National Institute for Health and Care Excellence

Draft for Consultation

Lyme disease: diagnosis and management

[G] Evidence review for the management of Lyme arthritis

NICE guideline

Evidence review

September 2017

Draft for Consultation

This evidence review was developed by the National Guideline Centre

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1 Management (arthritis)

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

1.2 Introduction

Arthritis related to Lyme disease can be a painful and disabling condition. The choice and duration of antibiotic treatment to resolve the condition is therefore important. It can present as arthritis of one joint or can affect many joints. It is often not recognised without a good history and until other causes of mono- or ply-arthritis are excluded.

The current treatment of Lyme arthritis is inconsistent in terms of both choice of antibiotic and duration of treatment. Presently the BNF states that 'doxycycline, amoxicillin [unlicensed indication] or cefuroxime (as cefuroxime axetil) are the antibacterials of choice for early Lyme disease or Lyme arthritis'. Current treatment is often determined by advice from the local or reference laboratory microbiologist and may differ from region to region.

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 arthritis 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 + 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)

	Steroids (corticosteroids; systemic, local injections) • Dexamethasone (local injection, IV) • Hydrocortisone (local injection, IV) • Methylprednisolone (local injection, IV) • Prednisolone (local injection, IV) Non-steroidal anti-inflammatory drugs (NSAIDs) Hydroxychloroquine sulfate (Plaquenil, Quinoric; oral)
Comparisons	• Any type of intervention compared to each other o If data are available consider: - Type of agent (within class or between class) - Route of administration - Duration of treatment: 1 month versus longer • Monotherapy versus polytherapy (any combination) • Antimicrobial treatment, steroids or NSAIDs compared to no treatment / placebo
Outcomes	**Critical:** 1. Quality of life (any validated measure) 2. Cure (resolution of symptoms related to Lyme arthritis) 3. Reduction of clinical symptoms related to Lyme arthritis 4. Relapse of symptoms related to Lyme arthritis **Important:** 5. Adverse events
Study design	• RCTs • Cohort studies (if no RCT evidence is found)

1.4 Clinical evidence

1.4.1 Included studies

Three RCTs were included in the review;[29,164,166] these are summarised in Table 2 below. One study included children, young people and adults above the age of 8 years,[164] 1 study included young people and adults 13 years or older[166] and 1 study was in adults only.[29] The diagnosis of Lyme arthritis was based on recurrent or chronic inflammatory arthritis and a positive blood test *B. burgdorferi* titre or a history of other Lyme disease-related symptoms, such as an erythema migrans or facial palsy. Evidence from these studies 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 compared to each other, versus steroids or non-steroidal anti-inflammatory drugs, versus hydroxychloroquine sulfate or versus placebo as treatment for people with arthritis-related Lyme disease.

One RCT[166] included an indirect intervention as people in the amoxicillin group had also received probenecid.

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 in adults and young people included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Caperton 1990[29]	(n=40) Ceftriaxone. 2 g intravenously in a 30-minute infusion daily. Vitamin preparation added to prevent people from detecting their treatment group by appearance or taste of solution. Duration 14 days. Concurrent medication or care: Not reported (n=20) Placebo. Duration 14 days. Concurrent medication or care: Not reported	n=60 Diagnosis: chronic inflammatory arthritis, 2 reactive antibody titres to *B. burgdorferi* in a titre at 1:64 or greater within 6 months of enrolment including a positive test within 2 weeks of starting therapy	Reduction in symptoms	29 people had been treated with at least 1 course of oral antibiotic for 2 to 10 weeks before entering the study
Steere 1985[164]	(n=20) Benzylpenicillin sodium or Penicillin G. 1.2 million U injected in each buttock weekly intramuscularly. Duration 3 weeks. Concurrent medication or care: other anti-inflammatory medications continued according to clinical indications (n=20) Placebo. 2 ml saline injected in each buttock weekly. Duration 3 weeks. Concurrent medication or care: other anti-inflammatory medications continued according to clinical indications	n=40 Diagnosis: living in an area endemic for Lyme disease; history of EM, meningitis, or Bell's palsy during the summer followed within 1 year by arthritis; or to have short recurrent attacks of oligoarticular arthritis not due to other known causes; onset of infection >1 year earlier; at least 1 actively inflamed joint	Cure	5 people in each group had previously received antibiotic therapy Most people received ancillary therapy (NSAIDs, hydroxychloroquine, intraarticular steroids) during treatment Serious indirectness: intramuscular route of administration
Steere 1994[166]	(n=23) Amoxicillin. 500 mg plus probenecid 500 mg	n=40 Diagnosis: initial	Cure Symptom relapse	Serious indirectness: people in the amoxicillin group

Study	Intervention and comparison	Population	Outcomes	Comments
	4 times per day. Duration 30 days. Concurrent medication or care: NSAIDs taken by people with marked joint inflammation, steroid infections were not allowed during antibiotic therapy (n=25) Doxycycline. 100 mg twice per day. Duration 30 days. Concurrent medication or care: NSAIDs taken by people with marked joint inflammation, steroid infections not allowed during antibiotic treatment	attack or intermittent episodes of arthritis in 1 or a few joints; at least 1 actively inflamed joint at the time of study entry; positive antibody response to *B. burgdorferi* determined by ELISA	Adverse events	also received probenecid 5 people in the amoxicillin group and 3 in the doxycycline group had received prior treatment with oral antibiotics <30 days and intraarticular steroids

1 See appendix D for full evidence tables.

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1.4.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: doxycycline (PO) versus amoxicillin (PO) plus probenecid

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with amoxicillin plus probenecid	Risk difference with doxycycline (95% CI)
Cure (resolution of arthritis at 3 months)	38 (1 study)	VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision	RR 1.01 (0.81 to 1.26)	889 per 1,000	9 more per 1,000 (from 169 fewer to 231 more)
Symptom relapse (subsequent complications at mean 3.3 years)	34 (1 study)	VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision	RR 0.36 (0.08 to 1.59)	312 per 1,000	200 fewer per 1,000 (from 287 fewer to 184 more)
Adverse events (side effects during treatment)	40 (1 study)	VERY LOW[1,2] due to risk of bias, indirectness	OR 0.09 (0.02 to 0.47)[4]	350 per 1,000	304 fewer per 1,000 (from 148 fewer to 339 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 because of a serious intervention indirectness
[3] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
[4] The Peto odds ratio method was used because of a zero event rate in the intervention arm

Table 4: Clinical evidence summary: ceftriaxone (IV) versus placebo

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with ceftriaxone (95% CI)
Reduction of symptoms (improvement at 1 month)	59 (1 study)	LOW[1] due to risk of bias	RR 4.87 (1.26 to 18.86)	100 per 1,000	387 more per 1,000 (from 26 more to 1,000 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

Table 5: Clinical evidence summary: benzylpenicillin (IM) versus placebo

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with benzylpenicillin (95% CI)
Cure (complete resolution at mean 33 months)	40 (1 study)	LOW[1] due to risk of bias	OR 10.63 (2.12 to 53.21)[2]	0 per 1,000	350 more per 1,000 (from 141 more to 559 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] The Peto odds ratio method was used because of a zero event rate in the control arm

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 6: 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/1.25 ml 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: intravenous.

Sources: Unit costs from NHS Electronic Drug Tariff January 2017,[118] except cefotaxime from BNF, January 2017[20] and ceftriaxone from EMIT March 2017;[38] dosage from BNF and BNF for Children January 2017,[20,21] exceptions below:

(a) Source of dosage from RCT in adults with EM: Steere 1983,[165] dosage for Lyme disease not available from BNF or BNF for children.

(b) Source of dosage from RCT in adults with neuroborreliosis: Pfister 1989[130] and Pfister 1991,[131] dosage for Lyme disease not available from BNF or BNF for children. [20,21]

(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.[21]

(e) Administration can vary in adults and children >1month: 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.[20]

(f) Source of dosage from RCT in adults with Lyme arthritis: Steere 1985:[164] 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. [20,21]

(g) Course duration for early Lyme 14-21 days; 28 days for Lyme arthritis. BNF January 2017.[20]

(h) Course duration for early Lyme 10-14 days; 28 days for Lyme arthritis. BNF January 2017.[20]

(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[41])
- 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).[115] 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 weighted average unit cost of non-elective inpatient stays and day cases for infectious disease in adults and children are summarised estimated in the table below using the NHS reference costs 2015/2016.[46]

Table 7: 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[46]

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 for example, 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 7, 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:

- Very Low quality evidence from 1 RCT showed a clinical benefit of oral doxycycline over oral amoxicillin with oral probenecid in terms of symptom relapse and adverse events. Very Low quality evidence from 1 RCT did not find any difference between the two treatment arms for cure rates.
- Low quality evidence from 1 RCT showed a clinical benefit of intravenous ceftriaxone over placebo for the reduction of symptoms.
- Low quality evidence from 1 RCT showed a clinical benefit of intramuscular phenoxymethylpenicillin over placebo for cure.

