as pain-free at end of trial (or at week at which 100% were pain-free): Week 8: 21/21 (100) Subgroup, patients with severe or moderate pain at baseline: Week 3: 10*/16 (63%*)	NR
	Comparator: No agent (non-adhesive foam dressing) (n=21)	N patients by VAS pain score category (0 to 10), n (%): <u>Baseline:</u> Mild: 8 Moderate: 8 Severe: 5 <u>Week 4:</u> Mild: 12 Moderate: 5 Severe: 4	Patients reported as pain-free at end of trial (or at week at which 100% were pain-free): Week 9: 13/21 (62) Subgroup, patients with severe or moderate pain at baseline: Week 4: 4/13 (31%*)	NR

Study name and location	Technology name	Pain score	Patients reporting being in pain, n (%)	Discomfort, n (%)
		Week 9: Mild: 17 (13 pain free) Moderate: 4 Severe: 0		
Forlee 2014 (Forlee et al. 2014) Study design: Single-arm trial Follow-up: 8 weeks (The wound was swabbed every 7 days) Location: South Africa Setting: Three secondary care centres	Intervention: Gelling fibre dressing containing silver (DURAFIBER™ Ag) (n=14)	NR	Patients reporting increased wound pain: Baseline: 5 (35.7) Week 8: 0 (0)	NR
Humbert 2006 (Humbert et al. 2006) Study Design: RCT Follow up: 6 weeks Location: France Setting: 17 sites that included dermatology, vascular, angiophlebology and dermatology practices; 85% of silver arm and 72.5%	Intervention: Silver (Biatain AG, n=40)	Difference in VAS pain score (timepoint unclear, presumably 6 weeks; raw score not reported): Significantly lower in silver arm, p=0.003	NR	Patient comfort with dressing in place after dressing changes: Excellent: 103 (52.0) Good: 67 (33.8) Medium: 25 (12.6) Mild: 3 (1.5) Very low: 0 (0.0) Proportion of dressing changes rated “excellent” or “good”: 86.8%, vs no agent p<0.001
	Comparator: No agent (calcium	Difference in VAS pain score (timepoint unclear,	NR	Patient comfort with dressing in place after dressing changes: Excellent: 56 (31.1)

Study name and location	Technology name	Pain score	Patients reporting being in pain, n (%)	Discomfort, n (%)
of no agent arm were outpatients.	alginate fibre dressing, n=40)	presumably 6 weeks; raw score not reported): Significantly lower in silver arm, p=0.003		Good: 71 (39.4) Medium: 40 (22.2) Mild: 10 (5.6) Very low: 3 (1.7) Proportion of dressing changes rated “excellent” or “good”: 70.5%, vs silver p<0.001
Manning 2020 (Manning et al. 2020) Associated Records: Conference abstract: Manning 2019 (Manning et al. 2019) Study Design: Single-arm trial Follow up: 12 weeks Location: USA Setting: Wound care clinic within a secondary care setting	Intervention: Bioabsorbable polymeric matrix containing ionic and metallic silver	NR	NR	NR
Meaume et al, 2005 (Meaume et al. 2005) Study design: RCT Follow-up: 4 weeks Location: UK Setting: 13 hospital centres	Intervention: Silver-releasing hydroalginate dressing (Silvercel) (ITT, n=51)	NR	NR	NR
	Comparator: No agent (pure calcium alginate dressing,	NR	NR	NR

Study name and location	Technology name	Pain score	Patients reporting being in pain, n (%)	Discomfort, n (%)
	Algosteril) (ITT, n=48)			
Melotte 1985 (Melotte et al. 1985) Study design: Prospective case series Follow-up: 6 weeks Location: Belgium Setting: NR	Intervention: 1% silver sulfadiazine cream Comparator: None	NR	NR	NR
Mölnlycke Health Care AB 2014 (NCT01036438) (NCT01036438 2009) Study design: RCT Follow-up: 8 weeks Location: Czech Republic, France, Germany and the Netherlands Setting: Unclear, appears to be hospital	Intervention: Silver (absorbent foam silver dressing, Mepilex Ag, ITT n=100) Comparator: No agent (absorbent foam silver dressing, Mepilex without silver, ITT n=101)	NR	NR	NR
Truchetet 2012 (Truchetet et al. 2012) Study design: Prospective case series	Intervention: Mepilex Ag (Mölnlycke Health Care) (n=794)	All wound pain intensity at baseline (VAS 0 to 100), mean (SD): 50 (24) All wound pain intensity at follow up (VAS 0 to 100), mean (SD): 24.6 (20.9)	NR	NR

Study name and location	Technology name	Pain score	Patients reporting being in pain, n (%)	Discomfort, n (%)
Follow up: Median 19 days (7 to 97) Location: France Setting: Private outpatient				
Woolstencroft 2018 (Woolstencroft 2018) Study design: Single-arm trial Follow-up: 4 weeks Location: UK Setting: Secondary care (10 tissue viability clinics)	Intervention: KerraContact™ Ag dressing with Ag Oxysalts™ (n=31)	Patients (n=25 with data pertaining to pain) reporting significant or complete reduction in pain (n %): 13 (52%)	NR	Patients reporting greater comfort with KerraContact™ dressing previous dressing: 17 (56%)
Harding 2016 (Harding et al. 2016) Study design: Prospective single-arm trial Follow-up: 8 weeks Location: UK and Poland Setting: 6 study centres, unclear setting	Intervention: AQUACEL Ag+ hydrofiber dressing Week 1-4, AQUACEL wound dressings Week 5-8 Clinically infected (n=10)	NR	NR	NR

Study name and location	Technology name	Pain score	Patients reporting being in pain, n (%)	Discomfort, n (%)
Lantis 2011 (Lantis and Gendics 2011) Study design: Prospective single-arm trial Follow-up: 12 weeks Location: USA Setting: Tertiary care wound practice	Intervention: a non-adhesive silver sulphadiazine, polyurethane foam dressing (Allevyn Ag Non-Adhesive) (n=24)	NR	Patients reporting spontaneous pain between dressing changes: Baseline (Week 0): 20 (83.3) Week 2: 17 (70.8) Week 4 (n=23): 11 (47.8) Week 8 (n=23): 7 (30.4) Treatment Discontinuation: 9 (37.5) Patients reporting moderate pain from the ulcer during the preceding week at baseline: <u>Baseline</u> No pain: NR Mild pain: NR Moderate pain: 14 (58.3) <u>12 weeks</u> No pain: 8 (33.3) Minimal pain: 4 (16.7) Moderate pain: 2 (8.3)	NR
Vanscheidt 2003 (Vanscheidt et al. 2003) Study design: Prospective single-arm trial	Intervention: Aquacel Ag (n=11 patients with infected wounds)	NR	NR	NR

Study name and location	Technology name	Pain score	Patients reporting being in pain, n (%)	Discomfort, n (%)
Follow-up: 28 days Location: France and Germany Setting: NR				
Jorgensen 2008 (Jorgensen et al. 2008) Study design: Prospective single-arm trial Follow-up: 31 days (± 2 days) Location: Denmark and Canada Setting: Outpatient clinics at 4 centres	Intervention: Silver and ibuprofen releasing foam dressing (Physiotulle Ag) n=24	Persistent wound pain (11-point NBS), mean (SD): Baseline: 6.3 (2.2) 12 hours after the first dressing application: 3.0 (1.7) Pain after dressing removal (11-point NBS), mean (SD): Day 3: 2.4 (2.2) Day 31: 1.1 (2.1)	NR	NR
Comparative studies of eligible agents				
Gago 2008 (Gago et al. 2008) Study design: Prospective cohort study Follow-up: 8 weeks Location: Spain Setting: Community health centre	Intervention 1: Acticoat™ (n=25)	NR	NR	NR
	Intervention 2: Comfeel™ or Biatain™ Ag (Comfeel n = 9) Biatin n = 16)	NR	NR	NR
	Intervention 3: Aquacel Ag (n=25)	NR	NR	NR
Miller et al 2010 (Miller et al. 2010)	Intervention: Nanocrystalline silver dressing (complete	NR	NR	NR

Study name and location	Technology name	Pain score	Patients reporting being in pain, n (%)	Discomfort, n (%)
Associated records: Trial registration: (ACTRN1260600009 4572 2006) and two papers (Miller et al. 2011a, Miller et al. 2011b) Study design: RCT Follow-up: 12 weeks Location: UK Setting: Community nursing services	case analysis, n=133)			
	Comparator: Cadexomer iodine dressing (complete case analysis, n=133)	NR	NR	NR
Molle 2023 (Molle et al. 2023) Design: Non-randomised clinical trial Follow-up: 30 days Location: NR Setting: NR	Intervention: Manuka honey	NR	NR	NR
	Comparator: Silver dressing	NR	NR	NR
Mosti et al, 2015 (Mosti et al. 2015) Study design: Pilot RCT Follow-up: 4 days Location: UK Setting: Community nursing services	Intervention: Silver (Silver-containing hydrofiber Aquacel Ag) (n=20)	Average VAS Pain score (1 to 10) Baseline: 4.65 Day 4: 2.5 Change from baseline: -35%, vs DACC p=0.89	NR	NR
	Comparator: DACC (microorganism-binding, Cutimed Sorbact) (n=20)	Average VAS Pain score (1 to 10) Baseline: 4.75 Day 4: 2.4	NR	NR

Study name and location	Technology name	Pain score	Patients reporting being in pain, n (%)	Discomfort, n (%)
		Change from baseline: -38%, vs silver, p=0.89		

Key: AMD – Antimicrobial dressing, ANOVA – Analysis of variance, CI – Confidence interval, DACC – Dialkylcarbamoyl chloride, HA – Hyaluronic acid, IQR – Interquartile range, ITT – Intention-to-treat, NBS – Numerical box scale, NR – Not reported, OHP – Octenidine dihydrochloride/phenoxyethanol, PCMP – Polyhexamethylene biguanide antimicrobial, PHMB – Polyhexamethylene biguanide, RCT – Randomised controlled trial, SD – Standard deviation, SE – standard error, UK – United Kingdom, USA – United States of America, VAS – Visual analogue scale

11.7.9 Health-Related Quality of Life

Study name and location	Technology name	Health-related quality of life score	Functional status, n (%)
Chitosan			
Mo 2015 (Mo et al. 2015)	Intervention: Chitosan (n=45)	NR	NR
Design: RCT Follow-up: 4 weeks Location: China Setting: 3 university hospital centres	Comparator: Vaseline gauze (n=45)	NR	NR
Orig et al 2016 (Orig and Singleton 2016)	Intervention: Chitosan (KytoCel dressing).	NR	NR
Design: Prospective single-arm trial Follow-up: Mean evaluation time 8.18 days. Location: NR Setting: Acute hospital ward			
Copper			
Dokic 2023 (Dokic S et al. 2023)	Intervention: Copper wound dressings (n=12)	NR	NR
Design: Prospective case series Follow-up: 3 months Location: Slovenia Setting: Hospital			
Melamed 2021	Intervention: Cupric oxide dressing	NR	NR

Study name and location	Technology name	Health-related quality of life score	Functional status, n (%)
(Melamed et al. 2021) Design: Single-arm trial Follow-up: 4 weeks of treatment and 2 weeks of follow up using unspecified "standard of care" dressings. Location: Israel Setting: Outpatient hospital clinic			
Treadwell 2022 (Treadwell T et al. 2022) Design: Prospective case series Follow-up: NR Location: Alabama, USA Setting: Medical centre	Intervention: Cupric oxide wound dressing (n=25)	NR	NR
DACC			
Bruce 2012 (Bruce 2012) Study design: Prospective case series	Intervention: Cutimed Sorbact Hydroactive dressing (n=13 patients, 14 wounds)	NR	NR

Study name and location	Technology name	Health-related quality of life score	Functional status, n (%)
Follow-up: 28 days (or until infection reduced) Location: UK and Ireland Setting: 4 community centres and 2 acute hospitals			
Enzyme Alginogel			
Durante 2012 (Durante 2012) Design: Prospective case series Follow-up: 60 days Location: Italy Setting: Hospital, with continuation in home setting	Intervention: Enzyme Alginogel (Flaminal - composed of hydrated alginate polymers in a polyethylene glycol matrix embedded with a patented antimicrobial enzymatic complex).	NR	NR
Jones et al 2018 (Jones and Oates 2018) Design: Prospective case series Follow-up: Unclear Location: UK Setting: Primary care (forms completed by district nurses).	Intervention: Enzyme Alginogel (Flaminal - a hydro-active, broad-spectrum Enzyme Alginogel,).	NR	NR

Study name and location	Technology name	Health-related quality of life score	Functional status, n (%)
King et al 2023 (King and Rolland 2023) Design: Prospective case series Follow-up: Unclear Location: UK Setting: Primary care (forms completed by district nurses)	Intervention: Enzyme Alginogel (Flaminal - a hydro-active, broad-spectrum Enzyme Alginogel)	NR	NR
Honey			
Biglari et al 2013 (Biglari et al. 2013) Design: Prospective case series Follow-up: 4.88 (SD 4.4) weeks Location: 9 sites in Germany and 1 in Austria Setting: Hospital	Intervention: Honey (various Medihoney™ dressing products)	NR	NR
Yang et al 2015 (Yang K et al. 2015) Design: Prospective single-arm study Follow-up: 4 weeks Location: USA Setting: Hospital	Intervention: Topical medical grade honey	NR	NR

Study name and location	Technology name	Health-related quality of life score	Functional status, n (%)
Moghazy et al 2010 (Moghazy et al. 2010) Design: Prospective single-arm trial Follow-up: 3 months Location: Egypt Setting: Referred to outpatient care from hospital admission	Intervention: Honey (Medium-pored non-sterile gauze saturated with honey, n=30).	NR	NR
Iodine			
Skog 1983 (Skog et al. 1983) Design: RCT Follow-up: 6 weeks Location: Sweden Setting: Mixed; at home (visiting nurse) or hospital clinic	Intervention: Cadexomer iodine (Iodosorb^, Perstorp AB) (n=38)	NR	NR
	Comparator: Standard treatment (n=36)	NR	NR
Octenidine			
Hammerle and Strohal, 2016 (Hammerle and Strohal 2016) Study design: Non-randomised trial Follow-up: 42 days Location: Austria Setting: Secondary care (single centre)	Intervention: Octenidine + foam or alginate (n=14 patients, 17 venous leg ulcers)	NR	NR
	Comparator: Octenidine gel alone with wound contact layer and suction gauze (n=15 patients, 15 venous leg ulcers)	NR	NR

Study name and location	Technology name	Health-related quality of life score	Functional status, n (%)
PHMB			
Vallejo et al 2022 (Vallejo et al. 2022) Associated records: Protocol: Vallejo et al 2021 (Vallejo 2021) Design: RCT Follow-up: 12 weeks Location: Australia Setting: 1 community wound clinic	Intervention: PHMB (topical PHMB as a soak in plain gauze for 15 minutes after debridement and at each dressing change, and then in a sustained dressing (AMD foam, or gel with PHMB, or Kerlix AMD gauze, H&R Healthcare, UK; ITT, n=25).	Total wound-related quality of life score, mean, SD: Week 1: 1.8 (0.8) Week 12: 0.87 (0.5), vs no agent p=0.15	NR
	Comparator: No agent (cleansing of the wound after and between treatments with clean water or saline, then non-medicated dressing products; ITT, n=25).	Total wound-related quality of life score, mean, SD: Baseline: 1.8 (1.0) Week 12: 1.1 (0.6), vs PHMB p=0.15	NR
Koullias 2022 (Koullias et al. 2022) Study design: Prospective case series Follow-up: 32 weeks Location: US Setting: Unclear (dressings applied by physicians in unclear settings)	Intervention: Type 1 collagen matrix plus polyhexamethylene biguanide antimicrobial (PCMP) barrier (n=67)	NR	NR
Silver			

