National Institute for Health and Care Excellence

Final

Lyme disease

[H] Evidence review for management of acrodermatitis chronica atrophicans

NICE guideline 95

Evidence review

April 2018

Final

This evidence review was developed by the National Guideline Centre

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1.1 Review question: What is the most clinically and cost-effective treatment for people with acrodermatitis chronica atrophicans related to Lyme disease?

1.2 Introduction

Acrodermatitis chronica atrophicans (ACA) is a chronic skin manifestation of Lyme disease usually presenting months or years after the infected tick bite, which may not be remembered. It causes inflammatory violet-coloured lesions, which are most often on the limbs. If untreated, the lesions may become fibrotic and tissue loss (atrophy) may occur. If treated early, the lesions may fully resolve; however, those presenting with later stages of ACA may have permanent skin damage even after the infection is treated. Involvement of the peripheral nervous system predominantly, in particular a sensory polyneuropathy, is described.

1.3 PICO table

For full details, see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	Adults (18 years and over), young people (12 to 17 years) and children (under 12 years) with symptoms consistent with acrodermatitis chronica atrophicans related to Lyme disease

Interventions	Antimicrobials, including but not limited to:
	• Penicillins
	  ○ Amoxicillin (oral, IV)
	  ○ Ampicillin (oral, IV)
	  ○ Benzylpenicillin sodium / Penicillin G (IV)
	  - Including Augmentin (Amoxicillin and clavulanic acid; oral, IV)
	  ○ Phenoxymethylpenicillin / Penicillin V (oral)
	• Tetracyclines
	  ○ Doxycycline (oral)
	  ○ Minocycline (oral)
	• Cephalosporins
	  ○ Cefotaxime (IV)
	  ○ Ceftriaxone (IV)
	  ○ Cefuroxime axetil (oral)
	• Macrolides
	  ○ Azithromycin (oral)
	  ○ Clarithromycin (oral, IV)
	• Fluoroquinolones
	  ○ Ciprofloxacin (oral, IV)
	  ○ Levofloxacin (oral, IV)
	  ○ Moxifloxacin (oral, IV)
	  ○ Nalidixic acid (oral)
	  ○ Norfloxacin (oral)

	○ Ofloxacin (oral, IV) ○ Rifampicin (oral, IV)
Comparisons	• Antimicrobial agents compared with each other ○ Type of antimicrobial agent ○ Route of administration ○ Duration of treatment: 1 month versus longer • Monotherapy versus polytherapy (any combination) • Antimicrobial agents compared to no treatment
Outcomes	**Critical:** 1. Quality of life (any validated measure) 2. Cure (resolution of ACA symptoms) 3. Reduction of ACA symptoms 4. Relapse of ACA symptoms **Important:** 5. Adverse events
Study design	• RCTs • Cohort studies (if no RCT evidence is found)

1.4 Clinical evidence

1.4.1 Included studies

One cohort study was included in the review;[1] this is summarised in Table 2 below. Evidence from this study is summarised in the clinical evidence summary below (Table 3).

See also the study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix F.

A search was conducted for randomised trials comparing the effectiveness of antibiotics versus each other or placebo as treatment for people with acrodermatitis chronica atrophicans related to Lyme disease. No randomised trials were identified. One prospective cohort study was included in the review. The study compared the clinical effectiveness of doxycycline for 20 and 30 days, phenoxymethylpenicillin for 20 and 30 days and ceftriaxone in adults.

1.4.2 Excluded studies

See the excluded studies list in appendix I.

1.4.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Aberer 1996[1]	Doxycycline 100 mg twice daily. Duration 20 days. (n=7) Doxycycline 100 mg twice daily. Duration 30 days. (n=6)	n=46 Diagnosis: acrodermatitis chronica atrophicans established by clinical and histological criteria and	Cure (resolution of symptoms)	

Study	Intervention and comparison	Population	Outcomes	Comments
	Phenoxymethylpenicillin 1.5 million IU 3 times daily. Duration 20 days. (n=5) Phenoxymethylpenicillin 1.5 million IU 3 times daily. Duration 30 days. (n=14) Ceftriaxone 2 g. Duration 15 days. (n=14)	presence of IgG antibodies against *B. burgdorferi*.		

See appendix D for full evidence tables.

1.4.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: Ceftriaxone versus Phenoxymethylpenicillin (PO – 20 days)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 20-day phenoxymethylpenicillin	Risk difference with ceftriaxone (95% CI)
Cure (no persisting symptoms at 6 months) no persisting symptoms	19 (1 study) 6 months	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.89 (0.52 to 1.55)	800 per 1,000	88 fewer per 1,000 (from 384 fewer to 440 more)

[a] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[b] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 4: Clinical evidence summary: Ceftriaxone versus Phenoxymethylpenicillin (PO – 30 days)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 30-day phenoxymethylpenicillin	Risk difference with ceftriaxone (95% CI)
Cure (no persisting symptoms at 6 months) no persisting symptoms	28 (1 study) 6 months	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.77 (0.54 to 1.1)	929 per 1,000	214 fewer per 1,000 (from 427 fewer to 93 more)

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 5: Clinical evidence summary: Doxycycline (PO – 20 days) versus Ceftriaxone

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ceftriaxone	Risk difference with 20-day doxycycline (95% CI)
Cure (no persisting	21	VERY LOW[1,2]	RR 0.4	714 per 1,000	429 fewer per 1,000

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ceftriaxone	Risk difference with 20-day doxycycline (95% CI)
symptoms at 6 months) no persisting symptoms	(1 study) 6 months	due to risk of bias, imprecision	(0.12 to 1.35)		(from 629 fewer to 250 more)

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 6: Clinical evidence summary: Doxycycline (PO – 30 days) versus Ceftriaxone

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ceftriaxone	Risk difference with 30-day doxycycline (95% CI)
Cure (no persisting symptoms at 6 months) no persisting symptoms	20 (1 study) 6 months	VERY LOW[1,2] due to risk of bias, imprecision	RR 1.33 (0.9 to 1.96)	714 per 1,000	236 more per 1,000 (from 71 fewer to 686 more)

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 7: Clinical evidence summary: Phenoxymethylpenicillin (20 days) versus Phenoxymethylpenicillin (30 days)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 30-day phenoxymethylpenicillin	Risk difference with 20-day phenoxymethylpenicillin (95% CI)
Cure (no persisting symptoms at 6 months) no persisting symptoms	19 (1 study) 6 months	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.86 (0.54 to 1.37)	929 per 1,000	130 fewer per 1,000 (from 427 fewer to 344 more)

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 8: Clinical evidence summary: Doxycycline (PO – 20 days) versus Phenoxymethylpenicillin (PO – 20 days)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 20-day phenoxymethylpenicillin	Risk difference with 20-day doxycycline (95% CI)
Cure (no persisting symptoms at 6 months) no persisting symptoms	12 (1 study) 6 months	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.36 (0.1 to 1.25)	800 per 1,000	512 fewer per 1,000 (from 720 fewer to 200 more)

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 9: Clinical evidence summary: Doxycycline (PO – 20 days) versus Phenoxymethylpenicillin (PO – 30 days)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 30-day phenoxymethylpenicillin	Risk difference with 20-day doxycycline (95% CI)
Cure (no persisting symptoms at 6 months) no persisting symptoms	21 (1 study) 6 months	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.31 (0.09 to 1)	929 per 1,000	641 fewer per 1,000 (from 845 fewer to 0 more)

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 10: Clinical evidence summary: Doxycycline (PO – 30 days) versus Phenoxymethylpenicillin (PO – 20 days)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 20-day phenoxymethylpenicillin	Risk difference with 30-day doxycycline (95% CI)
Cure (no persisting symptoms at 6 months) no persisting symptoms	11 (1 study) 6 months	VERY LOW[1,2] due to risk of bias, imprecision	RR 1.24 (0.75 to 2.05)	800 per 1,000	192 more per 1,000 (from 200 fewer to 840 more)

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 20-day phenoxymethylpenicillin	Risk difference with 30-day doxycycline (95% CI)
at very high risk of bias [2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs					

Table 11: Clinical evidence summary: Doxycycline (PO – 30 days) versus Phenoxymethylpenicillin (PO – 30 days)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 30-day phenoxymethylpenicillin	Risk difference with 30-day doxycycline (95% CI)
Cure (no persisting symptoms at 6 months) no persisting symptoms	20 (1 study) 6 months	VERY LOW[1,2] due to risk of bias, imprecision	RR 1.03 (0.79 to 1.35)	929 per 1,000	28 more per 1,000 (from 195 fewer to 325 more)
[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias [2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs					

Table 12: Clinical evidence summary: Doxycycline (PO – 20 days) versus Doxycycline (PO – 30 days)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 30-day doxycycline	Risk difference with 20-day doxycycline (95% CI)
Cure (no persisting symptoms at 6 months) no persisting symptoms	13 (1 study) 6 months	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.34 (0.12 to 0.96)	1,000 per 1,000	660 fewer per 1,000 (from 40 fewer to 880 fewer)
[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias [2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs					

See appendix F for full GRADE tables.

1.5 Economic evidence

1.5.1 Included studies

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix G.

1.5.2 Excluded studies

No relevant health economic studies were identified and excluded.

1.5.3 Unit costs

The following unit costs were presented to the committee to aid consideration of cost-effectiveness.