Children:

- No evidence in children was identified.

1.7.2 Health economic evidence statements

- No relevant economic evaluations were identified.

1.8 Recommendations

G1. For adults and young people (aged 12 and over) diagnosed with Lyme disease, offer antibiotic treatment according to their symptoms as described in Table 8.

G2. For children (under 12) diagnosed with Lyme disease, consider antibiotic treatment according to their symptoms as described in Table 9.

G3. Ask women whether they might be pregnant before offering antibiotic treatment for Lyme disease (see recommendation M1 on treatment in pregnancy).

G4. If symptoms worsen within the first day of antibiotic treatment, assess the person for Jarisch-Herxheimer reaction.

Table 8: Antibiotic treatment for Lyme disease in adults and young people (aged 12 and over) according to symptoms[a]

Symptoms	Treatment	First alternative	Second alternative
Erythema migrans	Doxycycline 100 mg twice per day or 200 mg once per day for 21 days	Amoxicillin 1 g 3 times per day for 21 days	Azithromycin 500 mg on 3 consecutive days each week for 3 consecutive weeks[c]
Non-focal symptoms	Doxycycline 100 mg twice per day or 200 mg once per day for 21 days	Amoxicillin 1 g 3 times per day for 21 days	Azithromycin 500 mg on 3 consecutive days each week for 3 consecutive weeks[c]

Symptoms	Treatment	First alternative	Second alternative
Lyme disease affecting the cranial nerves or peripheral nervous system	Doxycycline 100 mg twice per day or 200 mg once per day for 21 days	Amoxicillin 1 g 3 times per day for 21 days	
Lyme disease affecting the central nervous system	Intravenous ceftriaxone 2 g twice per day or 4 g once per day for 21 days (consider switching to oral doxycycline when no longer acutely unwell)	Doxycycline 200 mg twice per day or 400 mg once per day for 21 days	
Arthritis	Doxycycline 100 mg twice per day or 200 mg once per day for 28 days	Amoxicillin 1 g 3 times per day for 28 days	Intravenous ceftriaxone 2 g once per day for 28 days
Acrodermatitis chronica atrophicans	Doxycycline 100 mg twice per day or 200 mg once per day for 28 days	Amoxicillin 1 g 3 times per day for 28 days	Intravenous ceftriaxone 2 g once per day for 28 days
Carditis[b]	Doxycycline 100 mg twice per day or 200 mg once per day for 21 days	Intravenous ceftriaxone 2 g once per day for 21 days	
Carditis and haemodynamically unstable	Intravenous ceftriaxone 2 g once per day for 21 days (consider switching to oral doxycycline when no longer acutely unwell)		

[a] *For Lyme disease suspected during pregnancy, use appropriate antibiotics for stage of pregnancy.*

[b] *Do not use azithromycin to treat adults with cardiac abnormalities associated with Lyme disease because of its effect on QT interval.*

[c] *At the time of consultation (September 2017), azithromycin did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.*

1 **Table 9: Antibiotic treatment for Lyme disease in children (under 12) according to**
2 **symptoms[a]**

Symptoms	Treatment	Alternative
Erythema migrans	Amoxicillin 30 mg/kg 3 times per day for 21 days up to a maximum of 1 g/dose	Azithromycin 10 mg/kg on 3 consecutive days each week for 3 weeks[b]
Non-focal symptoms	Amoxicillin 30 mg/kg 3 times per day for 21 days up to a maximum of 1 g/dose	Azithromycin 10 mg/kg on 3 consecutive days each week for 3 weeks[b]
Lyme disease affecting the cranial nerves or peripheral nervous system	Amoxicillin 30 mg/kg 3 times per day for 21 days up to a maximum of 1 g/dose	
Lyme disease affecting the central nervous system	Intravenous ceftriaxone 80 mg/kg once per day for 21 days	
Arthritis	Amoxicillin 30 mg/kg 3 times per day 28 days up to a maximum of 1 g/dose	Intravenous ceftriaxone 80 mg/kg once per day for 28 days

Symptoms	Treatment	Alternative
Acrodermatitis chronica atrophicans	Amoxicillin 30 mg/kg 3 times per day 28 days up to a maximum of 1 g/dose	Intravenous ceftriaxone 80 mg/kg once per day for 28 days
Carditis[b]	Intravenous ceftriaxone 80 mg/kg once per day for 21 days	
Carditis and haemodynamically unstable	Intravenous ceftriaxone 80 mg/kg once per day for 21 days	

[a] *Specialist practice may include use of doxycycline for children aged 9 years and above in infections where doxycycline is considered first line in adult practice. At the time of consultation (September 2017), doxycycline did not have a UK marketing authorisation for this indication in children under 12 years and is contraindicated. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.*

[b] *At the time of consultation (September 2017), azithromycin did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.*

1.8.1 Research recommendations

RR1. Can a core outcome set be developed for clinical trials in management of Lyme disease?

RR2. What are the most clinically and cost-effective treatment options for different clinical presentations of Lyme disease in the UK?

See also rationales in appendix J of evidence report D.

1.9 Rationale and impact

1.9.1 Why the committee made the recommendations

The committee considered it important to standardise dose and duration of treatments for people with Lyme disease to ensure consistency and clarity for treatment across different presentations.

Lyme disease can cause inflammation affecting one or more joints.

The studies identified looked at antibiotic treatment in children, young people and adults. One study found that a 30-day course of doxycycline resulted in fewer symptom relapses and adverse events than 30 days of amoxicillin plus probenecid.

The committee agreed that longer courses of treatment are appropriate when treating arthritis associated with Lyme disease because it is difficult for antibiotics to penetrate to the synovium and synovial fluid.

Taking these factors into account, the committee decided that a 28-day course of doxycycline 200 mg daily should be offered to adults and young people (aged 12 and over) as initial treatment, with a 28-day course of amoxicillin recommended as an alternative treatment. A 28-day course was recommended, as the committee was aware that antibiotics are available in weekly packs. The committee also agreed that if oral doxycycline and amoxicillin are contraindicated or unsuitable, 28 days of intravenous ceftriaxone should be offered.

The committee agreed that the evidence supported similar treatment to adults for children under 12, with the same duration of treatment but using appropriate antibiotics for children and doses adjusted by weight.

1.9.2 Impact of the recommendations on practice

The recommendations aim to standardise antibiotic treatment, providing a consistent framework for good practice in managing Lyme disease. Overall, there may be changes to prescribing practices, but the impact is likely to be small.

1.10 The committee's discussion of the evidence

1.10.1 Interpreting the evidence

1.10.1.1 The outcomes that matter most

The guideline committee considered quality of life, the resolution of symptoms associated with arthritis, the reduction in symptoms related to arthritis and the reoccurrence of symptoms related to arthritis to be critical outcomes for decision-making. Adverse events were also considered to be important outcomes.

Resolution of symptoms, reduction in symptoms, symptom relapse and adverse events were the only outcomes for which data were available. No evidence for quality of life was found.

1.10.1.2 The quality of the evidence

The evidence came from 3 RCTs comprising 140 people and was of Low to Very Low quality due to risk of bias, imprecision and indirectness. There were particular concerns regarding the lack of blinding, which could have had a confounding effect on subjective outcomes, such as signs and symptoms that could not be measured by objective tests.

Many outcomes and the time point at which they were assessed were poorly defined in the included studies. In particular, it was not clear whether cure or reduction of symptoms referred to the resolution or improvement of the arthritic symptoms or of any Lyme disease symptoms. Similar ambiguity existed for the outcomes of reoccurrence of symptoms. Studies also varied in the outcomes they reported.

One of the studies included an indirect intervention. People in the amoxicillin group also received 500 mg probenecid, which was used to increase the effective body concentration of amoxicillin. Meta-analysis was not possible due to the different treatments regimens given in the studies.