Study name and location	Technology name	Health-related quality of life score	Functional status, n (%)
Degreef et al 1984 (Degreef and Michiels 1984) Study Design: Prospective case series Follow up: 4 weeks Location: Belgium Setting: Hospital	Intervention: Silver (1% silver sulfadiazine cream applied once a day in a thin layer of 2 to 3 mm and covered by a sterile bandage)	NR	NR
Dimakakos et al 2009 (Dimakakos et al. 2009) Study Design: RCT Follow-up: 9 weeks Location: Greece Setting: NR	Intervention: Silver releasing foam dressing (n=21)	NR	NR
	Comparator: No agent (non-adhesive foam dressing) (n=21)	NR	NR
Forlee 2014 (Forlee et al. 2014) Study design: Single-arm trial Follow-up: 8 weeks (The wound was swabbed every 7 days) Location: South Africa Setting: Three secondary care centres	Intervention: Gelling fibre dressing containing silver (DURAFIBER™ Ag) (n=14)	NR	NR

Study name and location	Technology name	Health-related quality of life score	Functional status, n (%)
Humbert 2006 (Humbert et al. 2006)	Intervention: Silver (Biatain AG, n=40)	NR	NR
Study Design: RCT Follow up: 6 weeks Location: France Setting: 17 sites that included dermatology, vascular, angiophlebology and dermatology practices; 85% of silver arm and 72.5% of no agent arm were outpatients.	Comparator: No agent (calcium alginate fibre dressing, n=40)	NR	NR
Manning 2020 (Manning et al. 2020) Associated Records: Conference abstract: Manning 2019 (Manning et al. 2019) Study Design: Single-arm trial Follow up: 12 weeks Location: USA Setting: Wound care clinic within a secondary care setting	Intervention: Bioabsorbable polymeric matrix containing ionic and metallic silver	NR	NR

Study name and location	Technology name	Health-related quality of life score	Functional status, n (%)
Meaume et al, 2005 (Meaume et al. 2005) Study design: RCT Follow-up: 4 weeks Location: UK Setting: 13 hospital centres	Intervention: Silver-releasing hydroalginate dressing (Silvercel) (ITT, n=51)	NR	NR
	Comparator: No agent (pure calcium alginate dressing, Algosteril) (ITT, n=48)	NR	NR
Melotte 1985 (Melotte et al. 1985) Study design: Prospective case series Follow-up: 6 weeks Location: Belgium Setting: NR	Intervention: 1% silver sulfadiazine cream Comparator: None	NR	NR
Molnlycke Health Care AB 2014 (NCT01036438) (NCT01036438 2009) Study design: RCT Follow-up: 8 weeks Location: Czech Republic, France, Germany and the Netherlands Setting: Unclear, appears to be hospital	Intervention: Silver (absorbent foam silver dressing, Mepilex Ag, ITT n=100)	NR	NR
	Comparator: No agent (absorbent foam silver dressing, Mepilex without silver, ITT n=101)	NR	NR

Study name and location	Technology name	Health-related quality of life score	Functional status, n (%)
Truchetet 2012 (Truchetet et al. 2012) Study design: Prospective case series Follow up: Median 19 days (7 to 97) Location: France Setting: Private outpatient	Intervention: Mepilex Ag (Mölnlycke Health Care)	NR	NR
Woolstencroft 2018 (Woolstencroft 2018) Study design: Single-arm trial Follow-up: 4 weeks Location: UK Setting: Secondary care (10 tissue viability clinics)	Intervention: KerraContactTM Ag dressing with Ag OxysaltsTM (Silver wound dressing with 2 non-adherent polyethene mesh contact layers and a polyester core)	NR	NR
Harding 2016 (Harding et al. 2016) Study design: Prospective single-arm trial Follow-up: 8 weeks Location: UK and Poland	Intervention: AQUACEL Ag+ hydrofiber dressing Week 1-4, AQUACEL wound dressings Week 5-8 Clinically infected (n=10)	NR	NR

Study name and location	Technology name	Health-related quality of life score	Functional status, n (%)
Setting: 6 study centres, unclear setting			
Lantis 2011 (Lantis and Gendics 2011) Study design: Prospective single-arm trial Follow-up: 12 weeks Location: USA Setting: Tertiary care wound practice	Intervention: a non-adhesive silver sulphadiazine, polyurethane foam dressing (Allevyn Ag Non-Adhesive) (n=24)	NR	NR
Vanscheidt 2003 (Vanscheidt et al. 2003) Study design: Prospective single-arm trial Follow-up: 28 days Location: France and Germany Setting: NR	Intervention: Aquacel Ag (n=11 patients with infected wounds)	NR	NR
Jorgensen 2008 (Jorgensen et al. 2008) Study design: Prospective single-arm trial	Intervention: Silver and ibuprofen releasing foam dressing (Physiotulle Ag) n=24	NR	NR

Study name and location	Technology name	Health-related quality of life score	Functional status, n (%)
Follow-up: 31 days (± 2 days) Location: Denmark and Canada Setting: Outpatient clinics at 4 centres			
Comparative studies of eligible agents			
Study design: Prospective cohort study Follow-up: 8 weeks Location: Spain Setting: Community health centre	Intervention 1: Acticoat™ (n=25)	NR	NR
	Intervention 2: Comfeel™ or Biatain™ Ag (Comfeel n = 9) Biatin n = 16)	NR	NR
	Intervention 3: Aquacel Ag (n=25)	NR	NR
Miller et al 2010 (Miller et al. 2010) Associated records: Trial registration: (ACTRN12606000094572 2006) and two papers (Miller et al. 2011a, Miller et al. 2011b) Study design: RCT Follow-up: 12 weeks Location: UK	Intervention: Nanocrystalline silver dressing (complete case analysis, n=133)	NR	NR
	Comparator: Cadexomer iodine dressing (complete case analysis, n=133)	NR	NR

Study name and location	Technology name	Health-related quality of life score	Functional status, n (%)
Setting: Community nursing services			
Molle 2023 (Molle et al. 2023) Design: Non-randomised clinical trial Follow-up: 30 days Location: NR Setting: NR	Intervention: Manuka honey	NR	NR
	Comparator: Silver dressing	NR	NR
Mosti et al, 2015 (Mosti et al. 2015) Study design: Pilot RCT Follow-up: 4 days Location: UK Setting: Community nursing services	Intervention: Silver (Silver-containing hydrofiber Aquacel Ag)	NR	NR
	Comparator: DACC (microorganism-binding, Cutimed Sorbact)	NR	NR

Key: AMD – Antimicrobial dressing, DACC – Dialkylcarbamoyl chloride, EQ-5D – EuroQol-5 dimension, HA – Hyaluronic acid, ITT – Intention-to-treat, NR – Not reported, OHP – Octenidine dihydrochloride/phenoxyethanol, PCMP – Polyhexamethylene biguanide antimicrobial, PHMB – Polyhexamethylene biguanide, RCT – Randomised controlled trial, SD – Standard deviation, UK – United Kingdom, USA – United States of America, VAS – Visual analogue scale.

11.7.10 Overall treatment-related adverse events

Study name and location	Technology name	Overall treatment-related adverse events, n (%) type	Overall serious treatment-related adverse events
Chitosan			
Mo 2015 (Mo et al. 2015)	Intervention: Chitosan (n=45)	No AEs reported to have occurred	No AEs reported to have occurred
Design: RCT Follow-up: 4 weeks Location: China Setting: 3 university hospital centres	Comparator: Vaseline gauze (n=45)	No AEs reported to have occurred	No AEs reported to have occurred
Orig et al 2016 (Orig and Singleton 2016) Design: Prospective single-arm trial Follow-up: Mean evaluation time 8.18 days. Location: NR Setting: Acute hospital ward	Intervention: Chitosan (KytoCel dressing).	NR	NR
Copper			
Dokic 2023 (Dokic S et al. 2023) Design: Prospective case series Follow-up: 3 months Location: Slovenia Setting: Hospital	Intervention: Copper wound dressings (n=12)	NR	NR
Melamed 2021 (Melamed et al. 2021)	Intervention: Cupric oxide dressing (n=13)	No AEs reported by patients	No SAEs reported by patients

Study name and location	Technology name	Overall treatment-related adverse events, n (%) type	Overall serious treatment-related adverse events
Design: Single-arm trial Follow-up: 4 weeks of treatment and 2 weeks of follow up using unspecified “standard of care” dressings. Location: Israel Setting: Outpatient hospital clinic			
Dokic 2023 (Dokic S et al. 2023) Design: Prospective case series Follow-up: 3 months Location: Slovenia Setting: Hospital	Intervention: Copper wound dressings (n=12)	NR	NR
DACC			
Bruce 2012 (Bruce 2012) Study design: Prospective case series Follow-up: 28 days (or until infection reduced) Location: UK and Ireland Setting: 4 community centres and 2 acute hospitals	Intervention: Cutimed Sorbact Hydroactive dressing (n=13 patients, 14 wounds)	NR	NR
Enzyme Alginogel			

Study name and location	Technology name	Overall treatment-related adverse events, n (%) type	Overall serious treatment-related adverse events
Durante 2012 (Durante 2012) Design: Prospective case series Follow-up: 60 days Location: Italy Setting: Hospital, with continuation in home setting	Intervention: Enzyme Alginogel (Flaminal gel) (n=23).	Overall adverse events: 2/23 (8.6*); 1 allergic reaction and 1 transient maceration	NR
Jones et al 2018 (Jones and Oates 2018) Design: Prospective case series Follow-up: Unclear Location: UK Setting: Primary care (forms completed by district nurses).	Intervention: Enzyme Alginogel (Flaminal - a hydro-active, broad-spectrum Enzyme Alginogel,).	NR	NR
King et al 2023 (King and Rolland 2023) Design: Prospective case series Follow-up: Unclear Location: UK Setting: Primary care (forms completed by district nurses)	Intervention: Enzyme Alginogel (Flaminal - a hydro-active, broad-spectrum Enzyme Alginogel).	NR	NR
Honey			
Biglari et al 2013 (Biglari et al. 2013)	Intervention: Honey (various Medihoney™)	Patients who experienced poor tolerance to dressing including skin reaction and pain (%):	NR

Study name and location	Technology name	Overall treatment-related adverse events, n (%) type	Overall serious treatment-related adverse events
Design: Prospective case series Follow-up: 4.88 (SD 4.4) weeks Location: 9 sites in Germany and 1 in Austria Setting: Hospital	dressing products, n=121 patients with 154 wounds)	1.3	
Yang et al 2015 (Yang K et al. 2015) Design: Prospective single-arm study Follow-up: 4 weeks Location: USA Setting: Hospital	Intervention: Topical medical grade honey	NR	NR
Moghazy et al 2010 (Moghazy et al. 2010) Design: Prospective single-arm trial Follow-up: 3 months Location: Egypt Setting: Referred to outpatient care from hospital admission	Intervention: Honey (Medium-pored non-sterile gauze saturated with honey).	NR	NR
Iodine			
Skog 1983 (Skog et al. 1983) Design: RCT Follow-up: 6 weeks	Intervention: Cadexomer iodine (Iodosorb^, Perstorp AB) (n=38)	Patients experiencing adverse events: 5 (4 with pain lasting 10 minutes to 2 hours at dressing application, 1 skin rash considered due to soap derivative rather than iodine)	NR

Study name and location	Technology name	Overall treatment-related adverse events, n (%) type	Overall serious treatment-related adverse events
Location: Sweden Setting: Mixed; at home (visiting nurse) or hospital clinic	Comparator: Standard treatment (n=36)	Patients experiencing adverse events: 1 (pain lasting 10 minutes to 2 hours at dressing application)	NR
Octenidine			
Hammerle and Strohal, 2016 (Hammerle and Strohal 2016) Study design: Non-randomised trial Follow-up: 42 days Location: Austria Setting: Secondary care (single centre)	Intervention: Octenidine + foam or alginate (n=14 patients, 17 venous leg ulcers)	No AEs occurred	No SAEs occurred
	Comparator: Octenidine gel alone with wound contact layer and suction gauze (n=15 patients, 15 venous leg ulcers)	No AEs occurred	No SAEs occurred
PHMB			
Vallejo et al 2022 (Vallejo et al. 2022) Associated records: Protocol: Vallejo et al 2021 (Vallejo 2021) Design: RCT Follow-up: 12 weeks Location: Australia Setting: 1 community wound clinic.	Intervention: PHMB (topical PHMB as a soak in plain gauze for 15 minutes after debridement and at each dressing change, and then in a sustained dressing (AMD foam, or gel with PHMB, or Kerlix AMD gauze, H&R Healthcare, UK; ITT, n=25).	NR	NR
	Comparator: No agent (cleansing of the wound after and between treatments with clean water or saline, then non-	NR	NR

Study name and location	Technology name	Overall treatment-related adverse events, n (%) type	Overall serious treatment-related adverse events
	medicated dressing products; ITT, n=25).		
Koullias 2022 (Koullias et al. 2022) Study design: Prospective case series Follow-up: 32 weeks Location: US Setting: Unclear (dressings applied by physicians in unclear settings)	Intervention: Type 1 collagen matrix plus polyhexamethylene biguanide antimicrobial (PCMP) barrier (n=67)	NR	NR
Silver			
Degreef et al 1984 (Degreef and Michiels 1984) Study Design: Prospective case series Follow up: 4 weeks Location: Belgium Setting: Hospital	Intervention: Silver (1% silver sulfadiazine cream applied once a day in a thin layer of 2 to 3 mm and covered by a sterile bandage) (n=23)	Formation of pseudomembranous structure in ulcer bed: 10/29 (34.5*)	NR
Dimakakos et al 2009 (Dimakakos et al. 2009) Study Design: RCT Follow-up: 9 weeks Location: Greece	Intervention: Silver releasing foam dressing (n=21)	No patients experienced AEs that could be attributed to the dressing.	NR
	Comparator: No agent (non-adhesive foam dressing) (n=21)	No patients experienced AEs that could be attributed to the dressing.	NR
Forlee 2014 (Forlee et al. 2014)	Intervention: Gelling fibre dressing containing silver (DURAFIBER™ Ag)	NR	NR

Study name and location	Technology name	Overall treatment-related adverse events, n (%) type	Overall serious treatment-related adverse events
Study design: Single-arm trial Follow-up: 8 weeks (The wound was swabbed every 7 days) Location: South Africa Setting: Three secondary care centres	(complete case analysis, n=14)		
Humbert 2006 (Humbert et al. 2006) Study Design: RCT Follow up: 6 weeks Location: France Setting: 17 sites that included dermatology, vascular, angiophlebology and dermatology practices; 85% of silver arm and 72.5% of no agent arm were outpatients.	Intervention: Silver (Biatain AG, n=40)	Patients experiencing treatment-related adverse events: 3/40 (7.5*) pain, itching and epidermitis Patients withdrawing due to adverse events for which a causal relationship with the dressing could not be ruled out: 1/40 (2.5*)	NR
	Comparator: No agent (calcium alginate fibre dressing, n=40)	Patients experiencing treatment-related adverse events: 3/40 (7.5*) pain, itching and redness/maceration Patients withdrawing due to adverse events for which a causal relationship with the dressing could not be ruled out: 2/40 (5*)	NR
Melotte 1985 (Melotte et al. 1985) Study design: Prospective case series Follow-up: 6 weeks Location: Belgium Setting: NR	Intervention: 1% silver sulfadiazine cream Comparator: None	NR	NR