Table 13: UK costs of antimicrobials

Class	Drug	Age	Preparation	Mg/unit	Cost/unit (£)	Units/day	Course duration (days)	Cost per course (£)
Penicillins	Amoxicillin	7 days-11 months	125 mg/1.25ml oral suspension paediatric	125	0.20	3	14–28	8.35–16.70
		1-4 years	250 mg/5 ml oral suspension	250	0.06	3	14–28	2.37–4.75
		>5 years	capsules	500	0.06	3	14–28 (g)	2.54–5.08
Penicillins	Phenoxymethylpenicillin	Adults (a)	tablets	250	0.04	4	10	1.49
Tetracyclines	Doxycycline	>12 years	capsules	100	0.11	2	10–28 (h)	2.18–6.09
Cephalosporins	Cefuroxime axetil	>3 months	tablets	250	1.27	4	14–28 (g)	70.88–141.76
Macrolide	Clarithromycin	>1 month	tablets	500	0.16	2	14–21	4.42–6.63
Macrolide	Azithromycin	<12 years	40 mg/1 ml oral suspension	40	0.27	10 mg/kg	9 (i)	Weight dependent
		Adults	tablets	500	0.42	1	9 (i)	3.75
Cephalosporins	Cefotaxime	Adults (b)	2 g powder for solution for injection vials (IV)	2,000	3.75	3	10	112.50
Cephalosporins	Ceftriaxone	>9 years (c)(d)	2 g powder for solution for injection vials (IV) (e)	2,000	1.03	1	14–21	14.42–21.63
Penicillins	Benzylpenicillin sodium	Adults (f)	600 mg powder for solution for injection vials (IM)	600	2.73	2	3	16.38

Abbreviations: IM: intramuscular; IV: intravenously.

Sources: Unit costs from NHS Electronic Drug Tariff January 2017,[119] except cefotaxime from BNF, January 2017[21] and ceftriaxone from EMIT March 2017;[39] dosage from BNF and BNF for Children January 2017[21,22], exceptions below:

(a) Source of dosage from RCT in adults with EM: Steere 1983,[166] dosage for Lyme disease not available from BNF or BNF for children.

(b) Source of dosage from RCT in adults with neuroborreliosis: Pfister 1989[131] and Pfister 1991,[132] dosage for Lyme disease not available from BNF or BNF for children.[21,22]

(c) For disseminated Lyme borreliosis.

(d) Dose for neonate and child up to 11 years (body weight <50 kg) 50-80 mg/kg once daily for 14-21 days. BNF for children January 2017.[22]

(e) Administration can vary in adults and children >1 month: IV infusion over 30 mins or IV injection over 5 mins or deep muscular injection (doses over 1 g divided between more than 1 site): 2 g per day for 14-21 days BNF January 2017.[21]

(f) Source of dosage from RCT in adults with Lyme arthritis: Steere 1985:[165] 1.2 million U injected in each buttock weekly intramuscularly. Duration 3 weeks. Dosage for Lyme disease not available from BNF or BNF for children.[21,22]

(g) Course duration for early Lyme 14-21 days; 28 days for Lyme arthritis. BNF January 2017.[21]

(h) Course duration for early Lyme 10-14 days; 28 days for Lyme arthritis. BNF January 2017.[21]

(i) Course dose and duration for adults: 500 mg once daily for 3 days for 3 weeks. For children under 12 years: 10 mg/kg once daily for 3 days for 3 weeks. Committee expert opinion.

The cost of intravenous antibiotics will vary depending on where these are administered and by whom. These costs will include some of the following cost components:

- antibiotic
- nursing time (for example, Band 6 nurse, £44 per hour, PSSRU 2016[42])
- clinic space and clerical time (for outpatient administration)
- travel time (for home administration)
- hospital bed (for inpatient administration)
- consumables (for example, cannula, needles, syringes, dressing, IV giving set and glucose or sodium chloride solution).

A large proportion of the total cost of intravenous antibiotics is likely to be the cost of administration rather than the drug itself. As a result, intravenous drugs that have multiple doses administered per day will be more costly than those administered once daily. This was explored in a detailed costing analysis conducted for the NICE CG102 (Meningitis [bacterial] and meningococcal septicaemia in under 16s).[116] In this analysis, they found that ceftriaxone was the cheapest antibiotic when compared to cefotaxime and benzylpenicillin. This was due to savings in staff time associated with once daily dosing, which offset the higher cost of the drug itself.

Inpatient administration

Intravenous antibiotics administered in an inpatient setting will incur the cost of an inpatient stay, which is assumed to include intravenous antibiotics treatment as part of the unit cost. The estimated weighted average unit cost of non-elective inpatient stays and day cases for infectious disease in adults and children are summarised in the table below using the NHS reference costs 2015/2016.[47]

Table 14: Unit costs of inpatient administration

Schedule	Currency description	Currency codes	Weighted average unit costs (per day)
Day-case adults	Standard/major/complex infectious diseases with/without single/multiple interventions, with/without CC	WJ01B, WJ01D, WJ01E, WJ02B, WJ02C,WJ02D, WJ02E, WJ03A, WJ03B, WJ03C, WJ03D, WJ03E, WJ03F, WJ03G	£352
Day-case paediatrics	Paediatric minor/major/intermediate infections with/without CC	PW01A, PW01B, PW01C, PW16A, PW16B, PW16C, PW16D, PW16E, PW17D, PW17E, PW17F, PW17G	£448
Non-elective inpatient short-stay adults	Standard/major/complex infectious diseases with/without single/multiple interventions, with/without CC	WJ01A, WJ01B, WJ01C, WJ01D, WJ01E, WJ02A, WJ02B, WJ02C,WJ02D, WJ02E, WJ03A, WJ03B, WJ03C, WJ03D, WJ03E, WJ03F, WJ03G	£432
Non-elective inpatient short-stay paediatrics	Paediatric minor/major/intermediate infections with/without CC	PW01A, PW01B, PW01C, PW16A, PW16B, PW16C, PW16D, PW16E, PW17D, PW17E, PW17F, PW17G	£521
Non-elective inpatient long-stay adults	Standard/major/complex infectious diseases with/without single/multiple interventions, with/without CC	WJ01A, WJ01B, WJ01C, WJ01D, WJ01E, WJ02A, WJ02B, WJ02C,WJ02D, WJ02E, WJ03A, WJ03B, WJ03C, WJ03D, WJ03E, WJ03F, WJ03G	£473
Non-elective inpatient long-stay paediatrics	Paediatric minor/major/intermediate infections with/without CC	PW01A, PW01B, PW01C, PW16A, PW16B, PW16C, PW16D, PW16E, PW17D, PW17E, PW17F, PW17G	£699

Source: NHS reference costs 2015/2016[47]

Outpatient administration

Intravenous antibiotics may also be administered as part of an outpatient parenteral antibiotic therapy (OPAT) service, which is available in some hospitals. This allows for administration in an outpatient clinic or in a home setting by a district nurse and is for people who require parenteral treatment but are otherwise stable and well enough not to be in hospital. There is currently no NHS reference cost for this service.

A UK study by Chapman 2009[30] reports that this type of service costs between 41% and 61% of the equivalent inpatient costs. Based on these estimates from Chapman 2009 and the unit cost for an adult day case in Table 14, the cost of OPAT would be approximately £144 to £215 per day. These costs would include the cost of the drug as well as the administration.

1.6 Resource impact

We do not expect recommendations resulting from this review area to have a significant impact on resources.

1.7 Evidence statements

1.7.1 Clinical evidence statements

Adults and young people (aged 12 and over):

- Very Low quality evidence from 1 cohort study showed that a 30-day course of oral doxycycline was clinically more effective than a 20-day course of oral doxycycline for cure.
- Very Low quality evidence from 1 cohort study comparing oral phenoxymethylpenicillin and oral doxycycline showed:
  - a 20-day or 30-day course of phenoxymethylpenicillin was clinically more effective than a 20-day course of doxycycline for cure
  - a 30-day course of doxycycline was clinically more effective than a 20-day course of phenoxymethylpenicillin for cure, but there was no difference when phenoxymethylpenicilin was given for 30-days.
- Very Low quality evidence from 1 cohort study showed a clinical benefit of a 15-day course of intravenous ceftriaxone over a 20-day course of oral doxycycline for cure.
- Very Low quality evidence from 1 cohort study found, however, a clinical benefit of oral doxycycline over intravenous ceftriaxone when doxycycline was given for 30 days.
- There was no clinically important difference between a 15-day course of intravenous ceftriaxone and a 20-day course of oral phenoxymethylpenicillin.
- Very Low quality evidence from 1 cohort study found a clinical benefit of a 30-day course of oral phenoxymethylpenicillin over a 15-day course of intravenous ceftriaxone for cure.
- Very Low quality evidence from 1 cohort study showed a clinical benefit of a 30-day course of oral phenoxymethylpenicillin over a 20-day course of oral phenoxymethylpenicillin in terms of cure rates.

Children (under 12 years):

- No evidence in children was identified.

1.7.2 Health economic evidence statements

No relevant economic evaluations were identified.

1.8 The committee's discussion of the evidence

1.8.1 Interpreting the evidence

1.8.1.1 The outcomes that matter most

The committee considered quality of life, cure or the resolution of symptoms related to acrodermatitis chronica atrophicans, reduction in symptoms related to acrodermatitis chronica atrophicans, and the relapse of symptoms related to acrodermatitis chronica atrophicans to be critical outcomes to decision-making. They also considered adverse events to be an important outcome.

Cure was the only outcome for which evidence could be found.

1.8.1.2 The quality of the evidence

The evidence came from 1 study with a small sample size and was of Very Low quality due to the non-randomised study design, risk of bias and imprecision. There were particular concerns about the selection of people, the general lack of blinding to the treatment allocation, and inadequately defined outcomes.

1.8.1.3 Benefits and harms

We identified only 1 non-randomised study, which compared the effectiveness of intravenous ceftriaxone, oral phenoxymethylpenicillin and oral doxycycline for this review. Cure defined as no persisting symptoms at 6 months was the only outcome reported. The study included 46 people with acrodermatitis chronica atrophicans. The clinical diagnosis was confirmed by histopathological findings and the presence of IgG antibodies against *Borrelia burgdorferi sensu lato*.

The evidence showed that a daily dose of 2 grams of intravenous ceftriaxone for 15 days was more effective than 100 milligrams doxycycline twice per day for 20 days. The treatment effect was, however, reversed when doxycycline was given for 30 days. There was no clinically important difference between ceftriaxone and a 20-day or 30-day treatment of 1.5 million IU (1 milligram roughly equals 1,666 IU; 1.5 million IU are therefore roughly 900 milligrams) oral phenoxymethylpenicillin 3 times per day.