1.10.1.3 Benefits and harms

We identified 3 RCTs assessing the effectiveness of antibiotics in people with Lyme arthritis. One study included children, young people and adults above the age of 8 years, 1 study included young people and adults 13 years or older and 1 study was in adults only. The diagnosis of Lyme arthritis was based on recurrent or chronic inflammatory arthritis and a positive blood test *B. burgdorferi* titre or a history of other Lyme disease-related symptoms, such as an erythema migrans or facial palsy.

The evidence showed that here was no difference in cure rates, but people had fewer symptom relapses and adverse events when taking 100 mg of oral doxycycline twice daily for 30 days compared to 500mg of oral amoxicillin plus 500 mg oral probenecid 4 times per day for 30 days. Therefore the committee determined that there was an overall clinical benefit of doxycycline.

People who received a daily intravenous infusion of 2 g ceftriaxone for 14 days showed better symptom improvement after 1 month than people who received placebo. Similarly, the cure rate, defined as a complete resolution of symptoms, was considerably higher in people who had received an intramuscular injection of 2.4 million IU (1.2 million IU in each buttock) of benzylpenicillin or penicillin G every week for 3 weeks compared to people who had received placebo. No person in the placebo group experienced a complete resolution of symptoms. People in both treatment arms had continued to take anti-inflammatory medications according to clinical indications during the trial.

The committee acknowledged that a 30-day course of doxycycline was more effective than a combination of amoxicillin plus probenecid for reducing symptom relapse. People in the doxycycline group also experienced fewer adverse events. The committee did not judge the evidence alone to be strong enough upon which to base a recommendation, but considered it in conjunction with current clinical practice and their own clinical experience and decided to recommend 100 mg of oral doxycycline twice per day for 28 days due to available pack sizes. In cases where doxycycline is contraindicated, 1 g of amoxicillin 3 times per day for 28-days should be given. The rationale for recommending 1 g amoxicillin 3 times per day, which is higher than the current practice dosage of 500 mg 3 times per day, is due to the included study using probenecid to increase the concentration of amoxicillin and the evidence identified for the reviews on the management of erythema migrans and arthritis related to Lyme disease.

1.10.2 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 for adults).

The BNF recommends doxycycline, amoxicillin or cefuroxime axetil as the antibacterials of choice for Lyme arthritis. The dose and duration of treatment for doxycycline the committee recommended is the same as that listed in the BNF. The committee recommended a higher dose of amoxicillin (1 g 3 times per day versus 500 mg 3 times per day in BNF). As noted above, the rationale for this higher dose is because the included study used probenecid to increase the concentration of amoxicillin; therefore, the committee decided to recommend 1 g amoxicillin 3 times per day as the preferred dose of amoxicillin. The committee considered that the additional minimal cost of treatment for a higher dose of amoxicillin would be offset by the improved quality of life as a result 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 arthritis. The committee did not consider that there was clinical evidence to support such a recommendation. Furthermore, cefuroxime axetil is much more expensive than the other oral antimicrobials (£141.76 for 500 mg 2 times per day for 28 days).

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

The committee agreed that this potential change in practice in terms of a higher dose of amoxicillin would not result in a significant resource impact given the relatively small number of people diagnosed with Lyme disease.

1.10.3 Other factors the committee took into account

The committee agreed that a longer course of treatment, for example 28 days, is justified, as it is harder for antibiotics to penetrate to the synovium and synovial fluid than other body compartments.

Although both intramuscular benzylpenicillin and intravenous ceftriaxone showed a clinical benefit over placebo, the committee agreed to recommend intravenous ceftriaxone for people with Lyme arthritis. Intramuscular administration is painful for the person. The intravenous route of administration for benzylpenicillin is likely to be effective for the treatment of Lyme-associated arthritis but requires multiple daily doses as opposed to intravenous ceftriaxone, which can be given once daily. Treatment with intravenous benzylpenicillin requires inpatient care for the duration of treatment; the committee therefore recommended ceftriaxone.

No evidence was found was treatment of children. Recommendations for children are based on those for adults with adjustment for current licensing. The committee was aware that 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. The guideline includes a recommendation that care of people under 18 years be discussed with a specialist and it would be expected that a person less than 18 years with mono- or poly-arthritis would be under the care of a specialist.

The committee made a research recommendation for the development of core outcome set for studies of Lyme disease treatment and a research recommendation for antibiotic management of Lyme disease. The details of the research recommendations are in appendix J of evidence report D.

References

1. Aberer E, Kahofer P, Binder B, Kinaciyan T, Schauperl H, Berghold A. Comparison of a two- or three-week regimen and a review of treatment of erythema migrans with phenoxymethylpenicillin. Dermatology. 2006; 212(2):160-167

2. Abrutyn E. New uses for old drugs. Infectious Disease Clinics of North America. 1989; 3(3):653-664

3. Agger WA, Callister SM, Jobe DA. In vitro susceptibilities of Borrelia burgdorferi to five oral cephalosporins and ceftriaxone. Antimicrobial Agents and Chemotherapy. 1992; 36(8):1788-1790

4. Agus B. The recognition and treatment of Lyme disease. Primary Care Update for Ob/Gyns. 1995; 2(6):200-203

5. Agwuh KN, MacGowan A. Pharmacokinetics and pharmacodynamics of the tetracyclines including glycylcyclines. Journal of Antimicrobial Chemotherapy. 2006; 58(2):256-265

6. Ahmed A. When is facial paralysis Bell palsy? current diagnosis and treatment. Cleveland Clinic Journal of Medicine. 2005; 72(5):398-405

7. Ahmed S, Rashid S, Chaudhary A, Bischof E. A patient with Lyme disease: complete heart block treated with antibiotics. Primary Care Cardiovascular Journal. 2013; 6(3):117-118

8. Alarcon GS, Mikhail IS. Antimicrobials in the treatment of rheumatoid arthritis and other arthritides: a clinical perspective. American Journal of the Medical Sciences. 1994; 308(3):201-209

9. Andiman WA. Lyme disease: epidemiology, etiology, clinical spectrum, diagnosis, and treatment. Advances in Pediatric Infectious Diseases. 1986; 1:163-186

10. Anonymous. Antibiotic prophylaxis of Lyme disease following recognized tick bite. Bacterial Zoonoses Branch, Division of Vector-Borne Infectious Diseases National Center for Infectious Diseases, Centers for Disease Control. Connecticut Medicine. 1991; 55(12):691-693

11. Arvikar SL, Steere AC. Diagnosis and treatment of Lyme arthritis. Infectious Disease Clinics of North America. 2015; 29(2):269-280

12. Auwaerter PG, Aucott J, Dumler JS. Lyme borreliosis (Lyme disease): molecular and cellular pathobiology and prospects for prevention, diagnosis and treatment. Expert Reviews in Molecular Medicine. 2004; 6(2):1-22

13. Bennet L, Danell S, Berglund J. Clinical outcome of erythema migrans after treatment with phenoxymethyl penicillin. Scandinavian Journal of Infectious Diseases. 2003; 35(2):129-131

14. Berende A, ter Hofstede HJ, Donders AR, van Middendorp H, Kessels RP, Adang EM et al. Persistent Lyme Empiric Antibiotic Study Europe (PLEASE)--design of a randomized controlled trial of prolonged antibiotic treatment in patients with persistent symptoms attributed to Lyme borreliosis. BMC Infectious Diseases. 2014; 14:543

15. Berger BW. Treating erythema chronicum migrans of Lyme disease. Journal of the American Academy of Dermatology. 1986; 15(3):459-463

16. Berger BW. Treatment of erythema chronicum migrans of Lyme disease. Annals of the New York Academy of Sciences. 1988; 539:346-351

17. Bernardino AL, Kaushal D, Philipp MT. The antibiotics doxycycline and minocycline inhibit the inflammatory responses to the Lyme disease spirochete Borrelia burgdorferi. Journal of Infectious Diseases. 2009; 199(9):1379-1388

18. Bhate C, Schwartz RA. Lyme disease: Part II. Management and prevention. Journal of the American Academy of Dermatology. 2011; 64(4):639-653

19. Bjark PH. Re: No prolonged antibiotic therapy for disease attributed to borreliosis. Tidsskrift for den Norske Laegeforening. 2016; 136(20):1702-1703

20. BMJ Group and the Royal Pharmaceutical Society of Great Britain. British National Formulary. Available from: https://www.evidence.nhs.uk/formulary/bnf/current Last accessed: 04 April 2017.