Study name and location	Technology name	Overall treatment-related adverse events, n (%) type	Overall serious treatment-related adverse events
Manning 2020 (Manning et al. 2020) Associated Records: Conference abstract: Manning 2019 (Manning et al. 2019) Study Design: Single-arm trial Follow up: 12 weeks Location: USA Setting: Wound care clinic within a secondary care setting	Intervention: Bioabsorbable polymeric matrix containing ionic and metallic silver	NR	NR
Meaume et al, 2005 (Meaume et al. 2005) Study design: RCT Follow-up: 4 weeks Location: UK Setting: 13 hospital centres	Intervention: Silver-releasing hydroalginate dressing (Silvercel) (ITT, n=51)	Local adverse events considered treatment-related (considered “certain” by investigator, dressing discontinued)*: 3/51 (5.8*) (1 peri-wound eczema and extension of slough, 1 dry wound, 1 unclear)	NR
	Comparator: No agent (pure calcium alginate dressing, Algosteril) (ITT, n=48)	Local adverse events considered treatment-related (considered “certain” by investigator, dressing discontinued)*, n (%): 1/48 (2*), pain during dressing change	NR
Molnlycke Health Care AB 2014 (NCT01036438) (NCT01036438 2009) Study design: RCT Follow-up: 8 weeks Location: Czech Republic, France,	Intervention: Silver (absorbent foam silver dressing, Mepilex Ag, ITT n=100)	Skin/subcutaneous AEs occurring in >5% of participants considered related to ulcer (not necessarily treatment): 14/100 (14.00)	NR
	Comparator: No agent (absorbent foam silver dressing, Mepilex without silver, ITT n=101)	Skin/subcutaneous AEs occurring in >5% of participants considered related to ulcer (not necessarily treatment): 19/101 (18.81)	NR

Study name and location	Technology name	Overall treatment-related adverse events, n (%) type	Overall serious treatment-related adverse events
Germany and the Netherlands Setting: Unclear, appears to be hospital			
Truchetet 2012 (Truchetet et al. 2012) Study design: Prospective case series Follow up: Median 19 days (7 to 97) Location: France Setting: Private outpatient	Intervention: Mepilex Ag (Mölnlycke Health Care)	NR	NR
Woolstencroft 2018 (Woolstencroft 2018) Study design: Single-arm trial Follow-up: 4 weeks Location: UK Setting: Secondary care (10 tissue viability clinics)	Intervention: KerraContactTM Ag dressing with Ag OxysaltsTM (Silver wound dressing with 2 non-adherent polyethene mesh contact layers and a polyester core)	NR	NR
Harding 2016 (Harding et al. 2016) Study design: Prospective single-arm trial Follow-up: 8 weeks	Intervention: AQUACEL Ag+ hydrofiber dressing Week 1-4, AQUACEL wound dressings Week 5-8 AEs not reported for clinically infected group separately; this data is for	NR	No SAEs occurred

Study name and location	Technology name	Overall treatment-related adverse events, n (%) type	Overall serious treatment-related adverse events
Location: UK and Poland Setting: 6 study centres, unclear setting	the whole population (n=42)		
Lantis 2011 (Lantis and Gendics 2011) Study design: Prospective single-arm trial Follow-up: 12 weeks Location: USA Setting: Tertiary care wound practice	Intervention: a non-adhesive silver sulphadiazine, polyurethane foam dressing (Allevyn Ag Non-Adhesive) (n=24, safety set n =33)	1/33 (3%*)	No SAEs occurred
Vanscheidt 2003 (Vanscheidt et al. 2003) Study design: Prospective single-arm trial Follow-up: 28 days Location: France and Germany Setting: NR	Intervention: Aquacel Ag (n=11 patients with infected wounds)	NR	No SAEs occurred
Jorgensen 2008 (Jorgensen et al. 2008) Study design: Prospective single-arm trial	Intervention: Silver and ibuprofen releasing foam dressing (Physiotulle Ag) n=24	Total adverse events: 4 (2 dermatitis, 2 local irritation/maceration)	No SAEs occurred

Study name and location	Technology name	Overall treatment-related adverse events, n (%) type	Overall serious treatment-related adverse events
Follow-up: 31 days ($\pm$ 2 days) Location: Denmark and Canada Setting: Outpatient clinics at 4 centres			
Comparative studies of eligible agents			
Gago 2008 (Gago et al. 2008) Study design: Prospective cohort study Follow-up: 8 weeks Location: Spain Setting: Community health centre	Intervention 1: Acticoat™ (n=25)	Number of AEs during dressing changes in the 8 week study period (n=189 changes): Maceration: 4 (2.1) Erythema: 0 (0) Excoriation: 0 (0) Vesicles: 1 (0.5) Bed staining: 1 (0.5) Peri-wound staining: 15 (7.9) Dressing remains in the wound: 6 (3.2)	NR
	Intervention 2: Comfeel™ or Biatain™ Ag (Comfeel n = 9) Biatin n = 16)	Number of AEs during dressing changes in the 8 week study period (n=291 changes): Maceration: 76 (2.12) Erythema: 23 (7.9) Excoriation: 13 (4.5) Vesicles: 0 (0) Bed staining: 3 (1) Peri-wound staining: 2 (0.7) Dressing remains in the wound: 6 (3.2)	NR
	Intervention 3: Aquacel Ag (n=25)	Number AEs during dressing changes in the 8 week study period (n=285 changes): Maceration: 11 (3.9) Erythema: 0 (0) Excoriation: 0 (0) Vesicles: 0 (0) Bed staining: 1 (0.4)	NR

Study name and location	Technology name	Overall treatment-related adverse events, n (%) type	Overall serious treatment-related adverse events
		Peri-wound staining: 1 (0.4) Dressing remains in the wound: 11 (3.6)	
Miller et al 2010 (Miller et al. 2010) Study design: RCT Follow-up: 12 weeks (data collected at 2 week intervals up to 12 weeks or wound closure) Location: UK Setting:	Intervention: Nanocrystalline silver dressing (Acticoats (nanocrystalline silver) with compression bandaging)	NR	NR
	Comparator: Cadexomer iodine dressing (Iodosorbs (cadexomer iodine) with compression bandaging)	NR	NR
Molle 2023 (Molle et al. 2023) Design: Non-randomised clinical trial Follow-up: Baseline then 15 and 30 days from baseline Location: NR Setting: NR	Intervention: Manuka honey	NR	NR
	Comparator: Silver dressing	NR	NR
Mosti et al, 2015 (Mosti et al. 2015) Study design: Pilot RCT Follow-up: 4 days Location: UK Setting: Community nursing services	Intervention: Silver (Silver-containing hydrofiber Aquacel Ag)	NR	No SAEs occurred
	Comparator: DACC (microorganism-binding, Cutimed Sorbact)	NR	No SAEs occurred

Key: AE – Adverse event, AMD – Antimicrobial dressing, DACC – Dialkylcarbamoyl chloride, HA – Hyaluronic acid, ITT – Intention-to-treat, NR – Not reported, OHP – Octenidine dihydrochloride/phenoxyethanol, PCMP – Polyhexamethylene biguanide antimicrobial, PHMB – Polyhexamethylene biguanide, RCT – Randomised controlled trial, SAE – Serious adverse events, SD – Standard deviation, UK – United Kingdom, USA – United States of America

11.7.11 Specific adverse events

Study name and location	Technology name	Skin discolouration, n (%)	Allergic reaction, n (%)	Increased pain due to dressing, n (%)
Chitosan				
Mo 2015 (Mo et al. 2015)	Intervention: Chitosan (n=45)	NR	NR	NR
Design: RCT Follow-up: 4 weeks Location: China Setting: 3 university hospital centres	Comparator: Vaseline gauze (n=45)	NR	NR	NR
Orig et al 2016 (Orig and Singleton 2016)	Intervention: Chitosan (Kytocel dressing). Wear time ranged from 2 to 7 days. Variety of secondary dressings used including super absorbent dressings, surgical pads and foams.	NR	NR	NR
Copper				
Dokic 2023 (Dokic S et al. 2023)	Intervention: Copper wound dressings (n=12)	NR	NR	NR
Design: Prospective case series Follow-up: 3 months Location: Slovenia Setting: Hospital				
Melamed 2021 (Melamed et al. 2021)	Intervention: Cupric oxide dressing	NR	NR	NR

Study name and location	Technology name	Skin discolouration, n (%)	Allergic reaction, n (%)	Increased pain due to dressing, n (%)
Design: Single-arm trial Follow-up: 4 weeks of treatment and 2 weeks of follow up using unspecified “standard of care” dressings. Location: Israel Setting: Outpatient hospital clinic				
Treadwell 2022 (Treadwell T et al. 2022) Design: Prospective case series Follow-up: NR Location: Alabama, USA Setting: Medical centre	Intervention: Cupric oxide wound dressing (n=25)	NR	NR	NR
DACC				
Bruce 2012 (Bruce 2012) Study design: Prospective case series Follow-up: 28 days (or until infection reduced) Location: UK and Ireland Setting: 4 community centres and 2 acute hospitals	Intervention: Cutimed Sorbact Hydroactive dressing (n=13 patients, 14 wounds)	NR	NR	Patients reporting “bearable” pain during dressing removal (n, %): 2/13 (15) patients reported ‘bearable’ pain during dressing removal
Enzyme Alginogel				
Durante 2012 (Durante 2012) Design: Prospective case series	Intervention: Enzyme Alginogel (Flaminal - composed of hydrated alginate polymers in a	NR	1/23 (4.3*)	NR

Study name and location	Technology name	Skin discolouration, n (%)	Allergic reaction, n (%)	Increased pain due to dressing, n (%)
Follow-up: 60 days Location: Italy Setting: Hospital, with continuation in home setting	polyethylene glycol matrix embedded with a patented antimicrobial enzymatic complex) (n=23).			
Jones et al 2018 (Jones and Oates 2018) Design: Prospective case series Follow-up: Unclear Location: UK Setting: Primary care (forms completed by district nurses)	Intervention: Enzyme Alginogel (Flaminal - a hydro-active, broad-spectrum Enzyme Alginogel,).	NR	NR	NR
King et al 2023 (King and Rolland 2023) Design: Prospective case series Follow-up: Unclear Location: UK Setting: Primary care (forms completed by district nurses).	Intervention: Enzyme Alginogel (Flaminal - a hydro-active, broad-spectrum Enzyme Alginogel).	NR	NR	NR
Honey				
Biglari et al 2013 (Biglari et al. 2013) Design: Prospective case series Follow-up: 4.88 (SD 4.4) weeks	Intervention: Honey (various Medihoney™ dressing products)	NR	NR	NR

Study name and location	Technology name	Skin discolouration, n (%)	Allergic reaction, n (%)	Increased pain due to dressing, n (%)
Location: 9 sites in Germany and 1 in Austria Setting: Hospital				
Yang et al 2015 (Yang K et al. 2015) Design: Prospective single-arm study Follow-up: 4 weeks Location: USA Setting: Hospital	Intervention: Topical medical grade honey	NR	NR	NR
Moghazy et al 2010 (Moghazy et al. 2010) Design: Prospective single-arm trial Follow-up: 3 months Location: Egypt Setting: Referred to outpatient care from hospital admission	Intervention: Honey (Medium-pored non-sterile gauze saturated with honey).	NR	NR	NR
Iodine				
Skog 1983 (Skog et al. 1983) Design: RCT Follow-up: 6 weeks Location: Sweden Setting: Mixed; at home (visiting nurse) or hospital clinic	Intervention: Cadexomer iodine (Iodosorb [®] , Perstorp AB) (n=38)	NR	NR	NR
	Comparator: Standard treatment (n=36)	NR	NR	NR
Octenidine				

Study name and location	Technology name	Skin discolouration, n (%)	Allergic reaction, n (%)	Increased pain due to dressing, n (%)
Hammerle and Strohal, 2016 (Hammerle and Strohal 2016) Study design: Non-randomised trial Follow-up: 42 days Location: Austria Setting: Secondary care (single centre)	Intervention: Octenidine + foam or alginate (n=14 patients, 17 venous leg ulcers)	NR	NR	NR
	Comparator: Octenidine gel alone with wound contact layer and suction gauze (n=15 patients, 15 venous leg ulcers)	NR	NR	NR
PHMB				
Vallejo et al 2022 (Vallejo et al. 2022) Associated records: Protocol: Vallejo et al 2021 (Vallejo 2021) Design: RCT Follow-up: 12 weeks Location: Australia Setting: 1 community wound clinic.	Intervention: PHMB (AMD foam, or gel with PHMB, or Kerlix AMD gauze, H&R Healthcare, UK; ITT, n=25).	NR	NR	NR
	Comparator: No agent (cleansing of the wound after and between treatments with clean water or saline, then non-medicated dressing products; ITT, n=25).	NR	NR	NR
Koullias 2022 (Koullias et al. 2022) Study design: Prospective case series Follow-up: 32 weeks Location: US	Intervention: Type 1 collagen matrix plus polyhexamethylene biguanide antimicrobial (PCMP) barrier (n=67)	NR	NR	NR

Study name and location	Technology name	Skin discolouration, n (%)	Allergic reaction, n (%)	Increased pain due to dressing, n (%)
Setting: Unclear (dressings applied by physicians in unclear settings)				
Silver				
Degreef et al 1984 (Degreef and Michiels 1984) Study Design: Prospective case series Follow up: 4 weeks Location: Belgium Setting: Hospital	Intervention: Silver (1% silver sulfadiazine cream applied once a day in a thin layer of 2 to 3 mm and covered by a sterile bandage) (n=29)	NR	Patients experiencing contact eczema considered related to ointment vehicle and not silver agent: 3/29 (10.3*)	NR
Dimakakos et al 2009 (Dimakakos et al. 2009) Study Design: RCT Follow-up: 9 weeks Location: Greece Setting: NR	Intervention: Silver releasing foam dressing (n=21)	NR	NR	NR
	Comparator: No agent (non-adhesive foam dressing) (n=21)	NR	NR	NR
Forlee 2014 (Forlee et al. 2014) Study design: Single-arm trial Follow-up: 8 weeks (The wound was swabbed every 7 days) Location: South Africa Setting: Three secondary care centres	Intervention: Gelling fibre dressing containing silver (DURAFIBER™ Ag) (n=14)	NR	NR	Pain at dressing application assessments (n=96), n (%): None: 92 (95.8) Mild: 2 (2.1) Moderate: 2 (2.1) Severe: 0 (0) Pain at dressing removal assessments (n=95), n(%): None: 84 (88.4) Mild: 6 (6.3) Moderate: 4 (4.2)

Study name and location	Technology name	Skin discolouration, n (%)	Allergic reaction, n (%)	Increased pain due to dressing, n (%)
				Severe: 1 (1.1)
Humbert 2006 (Humbert et al. 2006) Study Design: RCT Follow up: 6 weeks Location: France Setting: 17 sites that included dermatology, vascular, angiophlebology and dermatology practices; 85% of silver arm and 72.5% of no agent arm were outpatients.	Intervention: Silver (Biatain AG, n=40)	NR	NR	Pain during dressing removals (n=217), n (%): None: 170 (78.3) Mild: 45 (20.7) Moderate: 2 (0.9) Severe: 0 (0) Difference in proportion of patients with no pain at dressing changes: 78.3% vs 48.4% p<0.001
	Comparator: No agent (calcium alginate fibre dressing, n=40)	NR	NR	Pain during dressing removals (n=192), n (%): None: 93 (48.4) Mild: 63 (32.8) Moderate: 28 (14.6) Severe: 8 (4.2) Difference in proportion of patients with no pain at dressing changes: 78.3% vs 48.4%, p<0.001
Manning 2020 (Manning et al. 2020) Associated Records: Conference abstract: Manning 2019 (Manning et al. 2019) Study Design: Single-arm trial	Intervention: Bioabsorbable polymeric matrix containing ionic and metallic silver	NR	NR	NR