Compared to a 20-day treatment with 100 milligrams doxycycline twice daily, phenoxymethylpenicillin was more effective regardless of whether it was given for 20 or for 30 days. There was no clinically important difference between doxycycline and phenoxymethylpenicillin when doxycycline was given for 30 days instead of 20 days.

A 30-day treatment of 100 milligrams doxycycline twice per day was more effective than a 20-day treatment of an equivalent dose of doxycycline. There was no clinically important difference between a 20-day and a 30-day treatment of 1.5 million IU oral phenoxymethylpenicillin 3 times per day.

The committee considered the evidence to be limited, as it was based on a single study that had a non-randomised design and a small sample size. Based on the limited evidence showing a benefit of a longer duration of doxycycline treatment, evidence identified in the review of management of arthritis and their own clinical experience, the committee decided to recommend a 28-day course of 100 milligrams oral doxycycline twice per day for people with acrodermatitis chronica atrophicans. In cases when doxycycline is contraindicated, such as pregnancy, 1 gram oral amoxicillin 3 times per day for 28 days should be given instead.

No evidence was found for children and recommendations are extrapolated from those for adults. In children under the age of 12 amoxicillin is recommended as the antibiotic of choice. The guideline committee was aware that specialists do offer doxycycline in children aged 9 years and above as a result of indirect evidence from the United States and Scandinavia despite no licence or BNFC dose. There is also increasing indirect evidence from use in other conditions in the United States and Canada that doxycycline does not cause teeth staining when used for short course (less than 4 weeks) in children aged 2 years and older. UK specialist clinicians may choose to use doxycycline as second line where a CSF-penetrating oral antibiotic is required although the lack of direct evidence, lack of licence and lack of BNFC dose regimen has so far limited UK use in children aged 8 and under. Where used, in the United States and Canada, 1 dose regimen of doxycycline for children under 45 kilograms is: 5 milligram/kilogram in 2 divided doses on day 1 followed by 2.5 milligram/kilogram daily in 1 or 2 divided doses with a maximum for severe infections, up to 5 milligram/kilogram daily.

Azithromycin should be otherwise be offered in cases where amoxicillin is contraindicated.

No evidence was identified for adverse events; however, the guideline committee considered any potential harm of a longer duration antibiotic treatment, such as increased risk of side effects, to be outweighed by the potential benefit of resolution of symptoms and prevention of disease progression.

1.8.2 Cost effectiveness and resource use

No relevant health economic evidence was identified. The unit costs of different antimicrobials were presented to the committee. Both doxycycline and amoxicillin are low-cost generic antimicrobials (£6.09 and £10.16 respectively in adults).

The BNF recommends doxycycline, amoxicillin or cefuroxime axetil as the antibacterials of choice for Lyme disease. The dose and duration of treatment for doxycycline that the committee recommended is the same as that listed in the BNF for Lyme arthritis but is longer than that recommended for Lyme disease more generally (28 days versus 21 days). The clinical evidence summarised above supports this longer duration. The committee recommended a higher dose of amoxicillin (1 gram 3 times daily versus 500 milligrams 3 times daily in the BNF). The rationale for this higher dose is based on evidence for other presentations of Lyme that used probenecid to increase the concentration of amoxicillin; therefore, the committee decided to recommend 1 gram amoxicillin 3 times per day as the preferred dose of amoxicillin. The committee considered that the additional minimal cost of a longer duration of doxycycline or a higher dose of amoxicillin would be offset by the improved quality of life because of a reduction in symptoms and associated costs in the management of symptoms.

The BNF recommended cefuroxime axetil as one of their first choices for Lyme disease. The committee did not identify any evidence to support its use. Furthermore, cefuroxime axetil is much more expensive than the other oral antimicrobials (£141.76 for 500 milligrams 2 times per day for 28 days in adults).

The committee considered that where both doxycycline and amoxicillin are contraindicated intravenous ceftriaxone should be considered. The committee considered that the number of people for whom the drugs would be contraindicated would be small. The unit cost of 2 grams once daily for 21 days is £21.63. The committee also considered the cost of intravenous administration, which would include the cost of nurse time, clinic space and clerical time (if administered in an outpatient setting), nurse travel time (if administered at home) and disposables required for administration. These costs would likely be greater than the cost of the antibiotics themselves.

The recommendations for children closely reflect those for adults, unless drugs are contraindicated. For younger children oral suspension formulations may be required rather than tablets. The unit costs of the recommended antimicrobials for children are not dissimilar to those for adults.

The committee discussed the adverse event profiles of different antimicrobials and whether these may impact the costs of managing Lyme disease. Doxycycline adverse events for example, include photosensitivity, nausea and vomiting. In practice, if a patient experiences any of these adverse events, these would be managed by switching to another antimicrobial and therefore the cost to the NHS would be a consultation with a GP and additional antimicrobials. These costs are considered low and would be offset by the cure and reduction of symptoms after successful treatment of Lyme disease.

The committee agreed, as current practice is not established for the management of ACA, that these recommendations may lead to a change in practice for some. It agreed, however, that this potential change in practice would not result in a significant resource impact given the relatively small number of people diagnosed with Lyme disease.

1.8.3 Other factors the committee took into account

In addition to the evidence identified in this review, the committee also discussed evidence identified in other management reviews of this guideline and recommendations from European guidelines. The review on treatment of Lyme arthritis (see evidence review D) identified evidence for 30-day courses, and the committee considered that there were similarities in penetration of antibiotics to inflamed skin and to joints that justified a longer course of treatment. The French guideline[32] recommends 100 milligrams oral doxycycline twice per day for 21-28 days. The committee decided to recommend a treatment duration of 28 days to reduce any ambiguity related to the duration of treatment.

The committee decided to recommend 1 gram of oral amoxicillin 3 times per day for 28 days as an alternative to doxycycline based on evidence from reviews of treatment for other presentations of Lyme disease. The identified studies used probenecid in addition to amoxicillin to increase concentration of amoxicillin. This justified recommending the higher dose of 1 gram of amoxicillin compared to 500 milligrams as listed in the BNF.

Intravenous ceftriaxone was recommended for cases where both doxycycline and amoxicillin are contraindicated. This recommendation is based on Very Low quality evidence from 1 non-randomised study suggesting that doxycycline 100 milligrams twice daily for 30 days was more effective than a daily dose of 2 grams of intravenous ceftriaxone for 15 days and on evidence identified in other reviews on the management of other Lyme disease presentations.

The committee made general research recommendations on the development of core outcome set for trials of antibiotic treatment and for trials of treatment for Lyme disease. The details of the research recommendations can be found in appendix J of evidence report D.

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Appendices

Appendix A: Review protocols

Table 15: Review protocol for the management of acrodermatitis chronica atrophicans (ACA)

Question number: 4.7

Relevant section of Scope: management

Field	Content
Review question	What is the most clinically and cost-effective treatment for people with acrodermatitis chronica atrophicans related to Lyme disease?
Type of review question	Intervention A review of health economic evidence related to the same review question was conducted in parallel with this review. For details, see the health economic review protocol for this NICE guideline.
Objective of the review	The review questions on the condition-specific management of Lyme disease aim to identify the most effective treatment in different clinical scenarios. The questions have been developed in a way to identify the evidence for all potential populations and scenarios, even if clinical presentations are more diverse. The population for this review consists of people with acrodermatitis chronica atrophicans (ACA) related to Lyme disease.
Eligibility criteria – population / disease / condition / issue / domain	People with symptoms consistent with acrodermatitis chronica atrophicans related to Lyme disease
Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	Antimicrobials, including but not limited to: • Penicillins o Amoxicillin (oral, IV) o Ampicillin (oral, IV) o Benzylpenicillin sodium / Penicillin G (IV) - Including Augmentin (Amoxicillin and clavulanic acid; oral, IV) o Phenoxymethylpenicillin / Penicillin V (oral) • Tetracyclines o Doxycycline (oral) o Minocycline (oral) • Cephalosporins o Cefotaxime (IV) o Ceftriaxone (IV) o Cefuroxime axetil (oral) • Macrolides o Azithromycin (oral) o Clarithromycin (oral, IV) • Fluoroquinolones o Ciprofloxacin (oral, IV) o Levofloxacin (oral, IV) o Moxifloxacin (oral, IV) o Nalidixic acid (oral) o Norfloxacin (oral)

Field	Content
	○ Ofloxacin (oral, IV) ○ Rifampicin (oral, IV)
Eligibility criteria – comparator(s) / control or reference (gold) standard	• Antimicrobial agents compared with each other ○ If data are available, consider: - Type of antimicrobial agent (within class or between class) - Route of administration - Duration of treatment: 1 month versus longer • Monotherapy versus polytherapy (any combination) • Antimicrobial treatment compared to no treatment / placebo
Outcomes and prioritisation	**Critical:** 1. Quality of life (any validated measure) 2. Cure (resolution of ACA symptoms) 3. Reduction of ACA symptoms 4. Relapse of ACA symptoms **Important:** 5. Adverse events
Eligibility criteria – study design	• RCTs • Cohort studies (if no RCT evidence is found)
Other inclusion exclusion criteria	Date limits for search: none Language: English only Setting: all settings in which NHS care is provided or commissioned The following interventions will not be considered for inclusion: • Metronidazole • Trimethoprim
Proposed sensitivity / subgroup analysis, or meta-regression	The following groups will be considered separately if data are available (strata): • Children (under 12 years); young people and adults (12 years and over) • Onset of ACA less than 6 weeks; 6 weeks to 6 months; over 6 months Subgroups (to be investigated if heterogeneity is identified): • Pregnant women • People who are immunocompromised • People in whom a previous course of antimicrobial treatment or steroid treatment has failed
Selection process – duplicate screening / selection / analysis	Studies will be sifted by title and abstract. Potentially significant publications obtained in full text will then be assessed against the inclusion criteria specified in this protocol.
Data management (software)	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). GRADEpro will be used to assess the quality of evidence for each outcome Bibliographies, citations, study sifting and reference management will be managed using EndNote. Data extractions will be performed using EviBase, a platform designed and maintained by the National Guideline Centre (NGC)
Information sources – databases and dates	Clinical searches Medline, Embase, The Cochrane Library all years Health economic searches