21. BMJ Group and the Royal Pharmaceutical Society of Great Britain. British National Formulary for Children. Available from: https://www.evidence.nhs.uk/formulary/bnf/current Last accessed: 04 April 2017.

22. Borg R, Dotevall L, Hagberg L, Maraspin V, Lotric-Furlan S, Cimperman J et al. Intravenous ceftriaxone compared with oral doxycycline for the treatment of Lyme neuroborreliosis. Scandinavian Journal of Infectious Diseases. 2005; 37(6-7):449-454

23. Bratton RL, Whiteside JW, Hovan MJ, Engle RL, Edwards FD. Diagnosis and treatment of lyme disease. Mayo Clinic Proceedings. 2008; 83(5):566-571

24. Bremell D, Dotevall L. Oral doxycycline for Lyme neuroborreliosis with symptoms of encephalitis, myelitis, vasculitis or intracranial hypertension. European Journal of Neurology. 2014; 21(9):1162-1167

25. British Infection Association. The epidemiology, prevention, investigation and treatment of Lyme borreliosis in United Kingdom patients: A position statement by the British Infection Association. Journal of Infection. 2011; 62(5):329-338

26. Butler T, Jones PK, Wallace CK. Borrelia recurrentis infection: single-dose antibiotic regimens and management of the Jarisch-Herxheimer reaction. Journal of Infectious Diseases. 1978; 137(5):573-577

27. Cadavid D, Auwaerter PG, Rumbaugh J, Gelderblom H. Antibiotics for the neurological complications of Lyme disease. Cochrane Database of Systematic Reviews 2016, Issue 12. Art. No.: CD006978. DOI: 10.1002/14651858.CD006978.pub2.

28. Canadian Paediatric Society. How to diagnose and treat Lyme disease in children. Infectious Diseases and Immunization Committee, Canadian Paediatric Society. CMAJ. 1992; 147(2):169-178

29. Caperton EM, Heim-Duthoy KL, Matzke GR, Peterson PK, Johnson RC. Ceftriaxone therapy of chronic inflammatory arthritis. A double-blind placebo controlled trial. Archives of Internal Medicine. 1990; 150(8):1677-1682

30. Chapman AL, Dixon S, Andrews D, Lillie PJ, Bazaz R, Patchett JD. Clinical efficacy and cost-effectiveness of outpatient parenteral antibiotic therapy (OPAT): a UK perspective. Journal of Antimicrobial Chemotherapy. 2009; 64(6):1316-1324

31. Chen J, Field JA, Glickstein L, Molloy PJ, Huber BT, Steere AC. Association of antibiotic treatment-resistant Lyme arthritis with T cell responses to dominant

epitopes of outer surface protein a of Borrelia burgdorferi. Arthritis and Rheumatism. 1999; 42(9):1813-1822

32. Choo-Kang C, Tang E, Mattappallil A. The treatment of early lyme disease. US Pharmacist. 2010; 35(9):41-48

33. Christian CL. Management of asymptomatic Borrelia burgdorferi infection. Arthritis and Rheumatism. 1992; 35(11):1395

34. Cimmino MA. Recognition and management of bacterial arthritis. Drugs. 1997; 54(1):50-60

35. Cimmino MA, Accardo S. Long term treatment of chronic Lyme arthritis with benzathine penicillin. Annals of the Rheumatic Diseases. 1992; 51(8):1007-1008

36. Cimperman J, Maraspin V, Lotric-Furlan S, Ruzic-Sabljic E, Strle F. Lyme meningitis: a one-year follow up controlled study. Wiener Klinische Wochenschrift. 1999; 111(22-23):961-963

37. Coblyn JS, Taylor P. Treatment of chronic Lyme arthritis with hydroxychloroquine. Arthritis and Rheumatism. 1981; 24(12):1567-1569

38. Commercial Medicines Unit (CMU), Department of Health. Electronic market information tool (EMIT). 2011. Available from: http://cmu.dh.gov.uk/electronic-market-information-tool-emit/ Last accessed: 4 April 2017.

39. Committee on Infectious Diseases. Erratum: Treatment of lyme borreliosis (Pediatrics (July 1991) 88 (7-19)). Pediatrics. 1991; 88(4):840

40. Cuisset T, Hamilos M, Vanderheyden M. Coronary aneurysm in Lyme disease: treatment by covered stent. International Journal of Cardiology. 2008; 128(2):e72-e73

41. Curtis L, Burns A. Unit costs of health and social care 2016. Canterbury. Personal Social Services Research Unit University of Kent, 2016. Available from: http://www.pssru.ac.uk/project-pages/unit-costs/2016/

42. Dattwyler RJ, Grunwaldt E, Luft BJ. Clarithromycin in treatment of early Lyme disease: a pilot study. Antimicrobial Agents and Chemotherapy. 1996; 40(2):468-469

43. Dattwyler RJ, Halperin JJ. Failure of tetracycline therapy in early Lyme disease. Arthritis and Rheumatism. 1987; 30(4):448-450

44. Dattwyler RJ, Halperin JJ, Volkman DJ, Luft BJ. Treatment of late Lyme borreliosis - randomised comparison of ceftriaxone and penicillin. Lancet. 1988; 1(8596):1191-1194

45. Dattwyler RJ, Wormser GP, Rush TJ, Finkel MF, Schoen RT, Grunwaldt E et al. A comparison of two treatment regimens of ceftriaxone in late Lyme disease. Wiener Klinische Wochenschrift. 2005; 117(11-12):393-397

46. Department of Health. NHS reference costs 2015-16. 2016. Available from: https://www.gov.uk/government/publications/nhs-reference-costs-collection-guidance-for-2015-to-2016 Last accessed: 4 April 2017.

47. Dersch R, Freitag MH, Schmidt S, Sommer H, Rauer S, Meerpohl JJ. Efficacy and safety of pharmacological treatments for acute Lyme neuroborreliosis - a systematic review. European Journal of Neurology. 2015; 22(9):1249-1259

48. Dersch R, Freitag MH, Schmidt S, Sommer H, Rucker G, Rauer S et al. Efficacy and safety of pharmacological treatments for neuroborreliosis--protocol for a systematic review. Systems Review. 2014; 3:117

49. Dersch R, Rauer S. Treatment and long-term outcome of Lyme neuroborreliosis. Aktuelle neurologie. 2017; 43(10):608-614

50. Dersch R, Sommer H, Rauer S, Meerpohl JJ. Prevalence and spectrum of residual symptoms in Lyme neuroborreliosis after pharmacological treatment: a systematic review. Journal of Neurology. 2016; 263(1):17-24

51. Dhoot DS, Martin DF, Srivastava SK. Pediatric infectious posterior uveitis. International Ophthalmology Clinics. 2011; 51(1):113-128

52. Dinser R, Jendro MC, Schnarr S, Zeidler H. Antibiotic treatment of Lyme borreliosis: what is the evidence? Annals of the Rheumatic Diseases. 2005; 64(4):519-523

53. Dotevall L, Alestig K, Hanner P, Norkrans G, Hagberg L. The use of doxycycline in nervous system Borrelia burgdorferi infection. Scandinavian Journal of Infectious Diseases Supplement. 1988; 53:74-79

54. Eliassen KE, Berild D, Reiso H, Grude N, Christophersen KS, Finckenhagen C et al. Incidence and antibiotic treatment of erythema migrans in Norway 2005-2009. Ticks and Tick-Borne Diseases. 2017; 8(1):1-8

55. Eliassen KE, Hjetland R, Reiso H, Lindbaek M, Tschudi-Madsen H. Symptom load and general function among patients with erythema migrans: a prospective study with a 1-year follow-up after antibiotic treatment in Norwegian general practice. Scandinavian Journal of Primary Health Care. 2017; 35(1):75-83

56. Eppes SC. Diagnosis, treatment, and prevention of Lyme disease in children. Pediatric Drugs. 2003; 5(6):363-372

57. Esposito S, Baggi E, Villani A, Norbedo S, Pellegrini G, Bozzola E et al. Management of paediatric Lyme disease in non-endemic and endemic areas: data from the registry of the Italian Society for Pediatric Infectious Diseases. European Journal of Clinical Microbiology and Infectious Diseases. 2013; 32(4):523-529