Study name and location	Technology name	Skin discolouration, n (%)	Allergic reaction, n (%)	Increased pain due to dressing, n (%)
Follow up: 12 weeks Location: USA Setting: Wound care clinic within a secondary care setting				
Melotte 1985 (Melotte et al. 1985) Study design: Prospective case series Follow-up: 6 weeks Location: Belgium Setting: NR	Intervention: 1% silver sulfadiazine cream Comparator: None	NR	No allergic reactions occurred	NR
Meaume et al, 2005 (Meaume et al. 2005) Study design: RCT Follow-up: 4 weeks Location: UK Setting: 13 hospital centres	Intervention: Silver-releasing hydroalginate dressing (Silvercel) (ITT, n=51)	NR	NR	NR
	Comparator: No agent (pure calcium alginate dressing, Algosteril) (ITT, n=48)	NR	NR	NR
Molnlycke Health Care AB 2014 (NCT01036438) (NCT01036438 2009) Study design: RCT Follow-up: 8 weeks Location: Czech Republic, France, Germany and the Netherlands Setting: Unclear, appears to be hospital	Intervention: Silver (absorbent foam silver dressing, Mepilex Ag, ITT n=100)	NR	NR	NR
	Comparator: No agent (absorbent foam silver dressing, Mepilex without silver, ITT n=101)	NR	NR	NR

Study name and location	Technology name	Skin discolouration, n (%)	Allergic reaction, n (%)	Increased pain due to dressing, n (%)
Truchetet 2012 (Truchetet et al. 2012) Study design: Prospective case series Follow up: Median 19 days (7 to 97) Location: France Setting: Private outpatient	Intervention: Mepilex Ag (Mölnlycke Health Care)	NR	NR	NR
Woolstencroft 2018 (Woolstencroft 2018) Study design: Single-arm trial Follow-up: 4 weeks Location: UK Setting: Secondary care (10 tissue viability clinics)	Intervention: KerraContactTM Ag dressing with Ag OxysaltsTM (Silver wound dressing with 2 non-adherent polyethylene mesh contact layers and a polyester core)	NR	NR	NR
Harding 2016 (Harding et al. 2016) Study design: Prospective single-arm trial Follow-up: 8 weeks Location: UK and Poland Setting: 6 study centres, unclear setting	Intervention: AQUACEL Ag+ hydrofiber dressing Week 1-4, AQUACEL wound dressings Week 5-8 (clinically infected n=10)	NR	NR	NR
Lantis 2011 (Lantis and Gendics 2011)	Intervention: a non-adhesive silver sulphadiazine,	NR	NR	Severe pain on dressing removal (week 6): 1/33 (3%*)

Study name and location	Technology name	Skin discolouration, n (%)	Allergic reaction, n (%)	Increased pain due to dressing, n (%)
Study design: Prospective single-arm trial Follow-up: 12 weeks Location: USA Setting: Tertiary care wound practice	polyurethane foam dressing (Allevyn Ag Non-Adhesive) (n=24, safety set n =33)			
Vanscheidt 2003 (Vanscheidt et al. 2003) Study design: Prospective single-arm trial Follow-up: 28 days Location: France and Germany Setting: NR	Intervention: Aquacel Ag (n=11 patients with infected wounds)	Redness and inflammation: 27%		
Jorgensen 2008 (Jorgensen et al. 2008) Study design: Prospective single-arm trial Follow-up: 31 days (± 2 days) Location: Denmark and Canada Setting: Outpatient clinics at 4 centres	Intervention: Silver and ibuprofen releasing foam dressing (Physiotulle Ag) n=24	NR	NR	NR
Comparative studies of eligible agents				
Gago 2008 (Gago et al. 2008)	Intervention 1: Acticoat™ (n=25)	NR	NR	No pain experienced

Study name and location	Technology name	Skin discolouration, n (%)	Allergic reaction, n (%)	Increased pain due to dressing, n (%)
Study design: Prospective cohort study Follow-up: 8 weeks Location: Spain Setting: Community health centre	Intervention 2: Comfeel™ or Biatain™ Ag (Comfeel n = 9) Biatin n = 16)	NR	NR	No pain experienced
	Intervention 3: Aquacel Ag (n=25)	NR	NR	No pain experienced
Miller et al 2010 (Miller et al. 2010) Study design: RCT Follow-up: 12 weeks (data collected at 2 week intervals up to 12 weeks or wound closure) Location: UK Setting:	Intervention: Nanocrystalline silver dressing (Acticoats (nanocrystalline silver) with compression bandaging)	NR	NR	NR
	Comparator: Cadexomer iodine dressing (Iodosorbs (cadexomer iodine) with compression bandaging)	NR	NR	NR
Molle 2023 (Molle et al. 2023) Design: Non-randomised clinical trial Follow-up: 30 days Location: NR Setting: NR	Intervention: Manuka honey	NR	NR	NR
	Comparator: Silver dressing	NR	NR	NR
Mosti et al, 2015 (Mosti et al. 2015) Study design: Pilot RCT	Intervention: Silver (Silver-containing hydrofiber Aquacel Ag)	NR	NR	NR

Study name and location	Technology name	Skin discolouration, n (%)	Allergic reaction, n (%)	Increased pain due to dressing, n (%)
Follow-up: 4 days Location: UK Setting: Community nursing services	Comparator: DACC (microorganism-binding, Cutimed Sorbact)	NR	NR	NR

Key: AMD – Antimicrobial dressing, DACC – Dialkylcarbamoyl chloride, HA – Hyaluronic acid, ITT – Intention-to-treat, NR – Not reported, OHP – Octenidine dihydrochloride/phenoxyethanol, PCMP – Polyhexamethylene biguanide antimicrobial, PHMB – Polyhexamethylene biguanide, RCT – Randomised controlled trial, SD – Standard deviation, UK – United Kingdom, USA – United States of America

* - text states AE-related discontinuations were 3 in silver group and 1 in no agent group, while table 9 indicates 2 in each group.

11.8 Appendix H: Cost and market share of AMDs

Product	Agent	Sub-agent	Cost (GBP)	CPRD market share
Silvers				
Aquacel Ag+ Extra dressing 10cm x 10cm square (1 dressing)	Silver	Silver with anti-biofilm mechanisms	£5.11	1.19
Aquacel Ag+ Extra dressing 15cm x 15cm square (1 dressing)	Silver	Silver with anti-biofilm mechanisms	£9.64	0.63
Aquacel Ag+ Extra dressing 20cm x 30cm rectangular (1 dressing)	Silver	Silver with anti-biofilm mechanisms	£23.93	0.19
Aquacel Ag+ Extra dressing 4cm x 10cm rectangular (1 dressing)	Silver	Silver with anti-biofilm mechanisms	£3.12	0.00
Aquacel Ag+ Extra dressing 4cm x 20cm rectangular (1 dressing)	Silver	Silver with anti-biofilm mechanisms	£4.07	0.00
Aquacel Ag+ Extra dressing 4cm x 30cm rectangular (1 dressing)	Silver	Silver with anti-biofilm mechanisms	£6.08	0.00
Aquacel Ag+ Extra dressing 5cm x 5cm square (1 dressing)	Silver	Silver with anti-biofilm mechanisms	£2.15	0.44
Askina Calgitrol Thin dressing 5cm x 5cm square (1 dressing)	Silver	Elemental silver	£2.15	0.03

KerraCel Ag dressing 10cm x 12.5cm rectangular (1 dressing)	Silver	Silver salts and compounds	£4.86	0.02
KerraCel Ag dressing 15cm x 15cm square (1 dressing)	Silver	Silver salts and compounds	£9.16	0.04
KerraCel Ag dressing 20cm x 30cm rectangular (1 dressing)	Silver	Silver salts and compounds	£22.76	0.01
KerraCel Ag dressing 5cm x 5cm square (1 dressing)	Silver	Silver salts and compounds	£2.03	0.02
Silvercel Non-Adherent dressing 10cm x 20cm rectangular (1 dressing)	Silver	Elemental silver	£7.61	0.02
Silvercel Non-Adherent dressing 11cm x 11cm square (1 dressing)	Silver	Elemental silver	£4.09	0.04
Silvercel Non-Adherent dressing 5cm x 5cm square (1 dressing)	Silver	Elemental silver	£1.70	0.06
Sorbsan Silver Flat dressing 10cm x 10cm (1 dressing)	Silver	Silver salts and compounds	£4.00	0.00
Sorbsan Silver Flat dressing 10cm x 20cm (1 dressing)	Silver	Silver salts and compounds	£7.31	0.00
Sorbsan Silver Flat dressing 5cm x 5cm (1 dressing)	Silver	Silver salts and compounds	£1.58	0.00
Suprasorb Liquacel Ag dressing 10cm x 10cm square (1 dressing)	Silver	Elemental silver	£4.31	0.00

Suprasorb Liquacel Ag dressing 15cm x 15cm square (1 dressing)	Silver	Elemental silver	£8.13	0.00
Suprasorb Liquacel Ag dressing 5cm x 5cm square (1 dressing)	Silver	Elemental silver	£1.81	0.00
ActivHeal Aquafiber Ag dressing 10cm x 10cm square (1 dressing)	Silver	Silver salts and compounds	£4.06	0.00
ActivHeal Aquafiber Ag dressing 15cm x 15cm square (1 dressing)	Silver	Silver salts and compounds	£7.66	0.00
ActivHeal Aquafiber Ag dressing 2.7cm x 32cm rope (1 dressing)	Silver	Silver salts and compounds	£4.13	0.00
ActivHeal Aquafiber Ag dressing 5cm x 5cm square (1 dressing)	Silver	Silver salts and compounds	£1.70	0.00
Algicell Ag dressing 10.1cm x 20.3cm (1 dressing)	Silver	Silver salts and compounds	£7.08	0.00
Algicell Ag dressing 10.8cm x 10.8cm (1 dressing)	Silver	Silver salts and compounds	£3.56	0.00
Algicell Ag dressing 20.3cm x 30.5cm (1 dressing)	Silver	Silver salts and compounds	£19.00	0.00
Algicell Ag dressing 5cm x 5cm (1 dressing)	Silver	Silver salts and compounds	£1.23	0.00
Algisite Ag dressing 10cm x 10cm (1 dressing)	Silver	Unknown silver	£4.54	0.00

Algisite Ag dressing 10cm x 20cm (1 dressing)	Silver	Unknown silver	£8.35	0.00
Algisite Ag dressing 5cm x 5cm (1 dressing)	Silver	Unknown silver	£1.82	0.00
Biatain Alginate Ag dressing 10cm x 10cm (1 dressing)	Silver	Silver with anti-biofilm mechanisms	£4.33	0.09
Biatain Alginate Ag dressing 15cm x 15cm (1 dressing)	Silver	Silver with anti-biofilm mechanisms	£7.09	0.07
Biatain Alginate Ag dressing 5cm x 5cm (1 dressing)	Silver	Silver with anti-biofilm mechanisms	£1.77	0.10
Durafiber Ag dressing 10cm x 10cm square (1 dressing)	Silver	Silver salts and compounds	£4.68	0.87
Durafiber Ag dressing 15cm x 15cm square (1 dressing)	Silver	Silver salts and compounds	£8.81	0.33
Durafiber Ag dressing 20cm x 30cm rectangular (1 dressing)	Silver	Silver salts and compounds	£21.84	0.04
Durafiber Ag dressing 2cm x 45cm rectangular (1 dressing)	Silver	Silver salts and compounds	£4.69	0.02
Durafiber Ag dressing 4cm x 10cm rectangular (1 dressing)	Silver	Silver salts and compounds	£2.85	0.01

Durafiber Ag dressing 4cm x 20cm rectangular (1 dressing)	Silver	Silver salts and compounds	£3.71	0.00
Durafiber Ag dressing 4cm x 30cm rectangular (1 dressing)	Silver	Silver salts and compounds	£5.55	0.00
Durafiber Ag dressing 5cm x 5cm square (1 dressing)	Silver	Silver salts and compounds	£1.97	0.65
Exufiber Ag+ dressing 10cm x 10cm square (1 dressing)	Silver	Silver salts and compounds	£4.68	0.00
Exufiber Ag+ dressing 15cm x 15cm square (1 dressing)	Silver	Silver salts and compounds	£8.85	0.00
Exufiber Ag+ dressing 20cm x 30cm rectangular (1 dressing)	Silver	Silver salts and compounds	£21.84	0.00
Exufiber Ag+ dressing 4.5cm x 10cm rectangular (1 dressing)	Silver	Silver salts and compounds	£2.86	0.00
Exufiber Ag+ dressing 4.5cm x 20cm rectangular (1 dressing)	Silver	Silver salts and compounds	£3.71	0.00
Exufiber Ag+ dressing 4.5cm x 30cm rectangular (1 dressing)	Silver	Silver salts and compounds	£5.57	0.00
Exufiber Ag+ dressing 5cm x 5cm square (1 dressing)	Silver	Silver salts and compounds	£1.98	0.00

Melgisorb Ag dressing 10cm x 10cm (1 dressing)	Silver	Silver salts and compounds	£3.97	0.00
Melgisorb Ag dressing 15cm x 15cm (1 dressing)	Silver	Silver salts and compounds	£8.40	0.00
Melgisorb Ag dressing 5cm x 5cm (1 dressing)	Silver	Silver salts and compounds	£1.98	0.00
Suprasorb A + Ag dressing 10cm x 10cm (1 dressing)	Silver	Silver salts and compounds	£4.52	0.00
Suprasorb A + Ag dressing 10cm x 20cm (1 dressing)	Silver	Silver salts and compounds	£8.35	0.00
Suprasorb A + Ag dressing 5cm x 5cm (1 dressing)	Silver	Silver salts and compounds	£1.80	0.00
Tegaderm Alginate Ag dressing 10cm x 10cm (1 dressing)	Silver	Silver salts and compounds	£3.30	0.00
Tegaderm Alginate Ag dressing 5cm x 5cm (1 dressing)	Silver	Silver salts and compounds	£1.42	0.00
Urgosorb Silver dressing 10cm x 10cm (1 dressing)	Silver	Silver with anti-biofilm mechanisms	£3.98	0.05
Urgosorb Silver dressing 10cm x 20cm (1 dressing)	Silver	Silver with anti-biofilm mechanisms	£7.51	0.04

Urgosorb Silver dressing 5cm x 5cm (1 dressing)	Silver	Silver with anti-biofilm mechanisms	£1.67	0.01
UrgoClean Ag dressing 10cm x 10cm square (1 dressing)	Silver	Silver salts and compounds	£4.68	0.00
UrgoClean Ag dressing 15cm x 20cm rectangular (1 dressing)	Silver	Silver salts and compounds	£8.82	0.00
UrgoClean Ag dressing 6cm x 6cm square (1 dressing)	Silver	Silver salts and compounds	£2.06	0.00
Allevyn Ag Adhesive dressing 10cm x 10cm square (1 dressing)	Silver	Silver salts and compounds	£6.00	0.08
Allevyn Ag Adhesive dressing 12.5cm x 12.5cm square (1 dressing)	Silver	Silver salts and compounds	£7.89	0.03
Allevyn Ag Adhesive dressing 17.5cm x 17.5cm square (1 dressing)	Silver	Silver salts and compounds	£15.18	0.01
Allevyn Ag Adhesive dressing 7.5cm x 7.5cm square (1 dressing)	Silver	Silver salts and compounds	£3.81	0.03
Allevyn Ag Non-Adhesive dressing 10cm x 10cm square (1 dressing)	Silver	Silver salts and compounds	£6.71	0.03
Allevyn Ag Non-Adhesive dressing 15cm x 15cm square (1 dressing)	Silver	Silver salts and compounds	£12.71	0.00