Field	Content
	Medline, Embase, NHS Economic Evaluation Database (NHS EED), Health Technology Assessment (HTA) all years
Identify if an update	Not applicable
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10007
Highlight if amendment to previous protocol	For details, please see section 4.5 of Developing NICE guidelines: the manual.
Search strategy – for one database	For details, please see appendix B
Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as appendix D of the evidence report.
Data items – define all variables to be collected	For details, please see evidence tables in appendix D (clinical evidence tables) or H (health economic evidence tables).
Methods for assessing bias at outcome / study level	Standard study checklists were used to appraise individual studies critically. For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details, please see section 6.4 of Developing NICE guidelines: the manual. Meta-analysis will be conducted wherever possible (that is, where similar studies can be combined) In the absence of clinically established MIDs, standard MIDs for dichotomous (25% risk reduction or risk increase) and continuous outcomes (+/-0.5 standard deviation) will be used If heterogeneity is found, the influence of subgroups will be examined.
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details, please see the separate Methods report for this guideline.
Meta-bias assessment – publication bias, selective reporting bias	For details, please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details, please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
Rationale / context – what is known	For details, please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the NGC and chaired by Saul Faust in line with section 3 of Developing NICE guidelines: the manual. Staff from the NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details, please see Developing NICE guidelines: the manual.
Sources of funding / support	The NGC is funded by NICE and hosted by the Royal College of Physicians.
Name of sponsor	The NGC is funded by NICE and hosted by the Royal College of Physicians.
Roles of sponsor	NICE funds the NGC to develop guidelines for those working in the NHS, public health and social care in England.

Field	Content
PROSPERO registration number	Not registered

Table 16: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2001, abstract-only studies and studies from non-OECD countries or the US will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[117] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations', then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations', then it will usually be excluded from the guideline. If it is excluded, then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both, then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to exclude selectively the remaining studies. All studies excluded based on applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable).

	• OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the US will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2001 or later but that depend on unit costs and resource data entirely or predominantly before 2001 will be rated as 'Not applicable'. • Studies published before 2001 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual 2014, updated 2017 https://www.nice.org.uk/guidance/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869

For more detailed information, please see the Methodology Review.

B.1 Clinical search literature search strategy

The search for this review was constructed using population terms. An excluded studies filter was applied where appropriate.

Table 17: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 03 July 2017	Exclusions
Embase (OVID)	1974 – 03 July 2017	Exclusions
The Cochrane Library (Wiley)	Cochrane Reviews to 2017 Issue 7 of 12 CENTRAL to 2017 Issue 6 of 12 DARE, and NHSEED to 2015 Issue 2 of 4 HTA to 2016 Issue 4 of 4	None

Medline (Ovid) search terms

1.	exp Borrelia Infections/
2.	exp Lyme disease/
3.	Erythema Chronicum Migrans/
4.	(erythema adj3 migrans).ti,ab.
5.	lyme*.ti,ab.
6.	(tick* adj2 (bite* or bitten or biting or borne)).ti,ab.
7.	acrodermatitis chronica atrophicans.ti,ab.
8.	exp Ixodidae/
9.	(borreliosis or borrelia* or neuroborreliosis or ixodid or ixodidae or ixodes or b burgdorferi or b afzelii or b garinii or b bissettii or b valaisiana or b microti).ti,ab.
10.	(granulocyctic anaplasmosis or babesia or babesiosis).ti,ab.
11.	or/1-10
12.	letter/
13.	editorial/
14.	news/
15.	exp historical article/
16.	Anecdotes as Topic/
17.	comment/
18.	(letter or comment*).ti.
19.	or/12-18
20.	randomized controlled trial/ or random*.ti,ab.
21.	19 not 20
22.	animals/ not humans/

23.	exp Animals, Laboratory/
24.	exp Animal Experimentation/
25.	exp Models, Animal/
26.	exp Rodentia/
27.	(rat or rats or mouse or mice).ti.
28.	or/21-27
29.	11 not 28
30.	limit 29 to English language

Embase (Ovid) search terms

1.	exp Borrelia Infection/
2.	exp Lyme disease/
3.	Erythema Chronicum Migrans/
4.	(erythema adj3 migrans).ti,ab.
5.	lyme*.ti,ab.
6.	(tick* adj2 (bite* or bitten or biting or borne)).ti,ab.
7.	acrodermatitis chronica atrophicans.ti,ab.
8.	exp Ixodidae/
9.	(borreliosis or borrelia* or neuroborreliosis or ixodidae or ixodes or b burgdorferi or b afzelii or b garinii or b bissettii or b valaisiana or b microti).ti,ab.
10.	(granulocyctic anaplasmosis or babesia or babesiosis).ti,ab.
11.	or/1-10
12.	letter.pt. or letter/
13.	note.pt.
14.	editorial.pt.
15.	(letter or comment*).ti.
16.	or/12-15
17.	randomized controlled trial/ or random*.ti,ab.
18.	16 not 17
19.	animal/ not human/
20.	Nonhuman/
21.	exp Animal Experiment/
22.	exp Experimental animal/
23.	Animal model/
24.	exp Rodent/
25.	(rat or rats or mouse or mice).ti.
26.	or/18-25
27.	11 not 26
28.	limit 27 to English language

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Borrelia Infections] explode all trees
#2.	MeSH descriptor: [Lyme Disease] explode all trees
#3.	MeSH descriptor: [Erythema Chronicum Migrans] explode all trees
#4.	(erythema near/3 migrans):ti,ab
#5.	lyme*:ti,ab
#6.	(tick* near/2 (bite* or bitten or biting or borne)):ti,ab
#7.	acrodermatitis chronica atrophicans:ti,ab

#8.	MeSH descriptor: [Ixodidae] explode all trees
#9.	(borreliosis or borrelia* or neuroborreliosis or ixodidae or ixodes or ixodid or b burgdorferi or b afzelii or b garinii or b bissettii or b valaisiana or b microti):ti,ab
#10.	(granulocyctic anaplasmosis or babesia or babesiosis):ti,ab
#11.	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to Lyme disease population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics, economic modelling and quality of life studies.

Table 18: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	1946 – 03 July 2017	Exclusions Health economics studies Health economics modelling studies Quality of life studies
Embase	1974 – 03 July 2017	Exclusions Health economics studies Health economics modelling studies Quality of life studies
Centre for Research and Dissemination (CRD)	HTA - Inception – 03 July 2017 NHSEED - Inception to March 2015	None

Medline (Ovid) search terms

1.	exp Borrelia Infections/
2.	exp Lyme disease/
3.	Erythema Chronicum Migrans/
4.	(erythema adj3 migrans).ti,ab.
5.	lyme*.ti,ab.
6.	(tick* adj2 (bite* or bitten or biting or borne)).ti,ab.
7.	acrodermatitis chronica atrophicans.ti,ab.
8.	exp Ixodidae/
9.	(borreliosis or borrelia* or neuroborreliosis or ixodid or ixodidae or ixodes or b burgdorferi or b afzelii or b garinii or b bissettii or b valaisiana or b microti).ti,ab.
10.	(granulocyctic anaplasmosis or babesia or babesiosis).ti,ab.
11.	or/1-10
12.	letter/
13.	editorial/
14.	news/
15.	exp historical article/
16.	Anecdotes as Topic/

17.	comment/
18.	(letter or comment*).ti.
19.	or/12-18
20.	randomized controlled trial/ or random*.ti,ab.
21.	19 not 20
22.	animals/ not humans/
23.	exp Animals, Laboratory/
24.	exp Animal Experimentation/
25.	exp Models, Animal/
26.	exp Rodentia/
27.	(rat or rats or mouse or mice).ti.
28.	or/21-27
29.	11 not 28
30.	limit 29 to English language
31.	Economics/
32.	Value of life/
33.	exp "Costs and Cost Analysis"/
34.	exp Economics, Hospital/
35.	exp Economics, Medical/
36.	Economics, Nursing/
37.	Economics, Pharmaceutical/
38.	exp "Fees and Charges"/
39.	exp Budgets/
40.	budget*.ti,ab.
41.	cost*.ti.
42.	(economic* or pharmaco?economic*).ti.
43.	(price* or pricing*).ti,ab.
44.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
45.	(financ* or fee or fees).ti,ab.
46.	(value adj2 (money or monetary)).ti,ab.
47.	or/31-46
48.	exp models, economic/
49.	*Models, Theoretical/
50.	*Models, Organizational/
51.	markov chains/
52.	monte carlo method/
53.	exp Decision Theory/
54.	(markov* or monte carlo).ti,ab.
55.	econom* model*.ti,ab.
56.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
57.	or/48-56
58.	quality-adjusted life years/

59.	sickness impact profile/
60.	(quality adj2 (wellbeing or well being)).ti,ab.
61.	sickness impact profile.ti,ab.
62.	disability adjusted life.ti,ab.
63.	(qal* or qtime* or qwb* or daly*).ti,ab.
64.	(euroqol* or eq5d* or eq 5*).ti,ab.
65.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
66.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
67.	(hui or hui1 or hui2 or hui3).ti,ab.
68.	(health* year* equivalent* or hye or hyes).ti,ab.
69.	discrete choice*.ti,ab.
70.	rosser.ti,ab.
71.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
72.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
73.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
74.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
75.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
76.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
77.	or/58-76
78.	30 and 47
79.	30 and 57
80.	30 and 77

Embase (Ovid) search terms

1.	exp Borrelia Infection/
2.	exp Lyme disease/
3.	Erythema Chronicum Migrans/
4.	(erythema adj3 migrans).ti,ab.
5.	lyme*.ti,ab.
6.	(tick* adj2 (bite* or bitten or biting or borne)).ti,ab.
7.	acrodermatitis chronica atrophicans.ti,ab.
8.	exp Ixodidae/
9.	(borreliosis or borrelia* or neuroborreliosis or ixodidae or ixodes or b burgdorferi or b afzelii or b garinii or b bissettii or b valaisiana or b microti).ti,ab.
10.	(granulocyctic anaplasmosis or babesia or babesiosis).ti,ab.
11.	or/1-10
12.	letter.pt. or letter/
13.	note.pt.
14.	editorial.pt.
15.	Case report/ or Case study/
16.	(letter or comment*).ti.
17.	or/12-16
18.	randomized controlled trial/ or random*.ti,ab.