58. Fallon BA, Keilp JG, Corbera KM, Petkova E, Britton CB, Dwyer E et al. A randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy. Neurology. 2008; 70(13):992-1003

59. Fallon BA, Tager F, Fein L, Liegner K, Keilp J, Weiss N et al. Repeated antibiotic treatment in chronic Lyme disease. Journal of Spirochetal and Tick-borne Diseases. 1999; 6(4):94-102

60. Galev A, Zvetkov V, Genov K. Pulse therapy with ceftriaxone on Lyme neuroborreliosis. Problems of Infectious and Parasitic Diseases. 2005; 33(1):15-17

61. Garkowski A, Zajkowska J, Zajkowska A, Kulakowska A, Zajkowska O, Kubas B et al. Cerebrovascular manifestations of Lyme neuroborreliosis-a systematic review of published cases. Frontiers in Neurology. 2017; 8:146

62. Gasser R, Reisinger E, Eber B, Pokan R, Seinost G, Bergloff J et al. Cases of Lyme borreliosis resistant to conventional treatment: improved symptoms with cephalosporin plus specific beta-lactamase inhibition. Microbial Drug Resistance. 1995; 1(4):341-344

63. Gasser R, Reisinger E, Sedaj B, Horvarth R, Seinost G, Keplinger A et al. Oral treatment of late Lyme borreliosis with a combination of roxithromycin and co-trimoxazole--a pilot study on 18 patients. Acta Medica Austriaca. 1996; 23(3):99-101

64. Gasser R, Wendelin I, Reisinger E, Bergloff J, Feigl B, Schafhalter I et al. Roxithromycin in the treatment of Lyme disease--update and perspectives. Infection. 1995; 23 (Suppl.1):S39-43

65. Gerber MA, Shapiro ED, Burke GS, Parcells VJ, Bell GL. Lyme disease in children in southeastern Connecticut. Pediatric Lyme Disease Study Group. New England Journal of Medicine. 1996; 335(17):1270-1274

66. Gillies M, Ranakusuma A, Hoffmann T, Thorning S, McGuire T, Glasziou P et al. Common harms from amoxicillin: a systematic review and meta-analysis of randomized placebo-controlled trials for any indication. CMAJ. 2015; 187(1):E21-E31

67. Goodwin SD, Sproat TT, Russell WL. Management of Lyme disease. Clinical Pharmacy. 1990; 9(3):192-205

68. Hansen K, Hovmark A, Lebech AM, Lebech K, Olsson I, Halkier-Sørensen L et al. Roxithromycin in Lyme borreliosis: discrepant results of an in vitro and in vivo animal susceptibility study and a clinical trial in patients with erythema migrans. Acta Dermato-Venereologica. 1992; 72(4):297-300

69. Hassler D, Zoller L, Haude M, Hufnagel HD, Heinrich F, Sonntag HG. Cefotaxime versus penicillin in the late stage of Lyme disease: prospective, randomized therapeutic study. Infection. 1990; 18(1):16-20

70. Horton DB, Taxter AJ, Groh B, Sherry DD, Rose CD. Clinical and treatment factors associated with antibiotic-refractory Lyme arthritis in children. Arthritis and Rheumatology. 2017; 68(S10):3140-3143

71. Hu LT, Klempner MS. Update on the prevention, diagnosis, and treatment of Lyme disease. Advances in Internal Medicine. 2001; 46:247-275

72. Inboriboon PC. Early recognition and management of Lyme carditis. International Journal of Emergency Medicine. 2010; 3(4):489-490

73. Kaplan RF, Trevino RP, Johnson GM, Levy L, Dornbush R, Hu LT et al. Cognitive function in post-treatment Lyme disease: do additional antibiotics help? Neurology. 2003; 60(12):1916-1922

74. Karkkonen K, Stiernstedt SH, Karlsson M. Follow-up of patients treated with oral doxycycline for Lyme neuroborreliosis. Scandinavian Journal of Infectious Diseases. 2001; 33(4):259-262

75. Karlsson M, Hammers S, Nilsson-Ehle I, Malmborg AS, Wretlind B. Concentrations of doxycycline and penicillin G in sera and cerebrospinal fluid of patients treated for neuroborreliosis. Antimicrobial Agents and Chemotherapy. 1996; 40(5):1104-1107

76. Kersten A, Poitschek C, Rauch S, Aberer E. Effects of penicillin, ceftriaxone, and doxycycline on morphology of Borrelia burgdorferi. Antimicrobial Agents and Chemotherapy. 1995; 39(5):1127-1133

77. Kilic Muftuoglu I, Aydin Akova Y, Gur Gungor S. A case of Lyme disease accompanied by uveitis and white dot syndrome. Turkish Journal of Ophthalmology. 2016; 46(5):241-243

78. Klempner MS. Controlled trials of antibiotic treatment in patients with post-treatment chronic Lyme disease. Vector Borne and Zoonotic Diseases. 2002; 2(4):255-263

79. Klempner MS, Baker PJ, Shapiro ED, Marques A, Dattwyler RJ, Halperin JJ et al. Treatment trials for post-lyme disease symptoms revisited. American Journal of Medicine. 2013; 126(8):665-669

80. Korenberg EI, Vorobyeva NN, Moskvitina HG, Gorban Ln. Prevention of borreliosis in persons bitten by infected ticks. Infection. 1996; 24(2):187-189

81. Kowalski TJ, Berth WL, Mathiason MA, Agger WA. Oral antibiotic treatment and long-term outcomes of Lyme facial nerve palsy. Infection. 2011; 39(3):239-245

82. Kowalski TJ, Tata S, Berth W, Mathiason MA, Agger WA. Antibiotic treatment duration and long-term outcomes of patients with early Lyme disease from a Lyme disease-hyperendemic area. Clinical Infectious Diseases. 2010; 50(4):512-520

83. Krbkova L, Stanek G. Therapy of Lyme borreliosis in children. Infection. 1996; 24(2):170-173

84. Kuhn M, Grave S, Bransfield R, Harris S. Long term antibiotic therapy may be an effective treatment for children co-morbid with Lyme disease and autism spectrum disorder. Medical Hypotheses. 2012; 78(5):606-615

85. Laasila K, Laasonen L, Leirisalo-Repo M. Antibiotic treatment and long term prognosis of reactive arthritis. Annals of the Rheumatic Diseases. 2003; 62(7):655-658

86. Lantos PM, Brinkerhoff RJ, Wormser GP, Clemen R. Empiric antibiotic treatment of erythema migrans-like skin lesions as a function of geography: a clinical and cost effectiveness modeling study. Vector Borne and Zoonotic Diseases. 2013; 13(12):877-883

87. Lauhio A, Konttinen YT, Salo T, Tschesche H, Lahdevirta J, Woessner FJ et al. Placebo-controlled study of the effects of three-month lymecyclille treatment on serum matrix metalloproteinases in reactive arthritis. Annals of the New York Academy of Sciences. 1994; 732:424-426

88. Lauhio A, Leirisalo-Repo M, Lahdevirta J, Saikku P, Repo H. Double-blind, placebo-controlled study of three-month treatment with lymecycline in reactive arthritis, with special reference to Chlamydia arthritis. Arthritis and Rheumatism. 1991; 34(1):6-14

89. Liegner KB. Minocycline in Lyme disease. Journal of the American Academy of Dermatology. 1992; 26(2 Pt 1):263-264

90. Lipsker D, Antoni-Bach N, Hansmann Y, Jaulhac B. Long-term prognosis of patients treated for erythema migrans in France. British Journal of Dermatology. 2002; 146(5):872-876

91. Ljostad U, Eikeland R, Midgard R, Skogvoll E, Skarpass T, Berg A. Oral doxycycline vs. IV centriaxone for European Lyme neuro-borreliosis. A double-blind, randomized controlled clinical trial. European Journal of Neurology. 2008; 15(Suppl 3):338-389

92. Loewen PS, Marra CA, Marra F. Systematic review of the treatment of early Lyme disease Drugs. 1999; 57(2):157-173

93. Loewen PS, Marra CA, Marra F. Erratum: Systemic review of the treatment of early Lyme disease (Drugs (1999) 57 (2) (157-173)). Drugs. 2000; 59(3):476

94. Luft BJ, Halperin JJ, Volkman DJ, Dattwyler RJ. Ceftriaxone -an effective treatment of late Lyme borreliosis. Journal of Chemotherapy. 1989; 1(Suppl 4):917-919