Allevyn Ag Non-Adhesive dressing 20cm x 20cm square (1 dressing)	Silver	Silver salts and compounds	£18.62	0.00
Allevyn Ag Non-Adhesive dressing 5cm x 5cm square (1 dressing)	Silver	Silver salts and compounds	£3.56	0.01
Biatain Ag dressing 10cm x 10cm square (1 dressing)	Silver	Silver with anti-biofilm mechanisms	£8.82	0.17
Biatain Ag dressing 10cm x 20cm rectangular (1 dressing)	Silver	Silver with anti-biofilm mechanisms	£16.20	0.02
Biatain Ag dressing 12.5cm x 12.5cm square (1 dressing)	Silver	Silver with anti-biofilm mechanisms	£10.09	0.03
Biatain Ag dressing 15cm x 15cm square (1 dressing)	Silver	Silver with anti-biofilm mechanisms	£17.70	0.04
Biatain Ag dressing 18cm x 18cm square (1 dressing)	Silver	Silver with anti-biofilm mechanisms	£20.23	0.00
Biatain Ag dressing 20cm x 20cm square (1 dressing)	Silver	Silver with anti-biofilm mechanisms	£24.96	0.04
Biatain Ag dressing 5cm x 7cm rectangular (1 dressing)	Silver	Silver with anti-biofilm mechanisms	£3.62	0.03
PolyMem Silver dressing 10.8cm x 10.8cm square (1 dressing)	Silver	Elemental silver	£9.76	0.00

PolyMem Silver dressing 12.7cm x 8.8cm oval (1 dressing)	Silver	Elemental silver	£6.17	0.00
PolyMem Silver dressing 17cm x 19cm rectangular (1 dressing)	Silver	Elemental silver	£19.56	0.00
PolyMem Silver dressing 5cm x 7.6cm oval (1 dressing)	Silver	Elemental silver	£2.51	0.00
Aquacel Ag Foam dressing (adhesive) 10cm x 10cm (1 dressing)	Silver	Silver salts and compounds	£5.94	0.32
Aquacel Ag Foam dressing (adhesive) 12.5cm x 12.5cm (1 dressing)	Silver	Silver salts and compounds	£7.78	0.22
Aquacel Ag Foam dressing (adhesive) 17.5cm x 17.5cm (1 dressing)	Silver	Silver salts and compounds	£14.34	0.12
Aquacel Ag Foam dressing (adhesive) 21cm x 21cm (1 dressing)	Silver	Silver salts and compounds	£19.85	0.06
Aquacel Ag Foam dressing (adhesive) 25cm x 30cm (1 dressing)	Silver	Silver salts and compounds	£25.69	0.01
Aquacel Ag Foam dressing (adhesive) 8cm x 8cm (1 dressing)	Silver	Silver salts and compounds	£3.72	0.11
Aquacel Ag Foam dressing (non-adhesive) 10cm x 10cm (1 dressing)	Silver	Silver salts and compounds	£6.56	0.12
Aquacel Ag Foam dressing (non-adhesive) 15cm x 15cm (1 dressing)	Silver	Silver salts and compounds	£12.45	0.05

Aquacel Ag Foam dressing (non-adhesive) 15cm x 20cm (1 dressing)	Silver	Silver salts and compounds	£13.62	0.02
Aquacel Ag Foam dressing (non-adhesive) 20cm x 20cm (1 dressing)	Silver	Silver salts and compounds	£18.24	0.10
Aquacel Ag Foam dressing (non-adhesive) 5cm x 5cm (1 dressing)	Silver	Silver salts and compounds	£3.58	0.05
Biatain Silicone Ag dressing 10cm x 10cm (1 dressing)	Silver	Silver with anti-biofilm mechanisms	£5.68	0.31
Biatain Silicone Ag dressing 10cm x 20cm (1 dressing)	Silver	Silver with anti-biofilm mechanisms	£9.60	0.02
Biatain Silicone Ag dressing 10cm x 30cm (1 dressing)	Silver	Silver with anti-biofilm mechanisms	£14.41	0.01
Biatain Silicone Ag dressing 12.5cm x 12.5cm (1 dressing)	Silver	Silver with anti-biofilm mechanisms	£7.43	0.18
Biatain Silicone Ag dressing 15cm x 15cm (1 dressing)	Silver	Silver with anti-biofilm mechanisms	£12.23	0.06
Biatain Silicone Ag dressing 17.5cm x 17.5cm (1 dressing)	Silver	Silver with anti-biofilm mechanisms	£13.54	0.02
Biatain Silicone Ag dressing 7.5cm x 7.5cm (1 dressing)	Silver	Silver with anti-biofilm mechanisms	£3.60	0.11

Allevyn Ag Gentle Border dressing 10cm x 10cm (1 dressing)	Silver	Silver salts and compounds	£6.95	0.10
Allevyn Ag Gentle Border dressing 12.5cm x 12.5cm (1 dressing)	Silver	Silver salts and compounds	£8.93	0.06
Allevyn Ag Gentle Border dressing 17.5cm x 17.5cm (1 dressing)	Silver	Silver salts and compounds	£17.02	0.01
Allevyn Ag Gentle Border dressing 7.5cm x 7.5cm (1 dressing)	Silver	Silver salts and compounds	£4.62	0.03
Allevyn Ag Gentle dressing 10cm x 10cm (1 dressing)	Silver	Silver salts and compounds	£6.75	0.01
Allevyn Ag Gentle dressing 10cm x 20cm (1 dressing)	Silver	Silver salts and compounds	£11.15	0.02
Allevyn Ag Gentle dressing 15cm x 15cm (1 dressing)	Silver	Silver salts and compounds	£12.55	0.01
Allevyn Ag Gentle dressing 20cm x 20cm (1 dressing)	Silver	Silver salts and compounds	£18.58	0.00
Allevyn Ag Gentle dressing 5cm x 5cm (1 dressing)	Silver	Silver salts and compounds	£3.62	0.00
Mepilex Ag dressing 10cm x 10cm (1 dressing)	Silver	Silver salts and compounds	£6.51	0.54

Mepilex Ag dressing 10cm x 20cm (1 dressing)	Silver	Silver salts and compounds	£10.99	0.11
Mepilex Ag dressing 15cm x 15cm (1 dressing)	Silver	Silver salts and compounds	£12.38	0.15
Mepilex Ag dressing 20cm x 20cm (1 dressing)	Silver	Silver salts and compounds	£18.34	0.06
Mepilex Ag dressing 20cm x 50cm (1 dressing)	Silver	Silver salts and compounds	£68.82	0.00
Mepilex Border Ag dressing 10cm x 12.5cm (1 dressing)	Silver	Silver salts and compounds	£6.71	0.18
Mepilex Border Ag dressing 10cm x 20cm (1 dressing)	Silver	Silver salts and compounds	£9.77	0.03
Mepilex Border Ag dressing 10cm x 25cm (1 dressing)	Silver	Silver salts and compounds	£12.23	0.00
Mepilex Border Ag dressing 10cm x 30cm (1 dressing)	Silver	Silver salts and compounds	£14.66	0.00
Mepilex Border Ag dressing 15cm x 17.5cm (1 dressing)	Silver	Silver salts and compounds	£12.32	0.06
Mepilex Border Ag dressing 17cm x 20cm (1 dressing)	Silver	Silver salts and compounds	£15.96	0.01

Mepilex Border Ag dressing 7cm x 7.5cm (1 dressing)	Silver	Silver salts and compounds	£3.71	0.13
Silvercel dressing 10cm x 20cm rectangular (1 dressing)	Silver	Elemental silver	£8.13	0.04
Silvercel dressing 11cm x 11cm square (1 dressing)	Silver	Elemental silver	£4.38	0.07
Silvercel dressing 2.5cm x 30.5cm rectangular (1 dressing)	Silver	Elemental silver	£4.71	0.00
Silvercel dressing 5cm x 5cm square (1 dressing)	Silver	Elemental silver	£1.77	0.04
Urgotul Silver dressing 10cm x 12cm (1 dressing)	Silver	Silver salts and compounds	£3.37	1.21
Urgotul Silver dressing 15cm x 20cm (1 dressing)	Silver	Silver salts and compounds	£9.53	0.51
Askina Calgitrol Paste dressing (15 grams)	Silver	Silver salts and compounds	£7.16	0.01
Askina Calgitrol Paste dressing (100 grams)	Silver	Silver salts and compounds	£41.40	0.01
Acticoat 7 dressing 10cm x 12.5cm rectangular (1 dressing)	Silver	Elemental silver	£19.82	0.07
Acticoat 7 dressing 15cm x 15cm square (1 dressing)	Silver	Elemental silver	£35.64	0.02
Acticoat 7 dressing 5cm x 5cm square (1 dressing)	Silver	Elemental silver	£6.65	0.12

Acticoat dressing 10cm x 10cm square (1 dressing)	Silver	Elemental silver	£9.35	0.13
Acticoat dressing 10cm x 20cm rectangular (1 dressing)	Silver	Elemental silver	£14.62	0.03
Acticoat dressing 20cm x 40cm rectangular (1 dressing)	Silver	Elemental silver	£50.03	0.01
Acticoat dressing 5cm x 5cm square (1 dressing)	Silver	Elemental silver	£3.83	0.10
Acticoat Flex 3 dressing 10cm x 10cm square (1 dressing)	Silver	Elemental silver	£9.45	0.63
Acticoat Flex 3 dressing 10cm x 20cm rectangular (1 dressing)	Silver	Elemental silver	£14.78	0.16
Acticoat Flex 3 dressing 20cm x 40cm rectangular (1 dressing)	Silver	Elemental silver	£50.58	0.05
Acticoat Flex 3 dressing 5cm x 5cm square (1 dressing)	Silver	Elemental silver	£3.87	0.50
Acticoat Flex 7 dressing 10cm x 12.5cm rectangular (1 dressing)	Silver	Elemental silver	£20.04	0.08
Acticoat Flex 7 dressing 15cm x 15cm square (1 dressing)	Silver	Elemental silver	£36.04	0.04
Acticoat Flex 7 dressing 5cm x 5cm square (1 dressing)	Silver	Elemental silver	£6.73	0.11
Acticoat Moisture Control dressing 10cm x 10cm square (1 dressing)	Silver	Elemental silver	£18.33	0.00
Acticoat Moisture Control dressing 10cm x 20cm rectangular (1 dressing)	Silver	Elemental silver	£35.71	0.00

Acticoat Moisture Control dressing 5cm x 5cm square (1 dressing)	Silver	Elemental silver	£7.84	0.00
Actisorb Silver 220 dressing 10.5cm x 10.5cm (1 dressing)	Silver	Elemental silver	£2.73	0.41
Actisorb Silver 220 dressing 10.5cm x 19cm (1 dressing)	Silver	Elemental silver	£4.97	0.20
Actisorb Silver 220 dressing 6.5cm x 9.5cm (1 dressing)	Silver	Elemental silver	£1.74	0.20
Atrauman Ag dressing 10cm x 10cm (1 dressing)	Silver	Silver salts and compounds	£1.39	1.54
Atrauman Ag dressing 10cm x 20cm (1 dressing)	Silver	Silver salts and compounds	£2.72	1.15
Atrauman Ag dressing 5cm x 5cm (1 dressing)	Silver	Silver salts and compounds	£0.57	0.94
KerraContact Ag dressing 10cm x 12.5cm rectangular (1 dressing)	Silver	Silver salts and compounds	£8.04	0.18
KerraContact Ag dressing 15cm x 15cm square (1 dressing)	Silver	Silver salts and compounds	£14.10	0.11
KerraContact Ag dressing 20cm x 40cm rectangular (1 dressing)	Silver	Silver salts and compounds	£43.01	0.01
KerraContact Ag dressing 5cm x 5cm square (1 dressing)	Silver	Silver salts and compounds	£3.29	0.06

Promogran Prisma dressing 123 square cm (1 dressing)	Silver	Silver salts and compounds	£19.03	0.00
Promogran Prisma dressing 28 square cm (1 dressing)	Silver	Silver salts and compounds	£6.68	0.00
Silverlon Flex dressing 10cm x 10cm square (1 dressing)	Silver	Elemental silver	£6.60	0.00
Silverlon Flex dressing 10cm x 20cm rectangular (1 dressing)	Silver	Elemental silver	£10.35	0.00
Silverlon Flex dressing 20cm x 20cm square (1 dressing)	Silver	Elemental silver	£18.78	0.00
Silverlon Flex dressing 5cm x 5cm square (1 dressing)	Silver	Elemental silver	£3.36	0.00
Iodine				
Iodoflex paste dressing (5 grams)	Iodine	Cadexomer iodine	£4.54	1.00
Iodoflex paste dressing (10 grams)	Iodine	Cadexomer iodine	£9.07	1.00
Iodoflex paste dressing (17 grams)	Iodine	Cadexomer iodine	£14.37	1.00
Iodosorb ointment dressing (10 grams)	Iodine	Cadexomer iodine	£5.01	0.31
Iodosorb ointment dressing (20 grams)	Iodine	Cadexomer iodine	£10.03	0.31
Iodosorb powder dressing sachets (3 grams)	Iodine	Cadexomer iodine	£2.15	0.12

Inadine dressing 5cm x 5cm (1 dressing)	Iodine	Povidone iodine	£0.35	10.08
Inadine dressing 9.5cm x 9.5cm (1 dressing)	Iodine	Povidone iodine	£0.51	7.37
Povitulle dressing 5cm x 5cm (1 dressing)	Iodine	Povidone iodine	£0.29	6.57
Povitulle dressing 9.5cm x 9.5cm (1 dressing)	Iodine	Povidone iodine	£0.43	3.86
Honey				
Medihoney Antibacterial Honey Apinate dressing 10cm x 10cm square (1 dressing)	Honey	Manuka honey	£3.55	0.34
Medihoney Antibacterial Honey Apinate dressing 5cm x 5cm square (1 dressing)	Honey	Manuka honey	£2.09	0.52
Medihoney Gel Sheet dressing 10cm x 10cm (1 dressing)	Honey	Manuka honey	£4.38	0.14
Medihoney Gel Sheet dressing 5cm x 5cm (1 dressing)	Honey	Manuka honey	£1.83	0.15
Algivon dressing 10cm x 10cm (1 dressing)	Honey	Manuka honey	£4.41	0.00
Algivon dressing 5cm x 5cm (1 dressing)	Honey	Manuka honey	£2.57	0.00
Algivon Plus dressing 10cm x 10cm (1 dressing)	Honey	Manuka honey	£4.36	0.66
Algivon Plus dressing 5cm x 5cm (1 dressing)	Honey	Manuka honey	£2.54	0.53

Revamil Melginate dressing 10cm x 10cm (1 dressing)	Honey	Monofloral honey	£4.36	0.06
Revamil Melginate dressing 5cm x 5cm (1 dressing)	Honey	Monofloral honey	£2.54	0.00
Medihoney HCS dressing 11cm x 11cm square (1 dressing)	Honey	Manuka honey	£4.67	0.19
Medihoney HCS dressing 20cm x 20cm square (1 dressing)	Honey	Manuka honey	£18.84	0.02
Medihoney HCS dressing 20cm x 30cm rectangular (1 dressing)	Honey	Manuka honey	£29.31	0.00
Medihoney HCS dressing 6cm x 6cm square (1 dressing)	Honey	Manuka honey	£2.34	0.52
Medihoney HCS dressing with adhesive border 11cm x 11cm square (1 dressing)	Honey	Manuka honey	£3.19	0.06
Medihoney HCS dressing with adhesive border 15cm x 15cm square (1 dressing)	Honey	Manuka honey	£6.04	0.02
Medihoney HCS Surgical dressing with adhesive border 7.5cm x 20cm (1 dressing)	Honey	Manuka honey	£3.18	0.00
Actibalm dressing (10 grams)	Honey	Manuka honey	£2.55	0.00
Activon Medical Grade Manuka Honey dressing (20 grams)	Honey	Manuka honey	£2.46	0.62
Activon Medical Grade Manuka Honey dressing (25 grams)	Honey	Manuka honey	£2.87	0.62