19.	17 not 18
20.	animal/ not human/
21.	Nonhuman/
22.	exp Animal Experiment/
23.	exp Experimental animal/
24.	Animal model/
25.	exp Rodent/
26.	(rat or rats or mouse or mice).ti.
27.	or/19-26
28.	11 not 27
29.	limit 28 to English language
30.	health economics/
31.	exp economic evaluation/
32.	exp health care cost/
33.	exp fee/
34.	budget/
35.	funding/
36.	budget*.ti,ab.
37.	cost*.ti.
38.	(economic* or pharmaco?economic*).ti.
39.	(price* or pricing*).ti,ab.
40.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
41.	(financ* or fee or fees).ti,ab.
42.	(value adj2 (money or monetary)).ti,ab.
43.	or/30-42
44.	statistical model/
45.	exp economic aspect/
46.	44 and 45
47.	*theoretical model/
48.	*nonbiological model/
49.	stochastic model/
50.	decision theory/
51.	decision tree/
52.	monte carlo method/
53.	(markov* or monte carlo).ti,ab.
54.	econom* model*.ti,ab.
55.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
56.	or/46-55
57.	quality adjusted life year/
58.	"quality of life index"/
59.	short form 12/ or short form 20/ or short form 36/ or short form 8/
60.	sickness impact profile/

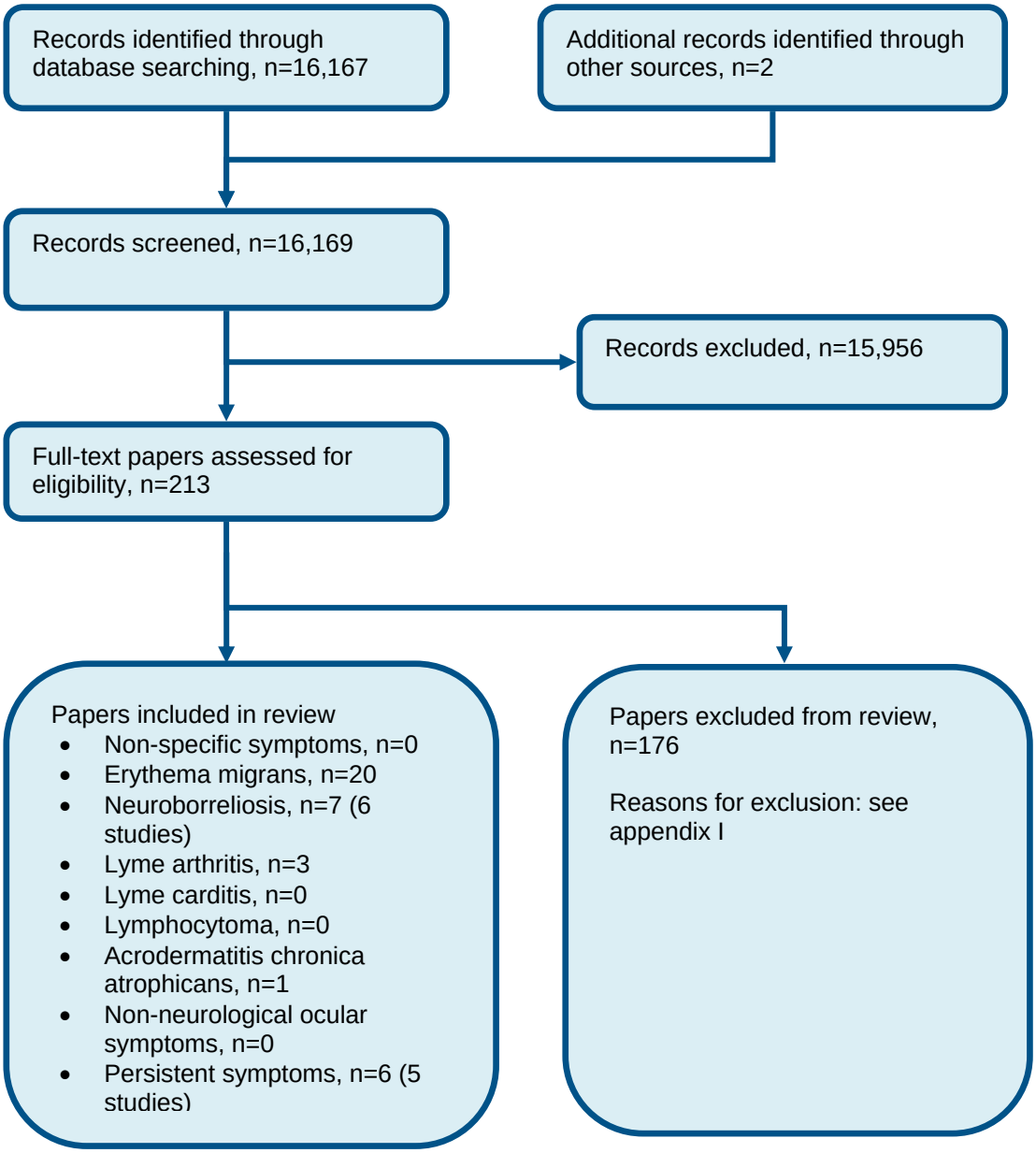
61.	(quality adj2 (wellbeing or well being)).ti,ab.
62.	sickness impact profile.ti,ab.
63.	disability adjusted life.ti,ab.
64.	(qal* or qtime* or qwb* or daly*).ti,ab.
65.	(euroqol* or eq5d* or eq 5*).ti,ab.
66.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
67.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
68.	(hui or hui1 or hui2 or hui3).ti,ab.
69.	(health* year* equivalent* or hye or hyes).ti,ab.
70.	discrete choice*.ti,ab.
71.	rosser.ti,ab.
72.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
73.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
74.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
75.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
76.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
77.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
78.	or/57-77
79.	29 and 43
80.	29 and 56
81.	29 and 78

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Borrelia Infections EXPLODE ALL TREES IN NHSEED,HTA
#2.	MeSH DESCRIPTOR Erythema Chronicum Migrans EXPLODE ALL TREES IN NHSEED,HTA
#3.	((erythema adj3 migrans)) IN NHSEED, HTA
#4.	(lyme*) IN NHSEED, HTA
#5.	((tick* adj2 (bite* or bitten or biting or borne))) IN NHSEED, HTA
#6.	(acrodermatitis chronica atrophicans) IN NHSEED, HTA
#7.	MeSH DESCRIPTOR Ixodidae EXPLODE ALL TREES IN NHSEED,HTA
#8.	((borreliosis or borrelia* or neuroborreliosis or ixodidae or ixodes or b burgdorferi or b afzelii or b garinii or b bissettii or b valaisiana or b microti)) IN NHSEED, HTA
#9.	((granulocyctic anaplasmosis or babesia or babesiosis)) IN NHSEED, HTA
#10.	MeSH DESCRIPTOR Lyme Disease EXPLODE ALL TREES IN NHSEED,HTA
#11.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the reviews of the management of specific clinical scenarios for Lyme disease



Appendix D: Clinical evidence tables

Study	Aberer 1996[1]
Study type	Prospective cohort study
Number of studies (number of participants)	1 (n=46)
Countries and setting	Conducted in Austria; Setting: Not reported
Line of therapy	first line
Duration of study	Follow up (post intervention): 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinical diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Acrodermatitis chronica atrophicans plus presence of IgG antibodies against Bb
Exclusion criteria	Not reported
Recruitment/selection of participants	Not reported
Age, gender and family origin	Age - Mean (range): 64 years (27-89). Gender (M:F): 15:31. Family origin: Not reported
Further population details	1. Immunosuppression: Not stated or unclear 2. Pregnancy: Not stated or unclear 3. Previous treatment failure: Not stated or unclear
Indirectness of population	No indirectness
Interventions	(n=14) Intervention 1: Antibiotics - Ceftriaxone. 2 g. Duration 15 days. Concurrent medication or care: Not reported

Study	Aberer 1996[1]
	(n=5) Intervention 2: Antibiotics - Phenoxymethylpenicillin. 1.5 M IU 3 times per day. Duration 20 days. Concurrent medication or care: Not reported (n=14) Intervention 3: Antibiotics - Phenoxymethylpenicillin. 1.5 M IU 3 times per day. Duration 30 days. Concurrent medication or care: Not reported (n=7) Intervention 4: Antibiotics - Doxycycline. 100 mg twice daily. Duration 20 days. Concurrent medication or care: Not reported (n=6) Intervention 5: Antibiotics - Doxycycline. 100 mg twice daily. Duration 30 days. Concurrent medication or care: Not reported
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CEFTRIAXONE versus PHENOXYMETHYLPENICILLIN Protocol outcome 1: Cure (resolution of symptoms) - Actual outcome: No persisting symptoms at 6 months; Group 1: 10/14, Group 2: 4/5 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CEFTRIAXONE versus PHENOXYMETHYLPENICILLIN Protocol outcome 1: Cure (resolution of symptoms) - Actual outcome: No persisting symptoms at 6 months; Group 1: 10/14, Group 2: 13/14 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CEFTRIAXONE versus DOXYCYLINE Protocol outcome 1: Cure (resolution of symptoms) - Actual outcome: No persisting symptoms at 6 months; Group 1: 10/14, Group 2: 2/7 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CEFTRIAXONE versus DOXYCYLINE	

Study	Aberer 1996[1]
	Protocol outcome 1: Cure (resolution of symptoms) - Actual outcome: No persisting symptoms at 6 months; Group 1: 10/14, Group 2: 6/6 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PHENOXYMETHYLPENICILLIN versus PHENOXYMETHYLPENICILLIN Protocol outcome 1: Cure (resolution of symptoms) - Actual outcome: No persisting symptoms at 6 months; Group 1: 4/5, Group 2: 13/14 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PHENOXYMETHYLPENICILLIN versus DOXYCYLINE Protocol outcome 1: Cure (resolution of symptoms) - Actual outcome: No persisting symptoms at 6 months; Group 1: 4/5, Group 2: 2/7 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PHENOXYMETHYLPENICILLIN versus DOXYCYLINE Protocol outcome 1: Cure (resolution of symptoms) - Actual outcome: No persisting symptoms at 6 months; Group 1: 4/5, Group 2: 6/6 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PHENOXYMETHYLPENICILLIN versus DOXYCYLINE Protocol outcome 1: Cure (resolution of symptoms) - Actual outcome: No persisting symptoms at 6 months; Group 1: 13/14, Group 2: 2/7 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement -

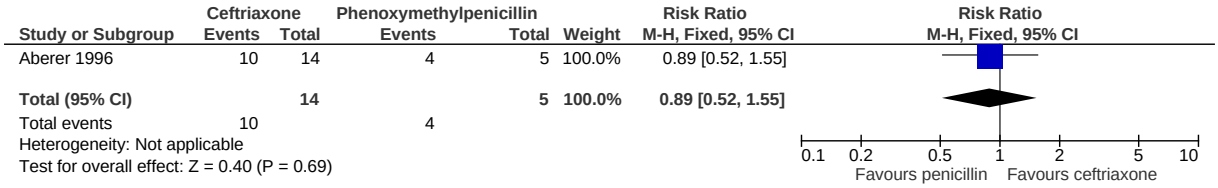
Study	Aberer 1996[1]
High, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PHENOXYMETHYLPENICILLIN versus DOXYCYLINE Protocol outcome 1: Cure (resolution of symptoms) - Actual outcome: No persisting symptoms at 6 months; Group 1: 13/14, Group 2: 6/6 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DOXYCYLINE versus DOXYCYLINE Protocol outcome 1: Cure (resolution of symptoms) - Actual outcome: No persisting symptoms at 6 months; Group 1: 2/7, Group 2: 6/6 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life; Reduction of clinical symptoms; Symptom relapse; Adverse events

Appendix E: Forest plots

E.1 Ceftriaxone versus Phenoxymethylpenicillin (PO – 20 days)

E.1.1 Acrodermatitis chronica atrophicans

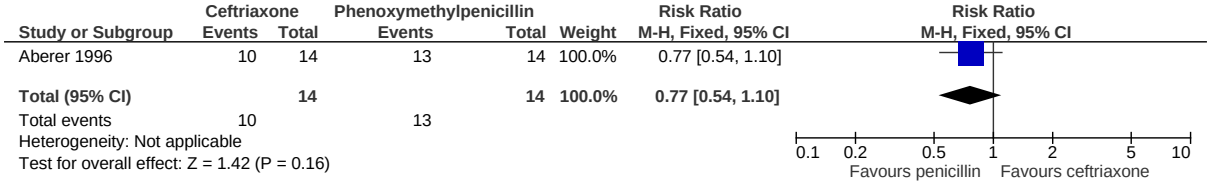
Figure 2: Cure (no persisting symptoms at 6 months)



E.2 Ceftriaxone versus Phenoxymethylpenicillin (PO – 30 days)

E.2.1 Acrodermatitis chronica atrophicans

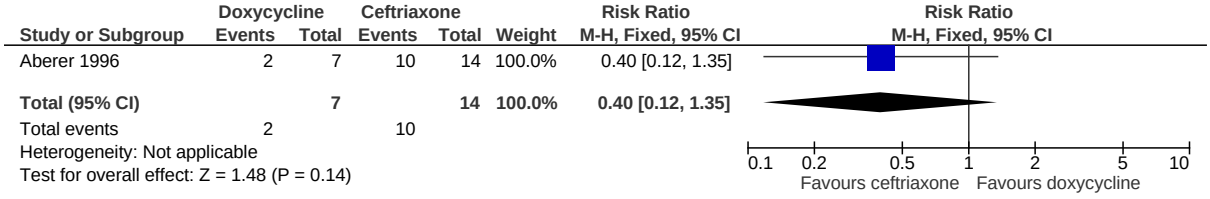
Figure 3: Cure (no persisting symptoms at 6 months)



E.3 Doxycycline (PO – 20 days) versus Ceftriaxone

E.3.1 Acrodermatitis chronica atrophicans

Figure 4: Cure (no persisting symptoms at 6 months)



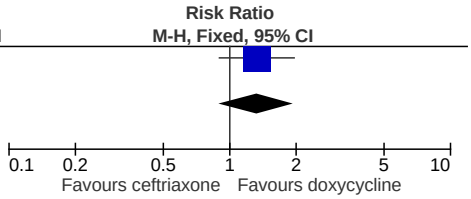
E.4 Doxycycline (PO – 30 days) versus Ceftriaxone

E.4.1 Acrodermatitis chronica atrophicans

Figure 5: Cure (no persisting symptoms at 6 months)

Study or Subgroup	Doxycycline Events	Total	Ceftriaxone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Aberer 1996	6	6	10	14	100.0%	1.33 [0.90, 1.96]
Total (95% CI)		**6**		**14**	**100.0%**	**1.33 [0.90, 1.96]**
Total events	6		10			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.42 (P = 0.16)



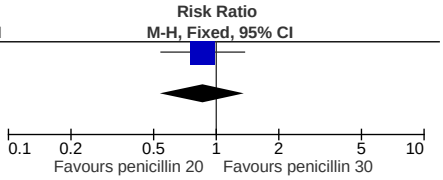
E.5 Phenoxymethylpenicillin (PO – 20 days) versus Phenoxymethylpenicillin (PO – 30 days

E.5.1 Acrodermatitis chronica atrophicans

Figure 6: Cure (no persisting symptoms at 6 months)

Study or Subgroup	Penicillin (20 days) Events	Total	Penicillin (30 days) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Aberer 1996	4	5	13	14	100.0%	0.86 [0.54, 1.37]
Total (95% CI)		**5**		**14**	**100.0%**	**0.86 [0.54, 1.37]**
Total events	4		13			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.63 (P = 0.53)



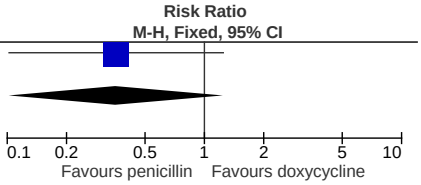
E.6 Doxycycline (PO – 20 days) versus Phenoxymethylpenicillin (PO – 20 days)

E.6.1 Acrodermatitis chronica atrophicans

Figure 7: Cure (no persisting symptoms at 6 months)

Study or Subgroup	Doxycycline Events	Total	Phenoxymethylpenicillin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Aberer 1996	2	7	4	5	100.0%	0.36 [0.10, 1.25]
Total (95% CI)		**7**		**5**	**100.0%**	**0.36 [0.10, 1.25]**
Total events	2		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.61 (P = 0.11)



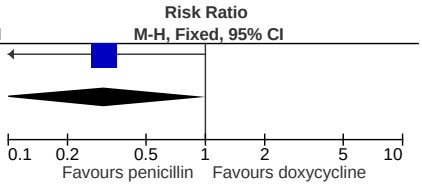
E.7 Doxycycline (PO – 20 days) versus Phenoxymethylpenicillin (PO – 30 days)

E.7.1 Acrodermatitis chronica atrophicans

Figure 8: Cure (no persisting symptoms at 6 months)

Study or Subgroup	Doxycycline Events	Total	Phenoxymethylpenicillin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Aberer 1996	2	7	13	14	100.0%	0.31 [0.09, 1.00]
Total (95% CI)		**7**		**14**	**100.0%**	**0.31 [0.09, 1.00]**
Total events	2		13			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.96 (P = 0.05)



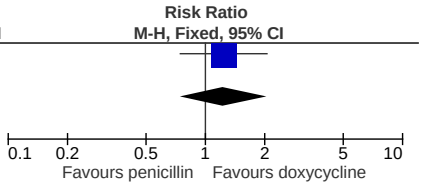
E.8 Doxycycline (PO – 30 days) versus Phenoxymethylpenicillin (PO – 20 days)

E.8.1 Acrodermatitis chronica atrophicans

Figure 9: Cure (no persisting symptoms at 6 months)

Study or Subgroup	Doxycycline Events	Total	Phenoxymethylpenicillin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Aberer 1996	6	6	4	5	100.0%	1.24 [0.75, 2.05]
Total (95% CI)		**6**		**5**	**100.0%**	**1.24 [0.75, 2.05]**
Total events	6		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.83 (P = 0.41)



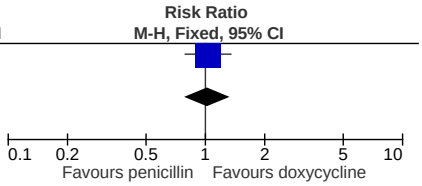
E.9 Doxycycline (PO – 30 days) versus Phenoxymethylpenicillin (PO – 30 days)

E.9.1 Acrodermatitis chronica atrophicans

Figure 10: Cure (no persisting symptoms at 6 months)

Study or Subgroup	Doxycycline Events	Total	Phenoxymethylpenicillin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Aberer 1996	6	6	13	14	100.0%	1.03 [0.79, 1.35]
Total (95% CI)		**6**		**14**	**100.0%**	**1.03 [0.79, 1.35]**
Total events	6		13			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.23 (P = 0.82)



E.10 Doxycycline (PO – 20 days) versus Doxycycline (PO – 30 days)

E.10.1 Acrodermatitis chronica atrophicans

Figure 11: Cure (no persisting symptoms at 6 months)

Appendix F:GRADE tables

Table 19: Clinical evidence profile: Ceftriaxone versus Phenoxymethylpenicillin (PO – 20 days)

Quality assessment							Number of participants		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ceftriaxone	20-day phenoxymethylpenicillin	Relative (95% CI)	Absolute		
Cure (no persisting symptoms at 6 months; follow-up 6 months; assessed with: no persisting symptoms)												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10/14 (71.4%)	4/5 (80%)	RR 0.89 (0.52 to 1.55)	88 fewer per 1,000 (from 384 fewer to 440 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 20: Clinical evidence profile: Ceftriaxone versus Phenoxymethylpenicillin (PO – 30 days)