95. Luft BJ, Volkman DJ, Halperin JJ, Dattwyler RJ. New chemotherapeutic approaches in the treatment of Lyme borreliosis. Annals of the New York Academy of Sciences. 1988; 539:352-361

96. Maraspin V, Cimperman J, Lotric-Furlan S, Pleterski-Rigler D, Strle F. Treatment of erythema migrans in pregnancy. Clinical Infectious Diseases. 1996; 22(5):788-793

97. Maraspin V, Cimperman J, Lotric-Furlan S, Pleterski-Rigler D, Strle F. Erythema migrans in pregnancy. Wiener Klinische Wochenschrift. 1999; 111(22-23):933-940

98. Maraspin V, Cimperman J, Lotric-Furlan S, Ruzic-Sabljic E, Jurca T, Picken RN et al. Solitary borrelial lymphocytoma in adult patients. Wiener Klinische Wochenschrift. 2002; 114(13-14):515-523

99. Maraspin V, Lotric-Furlan S, Cimperman J, Ruzic-Sabljic E, Strle F. Erythema migrans in the immunocompromised host. Wiener Klinische Wochenschrift. 1999; 111(22-23):923-932

100. Maraspin V, Lotric-Furlan S, Strle F. Development of erythema migrans in spite of treatment with antibiotics after a tick bite. Wiener Klinische Wochenschrift. 2002; 114(13-14):616-619

101. Maraspin V, Ruzic-Sabljic E, Strle F, Cimperman J, Jereb M, Preac-Mursic V. Persistence of Borrelia burgdorferi after treatment with antibiotics. Alpe Adria Microbiology Journal. 1995; 4(3):211-216

102. Marks CM, Nawn JE, Caplow JA. Antibiotic treatment for chronic Lyme disease -say no to the DRESS. JAMA Internal Medicine. 2016; 176(12):1745-1746

103. McGill IG, Bienenstock J. A comparative clinical trial of lymecycline. British Journal of Clinical Practice. 1965; 19:462-464

104. Meyerhoff J. Prolonged antibiotic treatment did not relieve chronic symptoms in Lyme disease. ACP Journal Club. 2002; 136(2):57

105. Meyerhoff J. Long-term antibiotics after ceftriaxone did not improve quality of life in persistent Lyme disease. Annals of Internal Medicine. 2016; 165(2):JC5

106. Millner MM, Thalhammer GH. Neuroborreliosis in childhood: treatment with penicillin sodium and ceftriaxone. Acta Dermatovenerologica Alpina, Panonica et Adriatica. 1996; 5(3-4):169-172

107. Millner MM, Thalhammer GH, Dittrich P, Spork KD, Brunner M, Georgopoulos A. Beta-lactam antibiotics in the treatment of neuroborreliosis in children: preliminary results. Infection. 1996; 24(2):174-177

108. Morales DS, Siatkowski RM, Howard CW, Warman R. Optic neuritis in children. Journal of Pediatric Ophthalmology and Strabismus. 2000; 37(5):254-259

109. Muellegger R, Zoechling N, Schluepen EM, Soyer HP, Hoedl S, Kerl et al. Polymerase chain reaction control of antibiotic treatment in dermatoborreliosis. Infection. 1996; 24(1):76-79

110. Muellegger RR, Zoechling N, Soyer HP, Hoedl S, Wienecke R, Volkenandt M et al. No detection of Borrelia burgdorferi-specific DNA in erythema migrans lesions after minocycline treatment. Archives of Dermatology. 1995; 131(6):678-682

111. Müllegger RR, Millner MM, Stanek G, Spork KD. Penicillin G sodium and ceftriaxone in the treatment of neuroborreliosis in children--a prospective study. Infection. 1991; 19(4):279-283

112. Nadelman RB, Nowakowski J, Fish D, Falco RC, Freeman K, McKenna D et al. Prophylaxis with single-dose doxycycline for the prevention of lyme disease after an Ixodes scapularis tick bite. New England Journal of Medicine. 2001; 345(2):79-84

113. Nadelman RB, Nowakowski J, Forseter G, Bittker S, Cooper D, Goldberg N et al. Failure to isolate Borrelia burgdorferi after antimicrobial therapy in culture-

documented Lyme borreliosis associated with erythema migrans: report of a prospective study. American Journal of Medicine. 1993; 94(6):583-588

114. Naglo AS, Wide K. Borrelia infection in children. Acta Paediatrica Scandinavica. 1989; 78(6):918-922

115. National Collaborating Centre for Women's and Children's Health. Meningitis (bacterial) and meningococcal septicaemia in under 16s: recognition, diagnosis and management. NICE clinical guideline 102. London. RCOG Press, 2010. Available from: http://guidance.nice.org.uk/CG102

116. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual. London. National Institute for Health and Care Excellence, 2014. Available from: http://www.nice.org.uk/article/PMG20/chapter/1%20Introduction%20and%20overview

117. Neumann R, Aberer E, Stanek G. Treatment and course of erythema chronicum migrans. Zentralblatt fur Bakteriologie, Mikrobiologie, und Hygiene - Series A, Medical Microbiology, Infectious Diseases, Virology, Parasitology. 1987; 263(3):372-376

118. NHS Business Services Authority. NHS electronic drug tariff March 2017. Available from: http://www.drugtariff.nhsbsa.nhs.uk/#/00446515-DC_2/DC00446511/Home Last accessed: 4 April 2017.

119. Nimmrich S, Becker I, Horneff G. Intraarticular corticosteroids in refractory childhood Lyme arthritis. Rheumatology International. 2014; 34(7):987-994

120. Nowakowski J, McKenna D, Nadelman RB, Cooper D, Bittker S, Holmgren D et al. Failure of treatment with cephalexin for Lyme disease. Archives of Family Medicine. 2000; 9(6):563-567

121. Nowakowski J, Nadelman RB, Forseter G, McKenna D, Wormser GP. Doxycycline versus tetracycline therapy for Lyme disease associated with erythema migrans. Journal of the American Academy of Dermatology. 1995; 32(2 Pt 1):223-227

122. Ogrinc K, Logar M, Lotric-Furlan S, Cerar D, Ruzic-Sabljic E, Strle F. Doxycycline versus ceftriaxone for the treatment of patients with chronic Lyme borreliosis. Wiener Klinische Wochenschrift. 2006; 118(21):696-701

123. Oksi J, Marjamaki M, Nikoskelainen J, Viljanen MK. Borrelia burgdorferi detected by culture and PCR in clinical relapse of disseminated Lyme borreliosis. Annals of Medicine. 1999; 31(3):225-232

124. Oksi J, Nikoskelainen J, Hiekkanen H, Lauhio A, Peltomaa M, Pitkäranta A et al. Duration of antibiotic treatment in disseminated Lyme borreliosis: a double-blind, randomized, placebo-controlled, multicenter clinical study. European Journal of Clinical Microbiology and Infectious Diseases. 2007; 26(8):571-581

125. Oksi J, Nikoskelainen J, Viljanen MK. Comparison of oral cefixime and intravenous ceftriaxone followed by oral amoxicillin in disseminated Lyme borreliosis. European Journal of Clinical Microbiology and Infectious Diseases. 1998; 17(10):715-719

126. Peltomaa M, Saxen H, Seppala I, Viljanen M, Pyykko I. Paediatric facial paralysis caused by Lyme borreliosis: a prospective and retrospective analysis. Scandinavian Journal of Infectious Diseases. 1998; 30(3):269-275

127. Pena CA, Mathews AA, Siddiqi NH, Strickland GT. Antibiotic therapy for lyme disease in a population-based cohort. Clinical Infectious Diseases. 1999; 29(3):694-695

128. Perronne C. Critical review of studies trying to evaluate the treatment of chronic Lyme disease. Presse Medicale. 2015; 44(7-8):828-831

129. Pfister HW, Einhaupl KM, Franz P, Garner C. Corticosteroids for radicular pain in Bannwarth's syndrome: a double-blind, randomized, placebo-controlled trial. Annals of the New York Academy of Sciences. 1988; 539(1):485-487

130. Pfister HW, Preac-Mursic V, Wilske B, Einhäupl KM. Cefotaxime vs penicillin G for acute neurologic manifestations in Lyme borreliosis. A prospective randomized study. Archives of Neurology. 1989; 46(11):1190-1194