L-Mesitran ointment dressing (20 grams)	Honey	Polyfloral honey	£3.93	0.05
L-Mesitran ointment dressing (50 grams)	Honey	Polyfloral honey	£9.96	0.05
L-Mesitran SOFT ointment dressing (15 grams)	Honey	Polyfloral honey	£3.64	0.02
Manuka Fill dressing (14.2 grams)	Honey	Manuka honey	£2.45	0.00
Manuka Fill dressing (42.5 grams)	Honey	Manuka honey	£4.50	0.00
MANUKAppli dressing (30 grams)	Honey	Manuka honey	£5.90	0.03
Medihoney Antibacterial Medical Honey dressing (20 grams)	Honey	Manuka honey	£4.13	0.07
Medihoney Antibacterial Medical Honey dressing (50 grams)	Honey	Manuka honey	£10.33	0.07
Medihoney Antibacterial Wound Gel dressing (10 grams)	Honey	Manuka honey	£2.81	0.37
Medihoney Antibacterial Wound Gel dressing (20 grams)	Honey	Manuka honey	£4.20	0.37
Melladerm Plus dressing (20 grams)	Honey	Polyfloral honey	£3.98	0.00
Melladerm Plus dressing (50 grams)	Honey	Polyfloral honey	£8.50	0.00
Melloxy dressing (20 grams)	Honey	Polyfloral honey	£4.10	0.00

Melloxy dressing (50 grams)	Honey	Polyfloral honey	£8.76	0.00
Revamil Balm 2g sachet (1 sachet)	Honey	Monofloral honey	£0.47	0.00
Revamil Balm dressing (15 grams)	Honey	Monofloral honey	£3.55	0.00
Revamil Balm dressing (50 grams)	Honey	Monofloral honey	£7.75	0.00
Revamil Wound Gel dressing (5 grams)	Honey	Monofloral honey	£1.29	0.00
Revamil Wound Gel dressing (18 grams)	Honey	Monofloral honey	£3.57	0.00
SurgihoneyRO dressing (20 grams)	Honey	Polyfloral honey	£9.23	0.02
SurgihoneyRO dressing (50 grams)	Honey	Polyfloral honey	£23.09	0.02
L-Mesitran Border sheet 10cm x 10cm square (1 dressing)	Honey	Polyfloral honey	£2.78	0.27
L-Mesitran Hydro sheet 10cm x 10cm square (1 dressing)	Honey	Polyfloral honey	£2.66	0.08
L-Mesitran Net sheet 10cm x 10cm square (1 dressing)	Honey	Polyfloral honey	£2.57	0.09
Actilite gauze dressing 10cm x 10cm (1 dressing)	Honey	Manuka honey	£1.28	2.53
Actilite gauze dressing 10cm x 20cm (1 dressing)	Honey	Manuka honey	£2.47	0.51

Actilite gauze dressing 20cm x 30cm (1 dressing)	Honey	Manuka honey	£6.95	0.07
Actilite gauze dressing 30cm x 30cm (1 dressing)	Honey	Manuka honey	£11.50	0.02
Actilite gauze dressing 30cm x 60cm (1 dressing)	Honey	Manuka honey	£19.87	0.01
Actilite gauze dressing 5cm x 5cm (1 dressing)	Honey	Manuka honey	£0.74	2.82
Activon Tulle gauze dressing 10cm x 10cm (1 dressing)	Honey	Manuka honey	£3.85	0.59
Activon Tulle gauze dressing 5cm x 5cm (1 dressing)	Honey	Manuka honey	£2.33	0.76
Medihoney Tulle dressing 10cm x 10cm (1 dressing)	Honey	Manuka honey	£3.11	0.17
Medihoney Tulle dressing 5cm x 5cm (1 dressing)	Honey	Manuka honey	£1.77	0.09
Melladerm Plus Tulle dressing 10cm x 10cm (1 dressing)	Honey	Polyfloral honey	£2.10	0.00
Revamil dressing 10cm x 10cm (1 dressing)	Honey	Monofloral honey	£2.97	0.01
Revamil dressing 10cm x 20cm (1 dressing)	Honey	Monofloral honey	£5.43	0.00
Revamil dressing 5cm x 5cm (1 dressing)	Honey	Monofloral honey	£1.76	0.00
Revamil dressing 8cm x 8cm (1 dressing)	Honey	Monofloral honey	£2.99	0.02

Revamil Collagen dressing 5cm x 5cm square (1 dressing)	Honey	Monofloral honey	£6.04	0.00
Chlorhexidine				
Chlorhexidine gauze dressing BP 10cm x 10cm (1 dressing)	Chlorhexidine	Chlorhexidine	£0.68	0.02
Chlorhexidine gauze dressing BP 5cm x 5cm (1 dressing)	Chlorhexidine	Chlorhexidine	£0.33	0.02
Copper				
MedCu dressing 10cm x 12cm (1 dressing)	Copper	Copper	£4.28	0.00
MedCu dressing 10cm x 20cm (1 dressing)	Copper	Copper	£6.96	0.00
MedCu dressing 5cm x 6cm (1 dressing)	Copper	Copper	£1.85	0.00
MedCu dressing with adhesive border 10cm x 10cm (1 dressing)	Copper	Copper	£4.56	0.00
MedCu dressing with adhesive border 10cm x 25cm (1 dressing)	Copper	Copper	£8.27	0.00
PHMB				
ActivHeal PHMB Foam Non-Adhesive dressing 10cm x 10cm square (1 dressing)	PHMB	PHMB in foam	£4.07	0.02
ActivHeal PHMB Foam Non-Adhesive dressing 10cm x 20cm rectangular (1 dressing)	PHMB	PHMB in foam	£6.83	0.00

ActivHeal PHMB Foam Non-Adhesive dressing 15cm x 15cm square (1 dressing)	PHMB	PHMB in foam	£6.83	0.00
ActivHeal PHMB Foam Non-Adhesive dressing 20cm x 20cm square (1 dressing)	PHMB	PHMB in foam	£10.00	0.00
ActivHeal PHMB Foam Non-Adhesive dressing 5cm x 5cm square (1 dressing)	PHMB	PHMB in foam	£1.96	0.01
ActivHeal PHMB Foam Non-Adhesive dressing 7.5cm x 7.5cm square (1 dressing)	PHMB	PHMB in foam	£3.24	0.01
ActivHeal PHMB Foam Silicone Border dressing 10cm x 10cm (1 dressing)	PHMB	PHMB in foam	£4.67	0.00
ActivHeal PHMB Foam Silicone Border dressing 10cm x 20cm (1 dressing)	PHMB	PHMB in foam	£7.59	0.00
ActivHeal PHMB Foam Silicone Border dressing 12.5cm x 12.5cm (1 dressing)	PHMB	PHMB in foam	£5.56	0.00
ActivHeal PHMB Foam Silicone Border dressing 15cm x 15cm (1 dressing)	PHMB	PHMB in foam	£7.59	0.00
ActivHeal PHMB Foam Silicone Border dressing 20cm x 20cm (1 dressing)	PHMB	PHMB in foam	£12.21	0.00
ActivHeal PHMB Foam Silicone Border dressing 8cm x 8cm (1 dressing)	PHMB	PHMB in foam	£3.03	0.00
Kendall AMD Antimicrobial foam dressing 10cm x 10cm square (1 dressing)	PHMB	PHMB in foam	£4.85	0.09

Kendall AMD Antimicrobial foam dressing 10cm x 20cm rectangular (1 dressing)	PHMB	PHMB in foam	£9.19	0.03
Kendall AMD Antimicrobial foam dressing 15cm x 15cm square (1 dressing)	PHMB	PHMB in foam	£9.19	0.01
Kendall AMD Antimicrobial foam dressing 2.5cm (4mm hole) (fenestrated) disc (1 dressing)	PHMB	PHMB in foam	£3.98	0.00
Kendall AMD Antimicrobial foam dressing 2.5cm (7mm hole) (fenestrated) disc (1 dressing)	PHMB	PHMB in foam	£3.98	0.00
Kendall AMD Antimicrobial foam dressing 20cm x 20cm square (1 dressing)	PHMB	PHMB in foam	£13.46	0.03
Kendall AMD Antimicrobial foam dressing 5cm x 5cm square (1 dressing)	PHMB	PHMB in foam	£2.57	0.06
Kendall AMD Antimicrobial foam dressing 8.8cm x 7.5cm rectangular (fenestrated) (1 dressing)	PHMB	PHMB in foam	£4.36	0.01
Kendall AMD Antimicrobial Plus foam dressing 10cm x 10cm square (1 dressing)	PHMB	PHMB in foam	£5.09	0.00
Kendall AMD Antimicrobial Plus foam dressing 8.8cm x 7.5cm rectangular (fenestrated) (1 dressing)	PHMB	PHMB in foam	£4.57	0.00
Kendall Telfa Clear dressing 10cm x 12.5cm (1 dressing)	PHMB	PHMB in foam	£1.70	0.00

Kendall Telfa Clear dressing 30cm x 30cm (1 dressing)	PHMB	PHMB in foam	£2.35	0.00
Kendall Telfa Clear dressing 30cm x 60cm (1 dressing)	PHMB	PHMB in foam	£3.00	0.00
Kendall Telfa Clear dressing 7.5cm x 7.5cm (1 dressing)	PHMB	PHMB in foam	£1.62	0.00
Prontosan Wound Gel dressing (30 ml)	PHMB	Unknown PHMB	£6.97	0.99
Prontosan Wound Gel X dressing (50 grams)	PHMB	Unknown PHMB	£12.75	0.27
Prontosan Wound Gel X dressing (250 grams)	PHMB	Unknown PHMB	£34.13	0.27
CelluDress - PHMB dressing 10cm x 10cm square (1 dressing)	PHMB	PHMB in hydrated biocellulose	£4.50	0.00
Suprasorb X + PHMB dressing 14cm x 20cm rectangular (1 dressing)	PHMB	PHMB in hydrated biocellulose	£12.80	0.25
Suprasorb X + PHMB dressing 5cm x 5cm square (1 dressing)	PHMB	PHMB in hydrated biocellulose	£2.83	0.36
Suprasorb X + PHMB dressing 9cm x 9cm square (1 dressing)	PHMB	PHMB in hydrated biocellulose	£5.63	0.37
Kerlix AMD Antimicrobial gauze dressing 11.4cm x 3.7m (1 dressing)	PHMB	PHMB coated gauze	£1.67	0.00
Kerlix AMD Antimicrobial Super Sponges 15.2cm x 17.1cm (2 devices)	PHMB	Unknown PHMB	£0.72	0.00

DACC				
Cutimed Sorbact Hydroactive B dressing 10cm x 10cm (1 dressing)	DACC	DACC	£7.75	0.01
Cutimed Sorbact Hydroactive B dressing 10cm x 20cm (1 dressing)	DACC	DACC	£12.41	0.00
Cutimed Sorbact Hydroactive B dressing 15cm x 15cm (1 dressing)	DACC	DACC	£14.58	0.01
Cutimed Sorbact Hydroactive B dressing 5cm x 6.5cm (1 dressing)	DACC	DACC	£4.35	0.01
Cutimed Sorbact Hydroactive dressing 14cm x 14cm (1 dressing)	DACC	DACC	£5.87	0.01
Cutimed Sorbact Hydroactive dressing 14cm x 24cm (1 dressing)	DACC	DACC	£9.40	0.00
Cutimed Sorbact Hydroactive dressing 19cm x 19cm (1 dressing)	DACC	DACC	£11.05	0.00
Cutimed Sorbact Hydroactive dressing 24cm x 24cm (1 dressing)	DACC	DACC	£16.74	0.00
Cutimed Sorbact Hydroactive dressing 7cm x 8.5cm (1 dressing)	DACC	DACC	£4.02	0.02
Cutimed Sorbact Gel dressing 7.5cm x 15cm rectangular (1 dressing)	DACC	DACC	£4.89	0.22
Cutimed Sorbact Gel dressing 7.5cm x 7.5cm square (1 dressing)	DACC	DACC	£2.90	0.59
Cutimed Siltec Sorbact B dressing 12.5cm x 12.5cm (1 dressing)	DACC	DACC	£7.05	0.05

Cutimed Siltec Sorbact B dressing 15cm x 15cm (1 dressing)	DACC	DACC	£8.73	0.01
Cutimed Siltec Sorbact B dressing 17.5cm x 17.5cm (1 dressing)	DACC	DACC	£12.21	0.00
Cutimed Siltec Sorbact B dressing 22.5cm x 22.5cm (1 dressing)	DACC	DACC	£18.58	0.01
Cutimed Siltec Sorbact B dressing 7.5cm x 7.5cm (1 dressing)	DACC	DACC	£2.75	0.10
Cutimed Sorbact dressing pad 10cm x 10cm (1 dressing)	DACC	DACC	£6.01	0.46
Cutimed Sorbact dressing pad 10cm x 20cm (1 dressing)	DACC	DACC	£9.38	0.37
Cutimed Sorbact dressing pad 7cm x 9cm (1 dressing)	DACC	DACC	£3.85	0.76
Cutimed Sorbact swab 4cm x 6cm (1 dressing)	DACC	DACC	£1.80	2.30
Cutimed Sorbact swab 7cm x 9cm (1 dressing)	DACC	DACC	£3.01	2.66
Cutimed Sorbion Sorbact dressing 10cm x 10cm square (1 dressing)	DACC	DACC	£6.17	0.01
Cutimed Sorbion Sorbact dressing 10cm x 20cm rectangular (1 dressing)	DACC	DACC	£9.65	0.02
Cutimed Sorbion Sorbact dressing 20cm x 20cm square (1 dressing)	DACC	DACC	£16.69	0.00
Cutimed Sorbion Sorbact dressing 20cm x 30cm rectangular (1 dressing)	DACC	DACC	£25.04	0.01

Enzyme alginogel				
Flaminal Forte gel dressing (15 grams)	Enzyme alginogel	Enzyme alginogel	£8.44	2.38
Flaminal Forte gel dressing (50 grams)	Enzyme alginogel	Enzyme alginogel	£27.96	2.38
Flaminal Hydro gel dressing (15 grams)	Enzyme alginogel	Enzyme alginogel	£8.44	0.97
Flaminal Hydro gel dressing (50 grams)	Enzyme alginogel	Enzyme alginogel	£27.96	0.97
Chitosan				
KytoCel dressing 10cm x 10cm square (1 dressing)	Chitosan	Chitosan	£1.93	0.00
KytoCel dressing 15cm x 15cm square (1 dressing)	Chitosan	Chitosan	£3.63	0.00
KytoCel dressing 2.5cm x 45cm rectangular (1 dressing)	Chitosan	Chitosan	£1.95	0.00
KytoCel dressing 4cm x 10cm rectangular (1 dressing)	Chitosan	Chitosan	£1.04	0.00
KytoCel dressing 4cm x 20cm rectangular (1 dressing)	Chitosan	Chitosan	£1.52	0.00
KytoCel dressing 4cm x 30cm rectangular (1 dressing)	Chitosan	Chitosan	£2.29	0.00
KytoCel dressing 5cm x 5cm square (1 dressing)	Chitosan	Chitosan	£0.81	0.00
MaxioCel dressing 10cm x 10cm square (1 dressing)	Chitosan	Chitosan	£1.88	0.00