Quality assessment							Number of participants		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ceftriaxone	30-day phenoxymethylpenicillin	Relative (95% CI)	Absolute		
Cure (no persisting symptoms at 6 months; follow-up 6 months; assessed with: no persisting symptoms)												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	10/14 (71.4%)	13/14 (92.9%)	RR 0.77 (0.54 to 1.1)	214 fewer per 1,000 (from 427 fewer to 93 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 21: Clinical evidence profile: Doxycycline (PO – 20 days) versus Ceftriaxone

Quality assessment							Number of participants		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	20-day doxycycline	ceftriaxone	Relative (95% CI)	Absolute		
Cure (no persisting symptoms at 6 months; follow-up 6 months; assessed with: no persisting symptoms)												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/7 (28.6%)	10/14 (71.4%)	RR 0.4 (0.12 to 1.35)	429 fewer per 1,000 (from 629 fewer to 250 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 22: Clinical evidence profile: Doxycycline (PO – 30 days) versus Ceftriaxone

Quality assessment							Number of participants		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	30-day doxycycline	Ceftriaxone	Relative (95% CI)	Absolute		
Cure (no persisting symptoms at 6 months; follow-up 6 months; assessed with: no persisting symptoms)												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	6/6 (100%)	10/14 (71.4%)	RR 1.33 (0.9 to 1.96)	236 more per 1,000 (from 71 fewer to 686 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 23: Clinical evidence profile: Phenoxymethylpenicillin (PO – 20 days) versus Phenoxymethylpenicillin (PO – 30 days)

Quality assessment	Number of participants	Effect	Quality	Importance

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	20-day phenoxymethylpenicillin	30-day phenoxymethylpenicillin	Relative (95% CI)	Absolute		
Cure (no persisting symptoms at 6 months; follow-up 6 months; assessed with: no persisting symptoms)												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/5 (80%)	13/14 (92.9%)	RR 0.86 (0.54 to 1.37)	130 fewer per 1,000 (from 427 fewer to 344 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 24: Clinical evidence profile: Doxycycline (PO – 20 days) versus Phenoxymethylpenicillin (PO – 20 days)

Quality assessment							Number of participants		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	20-day doxycycline	20-day phenoxymethylpenicillin	Relative (95% CI)	Absolute		
Cure (no persisting symptoms at 6 months; follow-up 6 months; assessed with: no persisting symptoms)												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/7 (28.6%)	4/5 (80%)	RR 0.36 (0.1 to 1.25)	512 fewer per 1,000 (from 720 fewer to 200 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 25: Clinical evidence profile: Doxycycline (PO – 20 days) versus Phenoxymethylpenicillin (PO – 30 days)

Quality assessment							Number of participants		Effect		Quality	Importance
Number	Design	Risk of	Inconsistency	Indirectness	Imprecision	Other	20-day	30-day	Relative	Absolute		

of studies		bias				considerations	doxycycline	phenoxymethylpenicillin	(95% CI)			
Cure (no persisting symptoms at 6 months; follow-up 6 months; assessed with: no persisting symptoms)												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	2/7 (28.6%)	13/14 (92.9%)	RR 0.31 (0.09 to 1)	641 fewer per 1,000 (from 845 fewer to 0 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 26: Clinical evidence profile: Doxycycline (PO – 30 days) versus Phenoxymethylpenicillin (PO – 20 days)

Quality assessment							Number of participants		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**30-day doxycycline**	**20-day phenoxymethylpenicillin**	**Relative (95% CI)**	**Absolute**		
Cure (no persisting symptoms at 6 months; follow-up 6 months; assessed with: no persisting symptoms)												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/6 (100%)	4/5 (80%)	RR 1.24 (0.75 to 2.05)	192 more per 1,000 (from 200 fewer to 840 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 27: Clinical evidence profile: Doxycycline (PO – 30 days) versus Phenoxymethylpenicillin (PO – 30 days)

Quality assessment							Number of participants		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**30-day doxycycline**	**30-day phenoxymethylpenicillin**	**Relative (95% CI)**	**Absolute**		
Cure (no persisting symptoms at 6 months; follow-up 6 months; assessed with: no persisting symptoms)												
1	observational	very	no serious	no serious	serious[2]	none	6/6	13/14	RR 1.03	28 more per	⊕OOO	CRITICAL

	studies	serious[1]	inconsistency	indirectness			(100%)	(92.9%)	(0.79 to 1.35)	1,000 (from 195 fewer to 325 more)	VERY LOW	

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

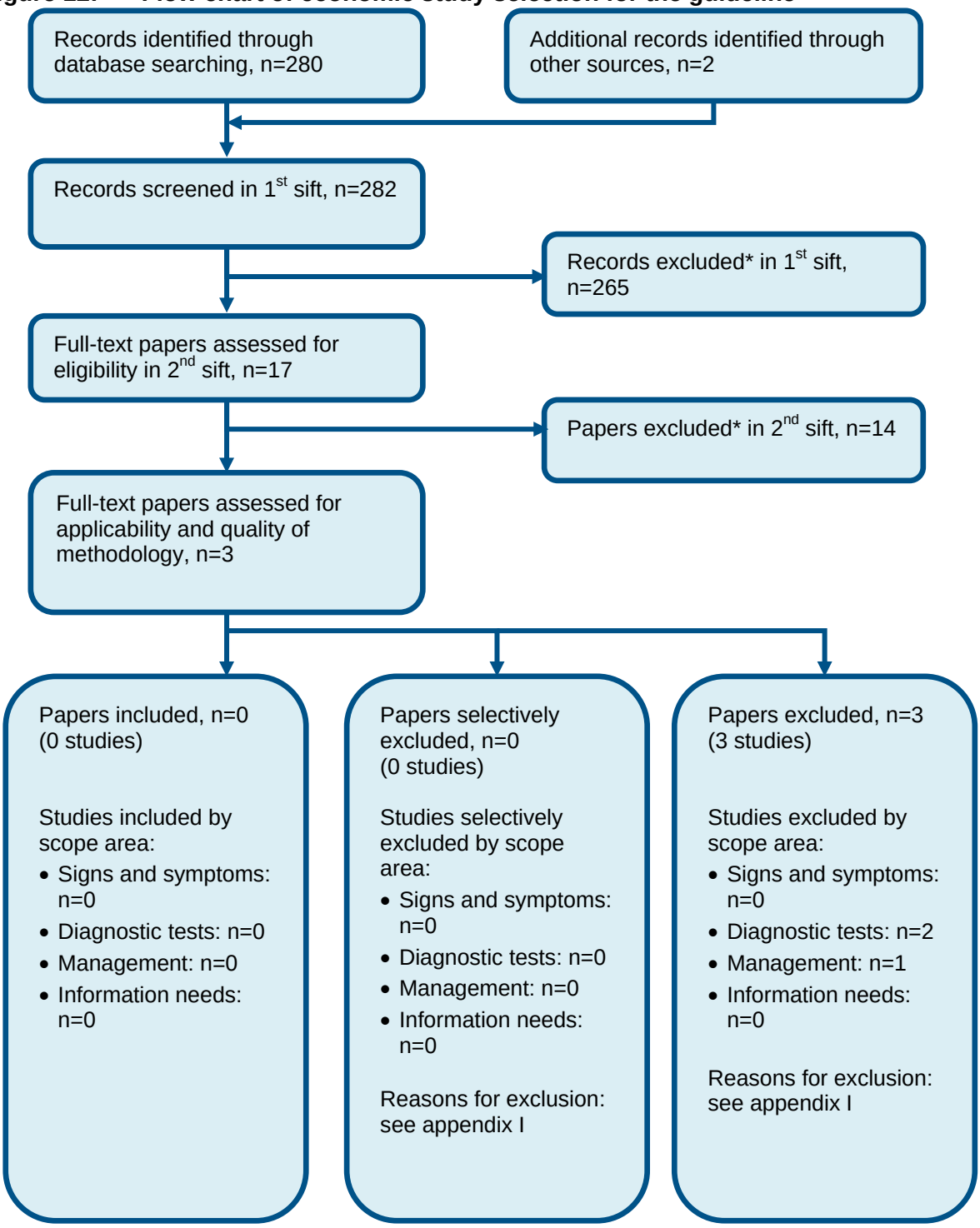
Table 28: Clinical evidence profile: Doxycycline (PO – 20 days) versus Doxycycline (PO – 30 days)

Quality assessment							Number of participants		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**20-day doxycycline**	**30-day doxycycline**	**Relative (95% CI)**	**Absolute**		
Cure (no persisting symptoms at 6 months; follow-up 6 months; assessed with: no persisting symptoms)												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	2/7 (28.6%)	6/6 (100%)	RR 0.34 (0.12 to 0.96)	660 fewer per 1,000 (from 40 fewer to 880 fewer)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Appendix G: Health economic evidence selection

Figure 12: Flow chart of economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H: Health economic evidence tables

None.