131. Pfister HW, Preac-Mursic V, Wilske B, Schielke E, Sorgel F, Einhaupl KM. Randomized comparison of ceftriaxone and cefotaxime in Lyme neuroborreliosis. Journal of Infectious Diseases. 1991; 163(2):311-318

132. Pirila V. The penicillin treatment of acrodermatitis atrophicans chronica. Acta Dermato-Venereologica. 1951; 31(5):576-591

133. Plorer A, Sepp N, Schmutzhard E, Krabichler S, Trobos S, Schauer G et al. Effects of adequate versus inadequate treatment of cutaneous manifestations of Lyme borreliosis on the incidence of late complications and late serologic status. Journal of Investigative Dermatology. 1993; 100(2):103-109

134. Plotkin SA, Peter G. Treatment of Lyme borreliosis. Pediatrics. 1991; 88(1):176-179

135. Puchalska B, Niemcunowicz-Janica A, Kondej Muszynska K, Trippner M. Lyme borreliosis--tick borne spirochaetosis among children. Roczniki Akademii Medycznej w Bialymstoku (1995). 1996; 41(1):59-61

136. Puri BK, Hakkarainen-Smith JS, Derham A, Monro JA. Co-administration of alpha-lipoic acid and glutathione is associated with no significant changes in serum bilirubin, alkaline phosphatase or gamma-glutamyltranspeptidase levels during the treatment of neuroborreliosis with intravenous ceftriaxone. Journal of Complementary and Integrative Medicine. 2015; 12(3):227-230

137. Puri BK, Hakkarainen-Smith JS, Monro JA. The potential use of cholestyramine to reduce the risk of developing Clostridium difficile-associated diarrhoea in patients receiving long-term intravenous ceftriaxone. Medical Hypotheses. 2015; 84(1):78-80

138. Rebman AW, Crowder LA, Kirkpatrick A, Aucott JN. Characteristics of seroconversion and implications for diagnosis of post-treatment Lyme disease syndrome: acute and convalescent serology among a prospective cohort of early Lyme disease patients. Clinical Rheumatology. 2015; 34(3):585-589

139. Renaud I, Cachin C, Gerster JC. Good outcomes of Lyme arthritis in 24 patients in an endemic area of Switzerland. Joint, Bone, Spine: Revue du Rhumatisme. 2004; 71(1):39-43

140. Rohacova H, Hancil J, Hulinska D, Mailer H, Havlik J. Ceftriaxone in the treatment of Lyme neuroborreliosis. Infection. 1996; 24(1):88-90

141. Rose CD, Fawcett PT, Eppes SC, Klein JD, Gibney K, Doughty RA. Pediatric Lyme arthritis: clinical spectrum and outcome. Journal of Pediatric Orthopaedics. 1994; 14(2):238-241

142. Rose CD, Fawcett PT, Gibney KM, Doughty RA. Residual serologic reactivity in children with resolved Lyme arthritis. Journal of Rheumatology. 1996; 23(2):367-369

143. Rubin DA, Sorbera C, Nikitin P, McAllister A, Wormser GP, Nadelman RB. Prospective evaluation of heart block complicating early Lyme disease. PACE - Pacing and Clinical Electrophysiology. 1992; 15(3):252-255

144. Salazar CA, Rothemich M, Drouin EE, Glickstein L, Steere AC. Human Lyme arthritis and the immunoglobulin G antibody response to the 37-kilodalton arthritis-related protein of Borrelia burgdorferi. Infection and Immunity. 2005; 73(5):2951-2957

145. Salazar JC, Gerber MA, Goff CW. Long-term outcome of Lyme disease in children given early treatment. Journal of Pediatrics. 1993; 122(4):591-593

146. Sanchez E, Vannier E, Wormser GP, Hu LT. Diagnosis, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: a review. JAMA. 2016; 315(16):1767-1777

147. Sandstrom M, Bredberg G, Asbrink E, Hovmark A, Holmkvist C. Brainstem response audiometry in chronic Lyme borreliosis. Scandinavian Audiology. 1989; 18(4):205-210

148. Schmidt BL, Aberer E, Stockenhuber C, Klade H, Breier F, Luger A. Detection of Borrelia burgdorferi DNA by polymerase chain reaction in the urine and breast milk of patients with Lyme borreliosis. Diagnostic Microbiology and Infectious Disease. 1995; 21(3):121-128

149. Selby G, Bridges SJ, Hanington L. Should Lyme disease affecting the nervous system be treated with oral or intravenous antibiotics? Archives of Disease in Childhood Education & Practice. 2008; 93(4):132-134

150. Shadick NA, Phillips CB, Logigian EL, Steere AC, Kaplan RF, Berardi VP et al. The long-term clinical outcomes of Lyme disease. A population-based retrospective cohort study. Annals of Internal Medicine. 1994; 121(8):560-567

151. Shadick NA, Phillips CB, Sangha O, Logigian EL, Kaplan RF, Wright EA et al. Musculoskeletal and neurologic outcomes in patients with previously treated lyme disease. Annals of Internal Medicine. 1999; 131(12):919-926

152. Shemenski J. Cimetidine as a novel adjunctive treatment for early stage Lyme disease. Medical Hypotheses. 2016; Epublication

153. Shoemaker RC, Hudnell HK, House DE, Kempen A, Pakes GE. Atovaquone plus cholestyramine in patients coinfected with Babesia microti and Borrelia burgdorferi refractory to other treatment. Advances in Therapy. 2006; 23(1):1-11

154. Sjowall J, Fryland L, Nordberg M, Sjogren F, Garpmo U, Jansson C et al. Decreased Th1-type inflammatory cytokine expression in the skin is associated with persisting symptoms after treatment of erythema migrans. PloS One. 2011; 6(3):e18220

155. Sjöwall J, Ledel A, Ernerudh J, Ekerfelt C, Forsberg P. Doxycycline-mediated effects on persistent symptoms and systemic cytokine responses post-neuroborreliosis: a randomized, prospective, cross-over study. BMC Infectious Diseases. 2012; 12:186

156. Skogman BH, Croner S, Nordwall M, Eknefelt M, Ernerudh J, Forsberg P. Lyme neuroborreliosis in children: a prospective study of clinical features, prognosis, and outcome. Pediatric Infectious Disease Journal. 2008; 27(12):1089-1094

157. Skogman BH, Croner S, Odkvist L. Acute facial palsy in children - a 2-year follow-up study with focus on Lyme neuroborreliosis. International Journal of Pediatric Otorhinolaryngology. 2003; 67(6):597-602

158. Skoldenberg B, Stiernstedt G, Karlsson M, Wretlind B, Svenungsson B. Treatment of Lyme borreliosis with emphasis on neurological disease. Annals of the New York Academy of Sciences. 1988; 539:317-323

159. Smith RP, Schoen RT, Rahn DW, Sikand VK, Nowakowski J, Parenti DL et al. Clinical characteristics and treatment outcome of early Lyme disease in patients with microbiologically confirmed erythema migrans. Annals of Internal Medicine. 2002; 136(6):421-428

160. Solomon SP, Hilton E, Weinschel BS, Pollack S, Grolnick E. Psychological factors in the prediction of Lyme disease course. Arthritis Care and Research. 1998; 11(5):419-426

161. Spathling S, J dK, P H. Therapy of Lyme arthritis with ceftriaxon - histological proof of spriochates in the synovialis after ineffective therapy. Zeitschrift für Rheumatologie. 1992; 51(Suppl 2):40-41

162. Stanek G, Breier F, Menzinger G, Schaar B, Hafner M, Partsch H. Erythema migrans and serodiagnosis by enzyme immunoassay and immunoblot with three borrelia species. Wiener Klinische Wochenschrift. 1999; 111(22-23):951-956

163. Steere AC, Green J, Hutchinson GJ, Rahn DW, Pachner AR, Schoen RT et al. Treatment of Lyme disease. Zentralblatt fur Bakteriologie, Mikrobiologie, und Hygiene - Series A, Medical Microbiology, Infectious Diseases, Virology, Parasitology. 1987; 263(3):352-356

164. Steere AC, Green J, Schoen RT, Taylor E, Hutchinson GJ, Rahn DW et al. Successful parenteral penicillin therapy of established Lyme arthritis. New England Journal of Medicine. 1985; 312(14):869-874