MaxioCel dressing 15cm x 15cm square (1 dressing)	Chitosan	Chitosan	£3.56	0.00
MaxioCel dressing 2.5cm x 30cm rectangular (1 dressing)	Chitosan	Chitosan	£1.27	0.00
MaxioCel dressing 20cm x 30cm rectangular (1 dressing)	Chitosan	Chitosan	£9.42	0.00
MaxioCel dressing 45cm x 45cm square (1 dressing)	Chitosan	Chitosan	£31.79	0.00
MaxioCel dressing 5cm x 5cm square (1 dressing)	Chitosan	Chitosan	£0.72	0.00
Octendine				
Octenilin Wound Gel dressing (20 ml)	Octendine	Octendine	£5.15	0.14
Octenilin Wound Gel dressing (250 ml)	Octendine	Octendine	£27.10	0.14

11.9 Appendix I: Additional probabilistic outcomes

11.9.1 Cost-effectiveness acceptability curves (CEAC)

Figure 11.311.4: Cost-effectiveness acceptability curve (CEAC)CEAC for chitosan (comparator) compared with iodine (intervention)

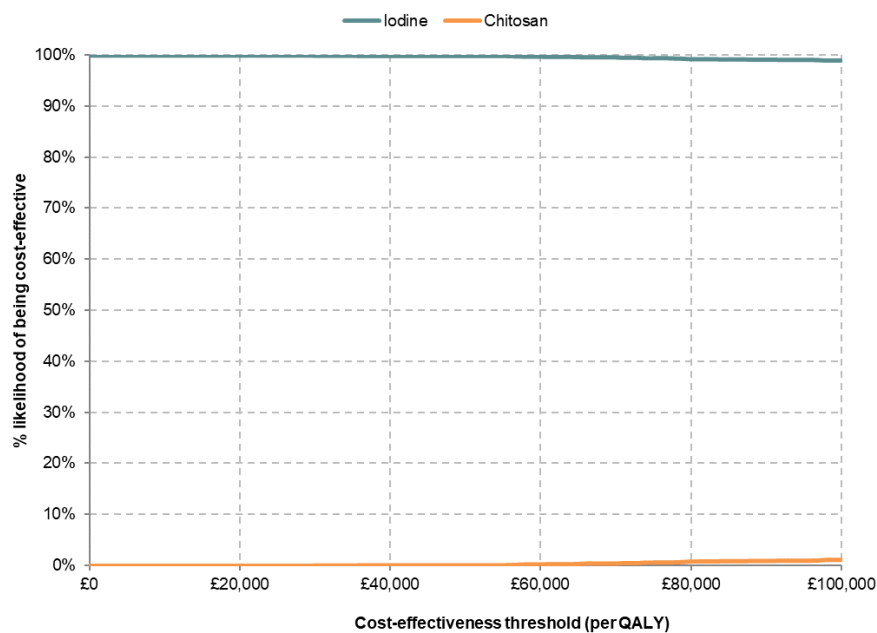


Figure 11.511.6: CEAC for copper (comparator) compared with iodine (intervention)

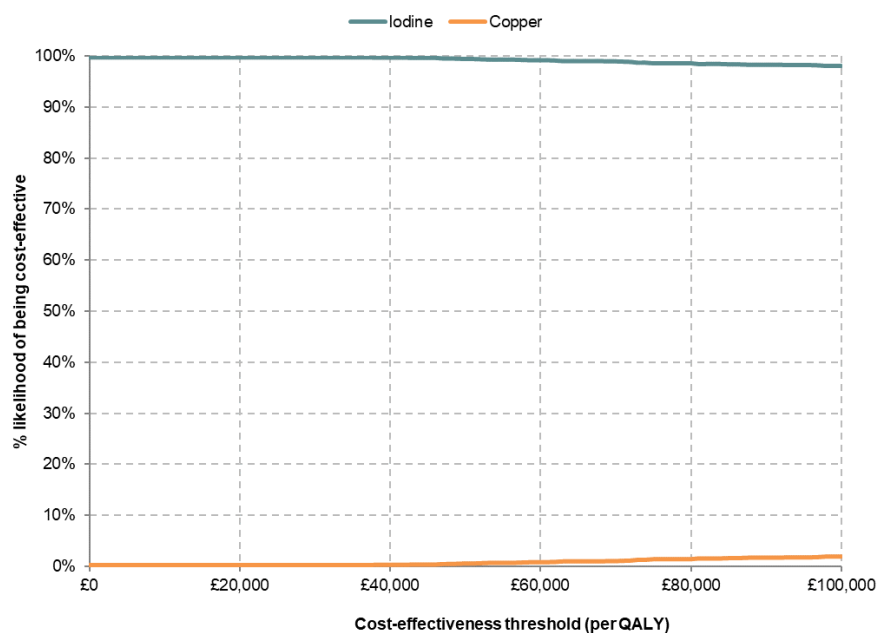


Figure 11.711.8: CEAC for honey (comparator) compared with iodine (intervention)

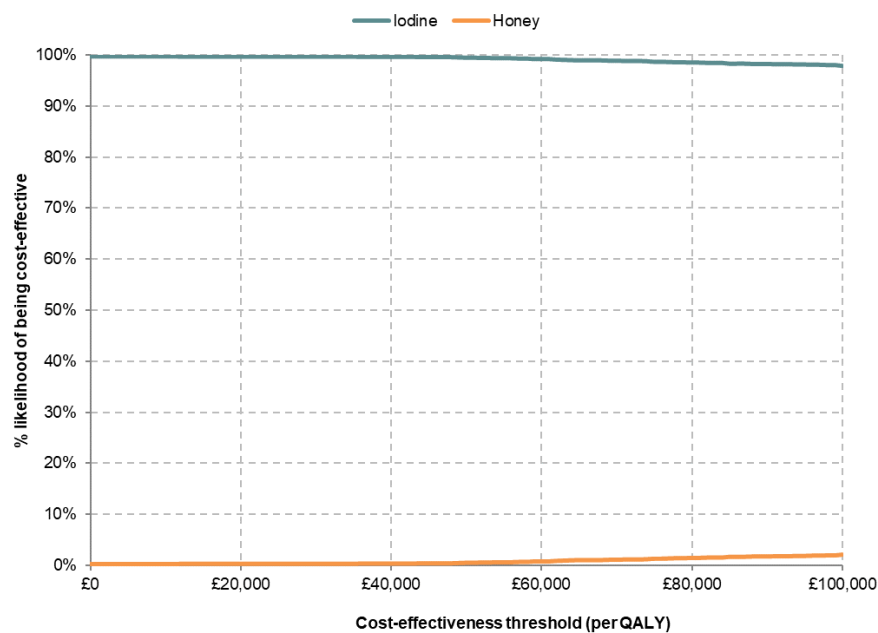


Figure 11.911.10: CEAC for PHMB (comparator) compared with iodine (intervention)

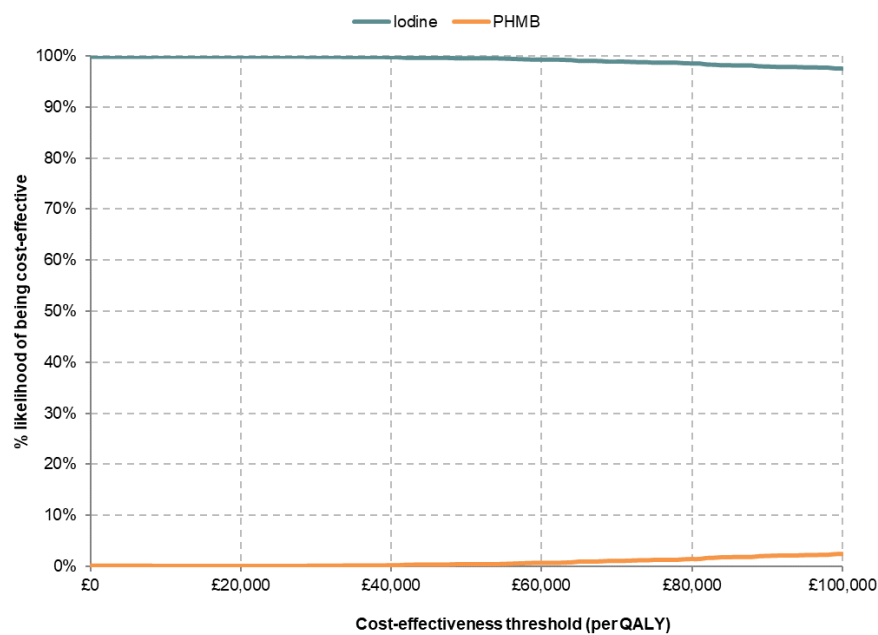


Figure 11.1111.12: CEAC for silver (comparator) compared with iodine (intervention)

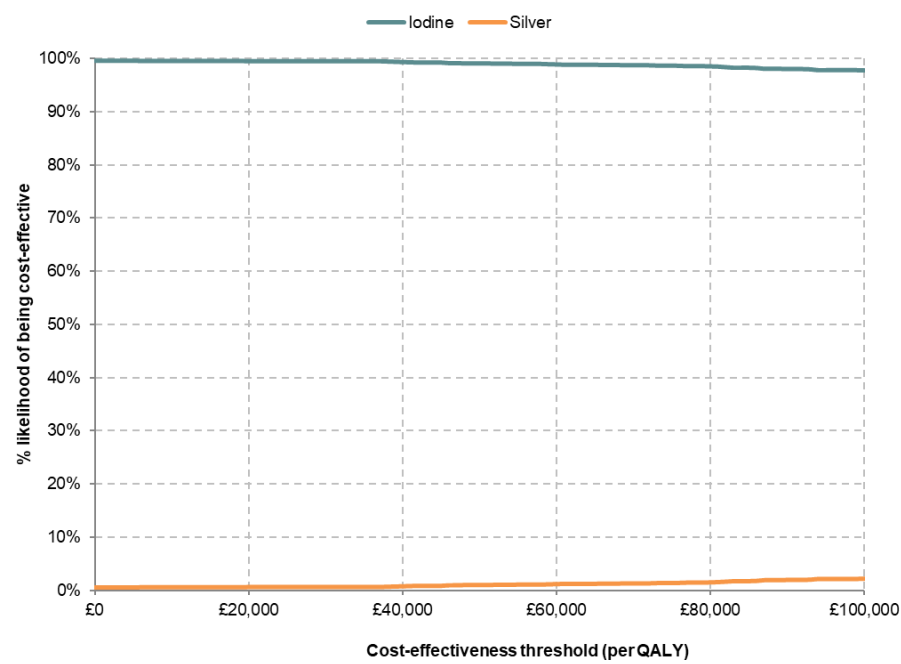


Figure 11.1311.14: Convergence plot for chitosan (comparator) compared with iodine (intervention)

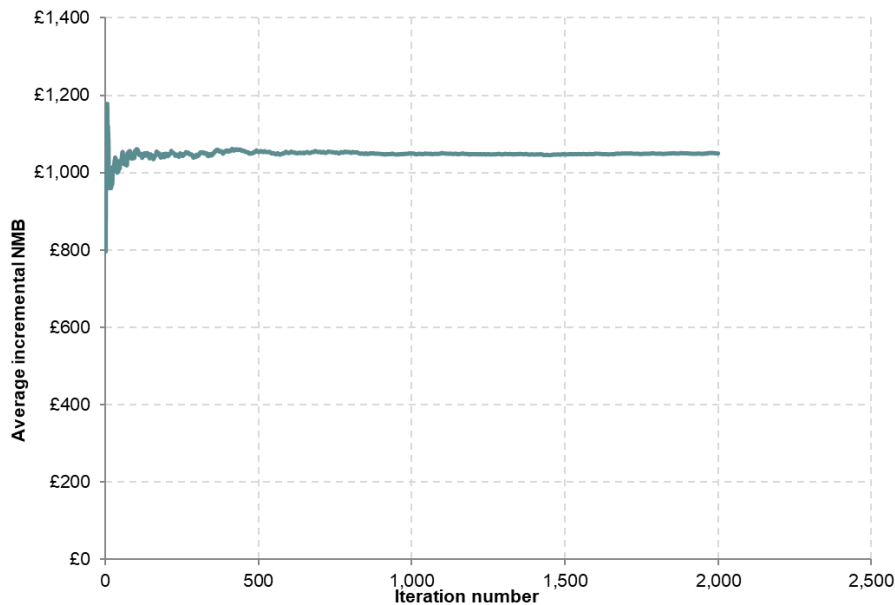


Figure 11.1511.16: Convergence plot for copper (comparator) compared with iodine (intervention)

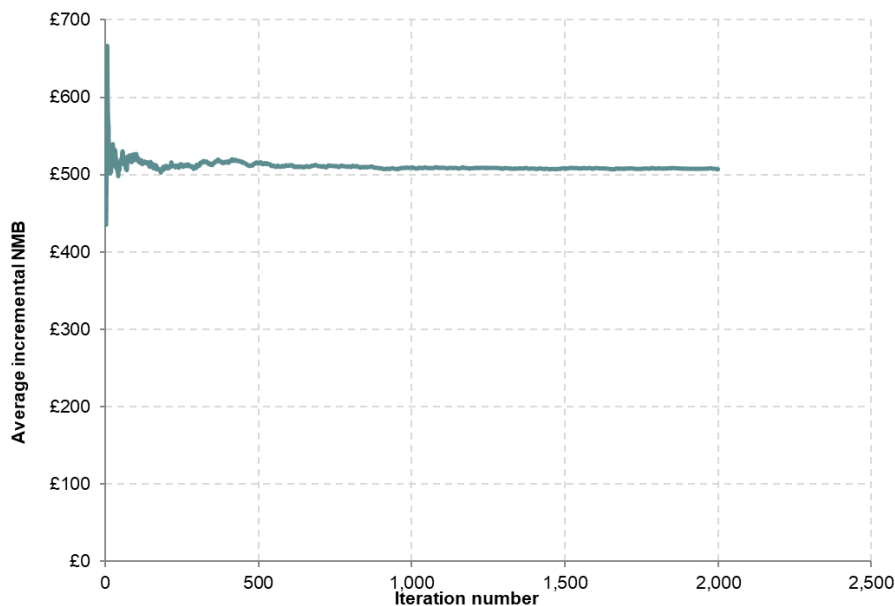


Figure 11.1711.18: Convergence plot for honey (comparator) compared with iodine (intervention)

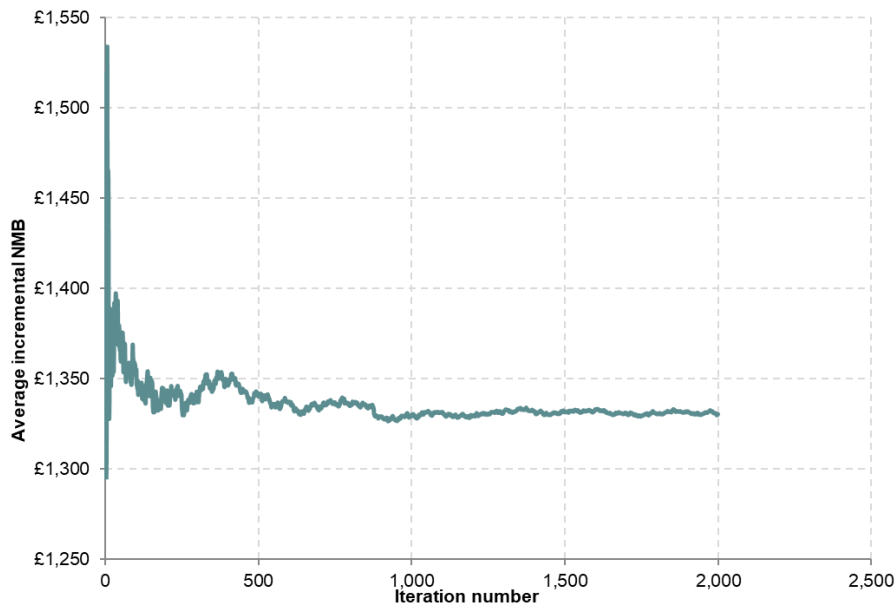


Figure 11.1911.20: Convergence plot for iodine (comparator) compared with iodine (intervention)