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 29: Studies excluded from the clinical management reviews

Reference	Reason for exclusion
Aberer 2006[2]	Excluded due to an incorrect intervention
Abrutyn 1989[3]	Excluded due to an incorrect study design
Agger 1992[4]	Excluded due to an incorrect study design
Agus 1995[5]	Excluded due to an incorrect study design
Agwuh 2006[6]	Excluded due to an incorrect study design
Ahmed 2005[7]	Excluded due to an incorrect study design
Ahmed 2013[8]	Excluded due to an incorrect study design
Alarcon 1994[9]	Excluded due to an incorrect study design
Andiman 1986[10]	Excluded due to an incorrect study design
Anonymous 1991[11]	Excluded due to an incorrect study design
Arvikar 2015[12]	Excluded due to an incorrect study design
Auwaerter 2004[13]	Excluded due to an incorrect study design
Bennet 2003[14]	Excluded due to an incorrect study design
Berende 2014[15]	Excluded due to an incorrect study design
Berger 1988[17]	Excluded due to an incorrect study design
Berger 1986[16]	Excluded due to an incorrect study design
Bernardino 2009[18]	Excluded due to an incorrect study design
Bhate 2011[19]	Excluded due to an incorrect study design
Bjark 2016[20]	Not available
Borg 2005[23]	Excluded due to an incorrect study design
Bratton 2008[24]	Excluded due to an incorrect study design
Bremell 2014[25]	Excluded due to an incorrect study design
British Infection Association 2011[26]	Excluded due to an incorrect study design
Butler 1978[27]	Excluded due to an incorrect population
Cadavid 2016[28]	Excluded due to an incorrect study design
Canadian Paediatric Society 1992[29]	Excluded due to an incorrect study design
Chen 1999[31]	Excluded due to an incorrect outcome
Choo-Kang 2010[33]	Excluded due to an incorrect study design
Christian 1992[34]	Excluded due to an incorrect study design
Cimmino 1992[36]	Excluded due to an incorrect study design
Cimmino 1997[35]	Excluded due to an incorrect study design
Cimperman 1999[37]	Excluded due to an incorrect study design
Coblyn 1981[38]	Excluded due to an incorrect study design
Committee on Infectious Diseases 1991[40]	Excluded due to an incorrect study design
Cuisset 2008[41]	Excluded due to an incorrect study design
Dattwyler 1996[43]	Excluded due to an incorrect comparison
Dattwyler 1987[44]	Excluded due to an incorrect study design
Dattwyler 1988[45]	Excluded due to an incorrect population
Dattwyler 2005[46]	Excluded due to an incorrect population

Reference	Reason for exclusion
Dersch 2015[48]	Excluded due to an incorrect study design
Dersch 2016[51]	Excluded due to an incorrect study design
Dersch 2014[49]	Excluded due to an incorrect study design
Dersch 2017[50]	Not available
Dhoot 2011[52]	Excluded due to an incorrect study design
Dinser 2005[53]	Excluded due to an incorrect study design
Dotevall 1988[54]	Excluded due to an incorrect study design
Eliassen 2017[55]	Excluded due to an incorrect study design
Eliassen 2017[56]	Excluded due to an incorrect intervention
Eppes 2003[57]	Excluded due to an incorrect study design
Esposito 2013[58]	Excluded due to an incorrect study design
Fallon 1999[60]	Excluded due to an incorrect intervention
Galev 2005[61]	Excluded due to an incorrect study design
Garkowski 2017[62]	Systematic review
Gasser 1996[64]	Not available
Gasser 1995[65]	Excluded due to an incorrect study design
Gasser 1995[63]	Excluded due to an incorrect study design
Gerber 1996[66]	Excluded due to an incorrect intervention
Gillies 2015[67]	Excluded due to an incorrect study design
Goodwin 1990[68]	Excluded due to an incorrect study design
Hansen 1992[69]	Excluded due to an incorrect intervention
Hassler 1990[70]	Excluded due to an incorrect population
Horton 2017[71]	Conference abstract
Hu 2001[72]	Excluded due to an incorrect study design
Inboriboon 2010[73]	Excluded due to an incorrect study design
Karkkonen 2001[75]	Excluded due to an incorrect study design
Karlsson 1996[76]	Excluded due to an incorrect outcome
Kersten 1995[77]	Excluded due to an incorrect study design
Kilic Muftuoglu 2016[78]	Excluded due to an incorrect study design
Klempner 2013[80]	Excluded due to an incorrect study design
Korenberg 1996[81]	Excluded due to an incorrect intervention
Kowalski 2010[83]	Excluded due to an incorrect outcome
Kowalski 2011[82]	Excluded due to an incorrect study design
Krbkova 1996[84]	Excluded due to an incorrect comparison
Kuhn 2012[85]	Excluded due to an incorrect study design
Laasila 2003[86]	Excluded due to an incorrect population
Lantos 2013[87]	Excluded due to an incorrect study design
Lauhio 1994[88]	Excluded due to an incorrect population
Lauhio 1991[89]	Excluded due to an incorrect population
Lempner 2002[79]	Excluded due to an incorrect study design
Liegner 1992[90]	Excluded due to an incorrect study design
Lipsker 2002[91]	Excluded due to an incorrect study design
Ljostad 2008[92]	Study abstract
Loewen 1999[93]	Excluded due to an incorrect study design
Loewen 2000[94]	Excluded due to an incorrect study design

Reference	Reason for exclusion
Luft 1988[96]	Excluded due to an incorrect outcome
Luft 1989[95]	Excluded due to an incorrect population
Maraspin 1995[102]	Excluded due to an incorrect study design
Maraspin 1996[97]	Excluded due to an incorrect study design
Maraspin 1999[98]	Excluded due to an incorrect study design
Maraspin 2002[99]	Excluded due to an incorrect study design
Maraspin 1999[100]	Excluded due to an incorrect study design
Maraspin 2002[101]	Excluded due to an incorrect population
Marks 2016[103]	Excluded due to an incorrect study design
McGill 1965[104]	Excluded due to an incorrect population
Meyerhoff 2002[105]	Excluded due to an incorrect study design
Meyerhoff 2016[106]	Excluded due to an incorrect study design
Millner 1996[107]	Excluded due to an incorrect outcome
Millner 1996[108]	Excluded due to an incorrect outcome
Morales 2000[109]	Excluded due to an incorrect study design
Muellegger 1995[111]	Excluded due to an incorrect study design
Muellegger 1996[110]	Excluded due to an incorrect comparison
Mullegger 1991[112]	Excluded due to an incorrect outcome
Nadelman 1993[114]	Excluded due to an incorrect study design
Nadelman 2001[113]	Excluded due to an incorrect population
Naglo 1989[115]	Excluded due to an incorrect study design
Neumann 1987[118]	Excluded due to an incorrect study design
Nimmrich 2014[120]	Excluded due to an incorrect study design
Nowakowski 2000[121]	Excluded due to an incorrect study design
Nowakowski 1995[122]	Excluded due to an incorrect study design
Ogrinc 2006[123]	Excluded due to an incorrect population
Oksi 1999[124]	Excluded due to an incorrect study design
Oksi 2007[125]	Excluded due to an incorrect population
Oksi 1998[126]	Excluded due to an incorrect population
Peltomaa 1998[127]	Excluded due to an incorrect comparison
Pena 1999[128]	Excluded due to an incorrect study design
Perronne 2015[129]	Not available
Pfister 1988[130]	Excluded due to an incorrect outcome
Pirila 1951[133]	Excluded due to an incorrect study design
Plorer 1993[134]	Excluded due to an incorrect study design
Plotkin 1991[135]	Excluded due to an incorrect study design
Puchalska 1996[136]	Excluded due to an incorrect study design
Puri 2015[137]	Excluded due to an incorrect comparison
Puri 2015[138]	Excluded due to an incorrect study design
Rebman 2015[139]	Excluded due to an incorrect study design
Renaud 2004[140]	Excluded due to an incorrect study design
Rohacova 1996[141]	Excluded due to an incorrect comparison
Rose 1994[142]	Excluded due to an incorrect study design
Rose 1996[143]	Excluded due to an incorrect intervention
Rubin 1992[144]	Excluded due to an incorrect study design

Reference	Reason for exclusion
Salazar 2005[145]	Excluded due to an incorrect intervention
Salazar 1993[146]	Excluded due to an incorrect study design
Sanchez 2016[147]	Excluded due to an incorrect study design
Sandstrom 1989[148]	Excluded due to an incorrect study design
Schmidt 1995[149]	Excluded due to an incorrect study design
Selby 2008[150]	Excluded due to an incorrect study design
Shadick 1994[151]	Excluded due to an incorrect study design
Shadick 1999[152]	Excluded due to an incorrect study design
Shemenski 2016[153]	Excluded due to an incorrect study design
Shoemaker 2006[154]	Excluded due to an incorrect intervention
Sjowall 2012[156]	Excluded due to an incorrect intervention
Sjowall 2011[155]	Excluded due to an incorrect study design
Skogman 2003[158]	Excluded due to an incorrect intervention
Skogman 2008[157]	Excluded due to an incorrect study design
Skoldenberg 1988[159]	Excluded due to an incorrect study design
Smith 2002[160]	Excluded due to an incorrect study design
Solomon 1998[161]	Excluded due to an incorrect intervention
Spathling 1992[162]	Article not in English
Stanek 1999[163]	Excluded due to an incorrect study design
Steere 1980[167]	Excluded due to an incorrect study design
Steere 1983[168]	Excluded due to an incorrect study design
Steere 1987[164]	Excluded due to an incorrect study design
Steurer 2016[169]	Article not in English
Stricker 2011[170]	Excluded due to an incorrect study design
Stricker 2010[171]	Excluded due to an incorrect study design
Strle 1996[172]	Excluded due to an incorrect outcome
Strle 1996[173]	Excluded due to an incorrect outcome
Strle 1992[174]	Excluded due to an incorrect study design
Strle 1993[175]	Excluded due to an incorrect outcome
Stupica 2015[177]	Excluded due to an incorrect comparison
Stupica 2011[176]	Excluded due to an incorrect comparison
Suarez-Magdalena 2017[178]	Not available
Thompson 2012[179]	Excluded due to an incorrect study design
Thorstrand 2002[180]	Excluded due to an incorrect study design
Thyresson 1949[181]	Excluded due to an incorrect study design
Torbahn 2016[182]	Excluded due to an incorrect study design
Tory 2010[183]	Excluded due to an incorrect comparison
Tseng 2017[184]	Excluded due to an incorrect outcome
Valesova 1996[185]	Excluded due to an incorrect comparison
Vazquez 2003[187]	Excluded due to an incorrect study design
Vazquez-Lopez 2016[186]	Excluded due to an incorrect study design
Wahlberg 1994[188]	Excluded due to an incorrect intervention
Weber 1988[190]	Excluded due to an incorrect study design
Weber 1987[189]	Excluded due to an incorrect population
Weissenbacher 2005[191]	Excluded due to an incorrect intervention

Reference	Reason for exclusion
White 2013[192]	Excluded due to an incorrect study design
Zochling 1996[193]	Excluded due to an incorrect study design

I.2 Excluded health economic studies

Table 30: Studies excluded from the health economic review

Reference	Reason for exclusion
None	None