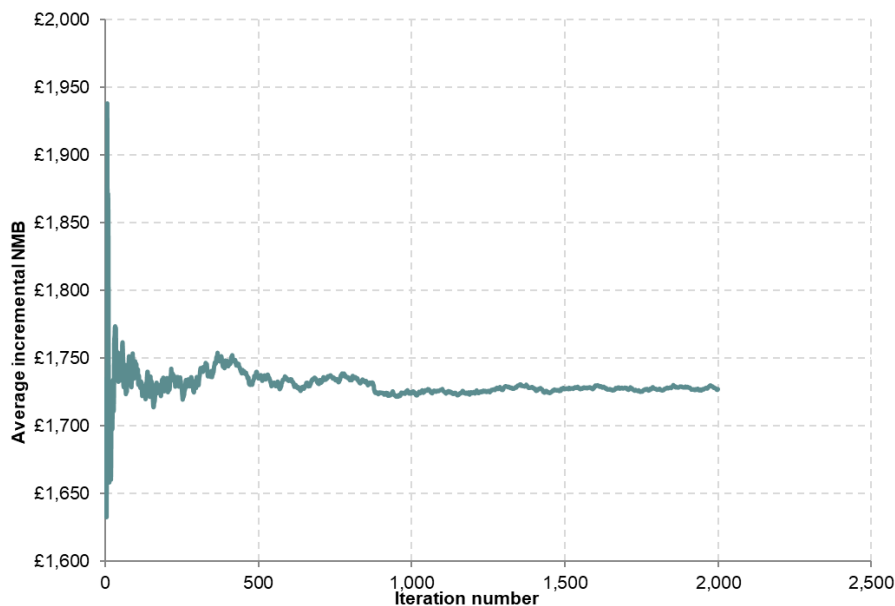
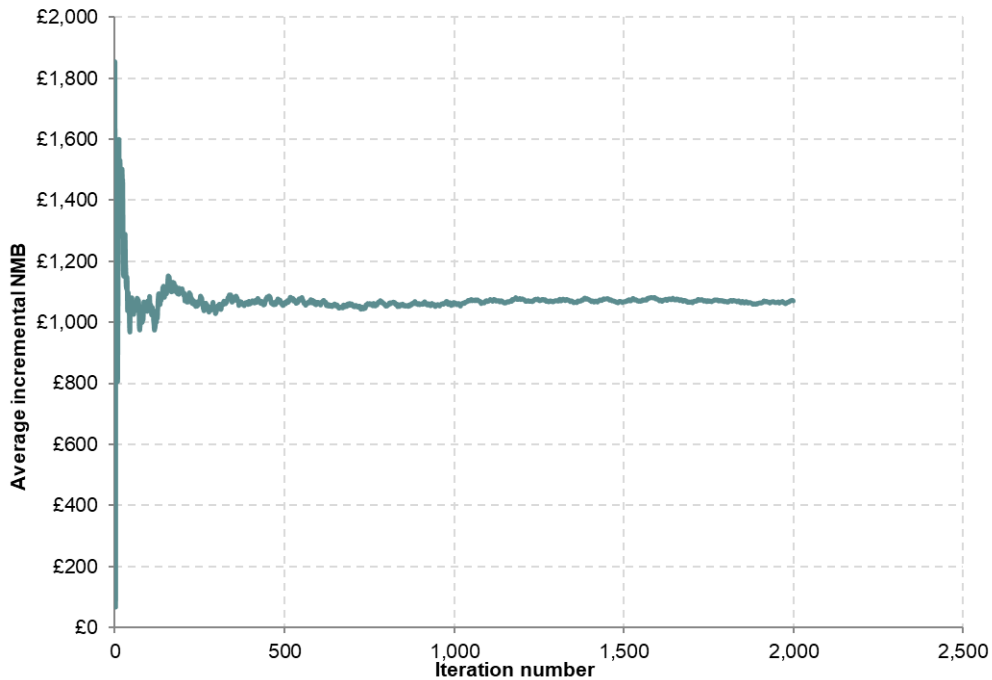


Figure 11.2111.22: Convergence plot for silver (comparator) compared with iodine (intervention)



11.10 *Appendix J: Scenario analysis results*

Table 11.2: Scenario results: Total costs

	Chitosan	Copper	Honey	Iodine	PHMB	Silver
Reference case	£7,294	£6,845	£7,417	£6,447	£7,755	£7,295
Cost scenarios						
Minimum cost of dressing containing agent	£6,959	£6,558	£7,157	£6,250	£7,403	£6,958
Maximum cost of dressing containing agent	£11,346	£10,238	£10,638	£8,895	£11,198	£11,450
Assume all dressings changed once a week (regardless of infection status)	£7,085	£6,669	£7,269	£6,321	£7,582	£7,099
Assume all dressings changed 3 time a week for infected unhealed wounds and once a week for non-infected unhealed wounds	£7,112	£6,687	£7,296	£6,327	£7,669	£7,136
Assume all dressings changed 3 time a week while infected, unhealed and once a week while non-infected, unhealed with minimum cost	£6,948	£6,550	£7,151	£6,240	£7,400	£6,949
Assume all dressings changed 3 time a week while infected, unhealed and once a week while non-infected, unhealed with maximum cost	£9,006	£8,176	£9,027	£7,398	£9,577	£9,301
Iodine cost to align with Cadaxomer iodine (to align with the efficacy)	£7,294	£6,862	£7,417	£6,664	£7,746	£7,297
Resource use						
Peri-pandemic resource use (2020) Published in Guest et al (2023) 1,153 people with venous leg ulcers in the THIN data base	£3,671	£3,433	£3,689	£3,190	£3,900	£3,671

Peri-pandemic resource use (2021) Published in Guest et al (2023). 733 people with venous leg ulcers in the THIN data base	£4,367	£4,089	£4,405	£3,816	£4,641	£4,367
Health state costs in the 'infected unhealed wound' health state 25% larger than the 'non-infected unhealed wound' health state	£7,504	£6,977	£7,745	£6,597	£8,184	£7,506
Health state costs in the 'infected unhealed wound' health state 250% larger than the 'non-infected unhealed wound' health state (£514 per cycle)	£8,556	£7,638	£9,381	£7,347	£10,325	£8,557
The cost of the infected unhealed health state 3.2 times more than that of an uninfected wound as per Guest et al (2018)	£9,144	£8,008	£10,298	£7,767	£11,524	£9,145
The cost of the healed health state set to £0	£6,301	£5,736	£6,482	£5,253	£6,889	£6,303
The cost of the infected unhealed health state 3.2 times more than that of an uninfected wound as per Guest et al (2018) and the "healed" health state set to £0.	£8,151	£6,899	£9,362	£6,573	£10,657	£8,153
Best practice scenarios						
Assumption that the people discontinue AMDs in the 'non-infected unhealed wound' health state and the treatment effect of AMDs remains (no AMD cost)	£6,996	£6,568	£7,182	£6,251	£7,488	£6,998

Assumption that the people discontinue AMDs in the 'non-infected unhealed wound' health state and automatically move onto second line basket	£7,249	£7,170	£7,339	£7,158	£7,499	£7,250
Efficacy and prescription time						
Equivalent efficacy data aligns with Table 7.5. No edits to the time at which the agent are prescribed.	£7,272	£7,269	£6,769	£6,774	£6,832	£7,271
Equivalent efficacy data aligns with Table 7.5 in a world where all agents are prescribed for 4 weeks	£7,272	£7,269	£7,248	£7,250	£7,273	£7,271
Equivalent efficacy data aligns with Table 7.5 in a world where all agents are prescribed for 12 weeks	£6,829	£6,809	£6,769	£6,774	£6,832	£6,824
Assumption that all agents are prescribed for 4 weeks	£7,294	£6,845	£7,524	£7,078	£7,645	£7,295
Assumption that all agents are prescribed for 12 weeks	£6,876	£6,196	£7,417	£6,447	£7,755	£6,896
The intercept of the curve informing the 4 to 12 week conversion ratio was to account for the healing rate of infected people only (allowing for 11% to be healed at 4 weeks).	£7,241	£6,696	£7,125	£5,849	£7,862	£7,243

Transition from "infected, unhealed wound" to "non-infected, unhealed wound" is informed by the healing rate and transition from "non-infected, unhealed wound" to "healed wound" is equivalent to Guest et al (2023)	£7,635	£7,554	£7,942	£7,709	£8,092	£7,636
Transition from "infected, unhealed wound" to "non-infected, unhealed wound" was equivalent	£7,282	£7,103	£7,199	£6,565	£7,459	£7,283
Ulcer reoccurrence parameters						
Assumption that a per-week rate of 0.1 ulcer infections reoccur (move to infected unhealed wound from non-infected unhealed wound)	£8,340	£7,855	£8,428	£7,413	£8,747	£8,342
Assumption that a per-week rate of 0.5 ulcer infections reoccur (move to infected unhealed wound from non-infected unhealed wound)	£9,838	£9,398	£9,900	£9,106	£10,132	£9,840
Assumption that a per-week rate of 0.1 ulcer infections reoccur for first line, and a per-week rate of 0.5 ulcer infections reoccur for second line	£9,704	£9,123	£9,569	£8,347	£9,934	£9,708
Discontinuation parameters						

Assumption that there is a per-week discontinuation rate of 0.25 from first line (infected AND non-infected, unhealed) to second line.	£7,370	£7,066	£7,519	£7,224	£7,614	£7,369
Utility parameters						
Health state utilities from Walzer et al (2018) (Walzer et al. 2018)	£7,294	£6,845	£7,417	£6,447	£7,755	£7,295
Health state utilities assuming 'infected unhealed wound' health state has utility 10% lower than 'non-infected unhealed' wound	£7,294	£6,845	£7,417	£6,447	£7,755	£7,295

Table 11.3: Scenario results: Total QALYs

	Chitosan	Copper	Honey	Iodine	PHMB	Silver
Reference case	0.692	0.699	0.688	0.703	0.684	0.692
Cost scenarios						
Minimum cost of dressing containing agent	0.692	0.699	0.688	0.703	0.684	0.692
Maximum cost of dressing containing agent	0.692	0.699	0.688	0.703	0.684	0.692
Assume all dressings changed once a week (regardless of infection status)	0.692	0.699	0.688	0.703	0.684	0.692
Assume all dressings changed 3 time a week for infected unhealed wounds and once a week for non-infected unhealed wounds	0.692	0.699	0.688	0.703	0.684	0.692
Assume all dressings changed 3 time a week while infected, unhealed and once a week while non-infected, unhealed with minimum cost	0.692	0.699	0.688	0.703	0.684	0.692
Assume all dressings changed 3 time a week while infected, unhealed and once a week while non-infected, unhealed with maximum cost	0.692	0.699	0.688	0.703	0.684	0.692
Iodine cost to align with Cadaxomer iodine (to align with the efficacy)	0.692	0.699	0.688	0.703	0.684	0.692
Resource use						
Peri-pandemic resource use (2020) Published in Guest et al (2023) 1,153 people with venous leg ulcers in the THIN data base	0.692	0.699	0.688	0.703	0.684	0.692

Peri-pandemic resource use (2021) Published in Guest et al (2023). 733 people with venous leg ulcers in the THIN data base	0.692	0.699	0.688	0.703	0.684	0.692
Health state costs in the 'infected unhealed wound' health state 25% larger than the 'non-infected unhealed wound' health state	0.692	0.699	0.688	0.703	0.684	0.692
Health state costs in the 'infected unhealed wound' health state 250% larger than the 'non-infected unhealed wound' health state (£514 per cycle)	0.692	0.699	0.688	0.703	0.684	0.692
The cost of the infected unhealed health state 3.2 times more than that of an uninfected wound as per Guest et al (2018)	0.692	0.699	0.688	0.703	0.684	0.692
The cost of the healed health state set to £0	0.692	0.699	0.688	0.703	0.684	0.692
The cost of the infected unhealed health state 3.2 times more than that of an uninfected wound as per Guest et al (2018) and the "healed" health state set to £0.	0.692	0.699	0.688	0.703	0.684	0.692
Best practice scenarios						
Assumption that the people discontinue AMDs in the 'non-infected unhealed wound' health state and the treatment effect of AMDs remains (no AMD cost)	0.692	0.699	0.688	0.703	0.684	0.692

Assumption that the people discontinue AMDs in the 'non-infected unhealed wound' health state and automatically move onto second line basket	0.688	0.689	0.686	0.688	0.684	0.688
Efficacy and prescription time						
Equivalent efficacy data aligns with Table 7.5. No edits to the time at which the agent are prescribed.	0.692	0.692	0.698	0.698	0.698	0.692
Equivalent efficacy data aligns with Table 7.5 in a world where all agents are prescribed for 4 weeks	0.692	0.692	0.692	0.692	0.692	0.692
Equivalent efficacy data aligns with Table 7.5 in a world where all agents are prescribed for 12 weeks	0.698	0.698	0.698	0.698	0.698	0.698
Assumption that all agents are prescribed for 4 weeks	0.692	0.699	0.688	0.695	0.687	0.692
Assumption that all agents are prescribed for 12 weeks	0.698	0.708	0.688	0.703	0.684	0.697
The intercept of the curve informing the 4 to 12 week conversion ratio was to account for the healing rate of infected people only (allowing for 11% to be healed at 4 weeks).	0.691	0.695	0.688	0.693	0.687	0.691

Transition from "infected, unhealed wound" to "non-infected, unhealed wound" is informed by the healing rate and transition from "non-infected, unhealed wound" to "healed wound" is equivalent to Guest et al (2023)	0.687	0.688	0.681	0.684	0.680	0.687
Transition from "infected, unhealed wound" to "non-infected, unhealed wound" was equivalent	0.692	0.695	0.692	0.702	0.689	0.692
Ulcer reoccurrence parameters						
Assumption that a per-week rate of 0.1 ulcer infections reoccur (move to infected unhealed wound from non-infected unhealed wound)	0.677	0.685	0.674	0.690	0.671	0.677
Assumption that a per-week rate of 0.5 ulcer infections reoccur (move to infected unhealed wound from non-infected unhealed wound)	0.657	0.663	0.654	0.666	0.652	0.657
Assumption that a per-week rate of 0.1 ulcer infections reoccur for first line, and a per-week rate of 0.5 ulcer infections reoccur for second line	0.659	0.667	0.659	0.677	0.654	0.659
Discontinuation parameters						

Assumption that there is a per-week discontinuation rate of 0.25 from first line (infected AND non-infected, unhealed) to second line.	0.693	0.701	0.693	0.713	0.683	0.693
Utility parameters						
Health state utilities from Walzer et al (2018) (Walzer et al. 2018)	0.530	0.547	0.510	0.548	0.492	0.530
Health state utilities assuming 'infected unhealed wound' health state has utility 10% lower than 'non-infected unhealed' wound	0.687	0.695	0.680	0.700	0.674	0.687