165. Steere AC, Hutchinson GJ, Rahn DW, Sigal LH, Craft JE, DeSanna ET et al. Treatment of the early manifestations of Lyme disease. Annals of Internal Medicine. 1983; 99(1):22-26

166. Steere AC, Levin RE, Molloy PJ, Kalish RA, Abraham IJH, Liu NY et al. Treatment of Lyme arthritis. Arthritis and Rheumatism. 1994; 37(6):878-888

167. Steere AC, Malawista SE, Newman JH, Spieler PN, Bartenhagen NH. Antibiotic therapy in Lyme disease. Annals of Internal Medicine. 1980; 93(1 I):1-8

168. Steere AC, Pachner AR, Malawista SE. Neurologic abnormalities of Lyme disease: successful treatment with high-dose intravenous penicillin. Annals of Internal Medicine. 1983; 99(6):767-772

169. Steurer J. Month-long antibiotic therapy has no effect in persistent symptoms of Lyme disease. Praxis. 2016; 105(12):723-724

170. Stricker RB, Delong AK, Green CL, Savely VR, Chamallas SN, Johnson L. Benefit of intravenous antibiotic therapy in patients referred for treatment of neurologic Lyme disease. International Journal of General Medicine. 2011; 4:639-646

171. Stricker RB, Green CL, Savely VR, Chamallas SN, Johnson L. Safety of intravenous antibiotic therapy in patients referred for treatment of neurologic Lyme disease. Minerva Medica. 2010; 101(1):1-7

172. Strle F, Maraspin V, Lotric-Furlan S, Ruzic-Sabljic E, Cimperman J. Azithromycin and doxycycline for treatment of borrelia culture-positive erythema migrans. Infection. 1996; 24(1):64-68

173. Strle F, Maraspin V, Pleterski-Rigler D, Lotric-Furlan S, Ruzic-Sabljic E, Jurca T et al. Treatment of borrelial lymphocytoma. Infection. 1996; 24(1):80-84

174. Strle F, Pleterski-Rigler D, Stanek G, Pejovnik-Pustinek A, Ruzic E, Cimperman J. Solitary borrelial lymphocytoma: report of 36 cases. Infection. 1992; 20(4):201-206

175. Strle F, Preac-Mursic V, Cimperman J, Ruzic E, Maraspin V, Jereb M. Azithromycin versus doxycycline for treatment of erythema migrans: clinical and microbiological findings. Infection. 1993; 21(2):83-88

176. Stupica D, Lusa L, Cerar T, Ruzic-Sabljic E, Strle F. Comparison of post-lyme borreliosis symptoms in erythema migrans patients with positive and negative borrelia burgdorferi sensu lato skin culture. Vector-Borne and Zoonotic Diseases. 2011; 11(7):883-889

177. Stupica D, Lusa L, Maraspin V, Bogovic P, Vidmar D, O'Rourke M et al. Correlation of culture positivity, PCR positivity, and burden of Borrelia burgdorferi sensu lato in skin samples of erythema migrans patients with clinical findings. PloS One. 2015; 10(9):e0136600

178. Suarez-Magdalena O, Fernandez-Jorge B, Campo-Cerecedo F, Varela-Veiga A. Atrophoderma of Pasini and Pierini associated with Borrelia burgdorferi treated with doxycycline. Piel. 2017; 32(2):120-122

179. Thompson AD, Cohn KA, Shah SS, Lyons T, Welsh EJ, Hines EM et al. Treatment complications in children with Lyme meningitis. Pediatric Infectious Disease Journal. 2012; 31(10):1032-1035

180. Thorstrand C, Belfrage E, Bennet R, Malmborg P, Eriksson M. Successful treatment of neuroborreliosis with ten day regimens. Pediatric Infectious Disease Journal. 2002; 21(12):1142-1145

181. Thyresson N. The penicillin treatment of acrodermatitis atrophicans chronica (Herxheimer). Acta Dermato-Venereologica. 1949; 29(6):572-621

182. Torbahn G, Hofmann H, Allert R, Freitag MH, Dersch R, Fingerle V et al. Efficacy and safety of pharmacological agents in the treatment of erythema migrans in early Lyme borreliosis-systematic review protocol. Systems Review. 2016; 5:73

183. Tory HO, Zurakowski D, Sundel RP. Outcomes of children treated for Lyme arthritis: results of a large pediatric cohort. Journal of Rheumatology. 2010; 37(5):1049-1055

184. Tseng YJ, Demaria A, Goldmann DA, Mandl KD. Claims-based diagnostic patterns of patients evaluated for lyme disease and given extended antibiotic therapy. Vector-Borne and Zoonotic Diseases. 2017; 17(2):116-122

185. Valesova H, Mailer J, Havlik J, Hulinska D, Hercogova J. Long-term results in patients with Lyme arthritis following treatment with ceftriaxone. Infection. 1996; 24(1):98-102

186. Vazquez-Lopez ME, Diez-Morrondo C, Sanchez-Andrade A, Pego-Reigosa R, Diaz P, Castro-Gago M. Articular manifestations in patients with Lyme disease. Reumatologia Clinica. 2016; 12(6):327-330

187. Vazquez M, Sparrow SS, Shapiro ED. Long-term neuropsychologic and health outcomes of children with facial nerve palsy attributable to Lyme disease. Pediatrics. 2003; 112(2):e93-97

188. Wahlberg P, Granlund H, Nyman D, Panelius J, Seppala I. Treatment of late Lyme borreliosis. Journal of Infection. 1994; 29(3):255-261

189. Weber K, Neubert U, Thurmayr R. Antibiotic therapy in early erythema migrans disease and related disorders. Zentralblatt fur Bakteriologie, Mikrobiologie, und Hygiene - Series A, Medical Microbiology, Infectious Diseases, Virology, Parasitology. 1987; 263(3):377-388

190. Weber K, Preac-Mursic V, Neubert U, Thurmayr R, Herzer P, Wilske B et al. Antibiotic therapy of early European Lyme borreliosis and acrodermatitis chronica atrophicans. Annals of the New York Academy of Sciences. 1988; 539:324-345

191. Weissenbacher S, Ring J, Hofmann H. Gabapentin for the symptomatic treatment of chronic neuropathic pain in patients with late-stage lyme borreliosis: a pilot study. Dermatology. 2005; 211(2):123-127

192. White B, Seaton RA, Evans TJ. Management of suspected lyme borreliosis: experience from an outpatient parenteral antibiotic therapy service. QJM. 2013; 106(2):133-138

193. Zochling N, Mullegger RR, Schluepen EM, Soyer HP, Hodl S, Wienecke R et al. Minocycline in early Lyme Borreliosis. Acta Dermatovenerologica Alpina, Panonica et Adriatica. 1996; 5(3-4):163-168

Appendices

Appendix A: Review protocols

Table 10: Review protocol for the management of Lyme arthritis

Question number: 4.4

Relevant section of Scope: management

Field	Content
Review question	What is the most clinically and cost-effective treatment for people with arthritis 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 arthritis related to Lyme disease. This review is only concerned with the treatment of Lyme disease as the underlying cause of arthritic symptoms and not with the treatment or management of arthritic symptoms directly.
Eligibility criteria – population / disease / condition / issue / domain	People with symptoms consistent with arthritis related to Lyme disease
Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	• Antimicrobials, including but not limited to: ○ Penicillins - Amoxicillin (oral, IV) - Ampicillin (oral, IV) - Benzylpenicillin sodium / Penicillin G (IV) -Including Augmentin (Amoxicillin + 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)

Field	Content
	○ Nalidixic acid (oral) ○ Norfloxacin (oral) ○ Ofloxacin (oral, IV) • Rifampicin (oral, IV) • Steroids (corticosteroids; systemic, local injections) ○ Dexamethasone (local injection, IV) ○ Hydrocortisone (local injection, IV) ○ Methylprednisolone (local injection, IV) ○ Prednisolone (local injection, IV) • Non-steroidal anti-inflammatory drugs (NSAIDs) • Hydroxychloroquine sulfate (Plaquenil, Quinoric; oral)
Eligibility criteria – comparator(s) / control or reference (gold) standard	• Any type of intervention compared to each other ○ If data are available consider: - Type of agent (within class or between class) - Route of administration - Duration of treatment: 1 month versus longer • Monotherapy versus polytherapy (any combination) • Antimicrobial treatment, steroids or NSAIDs compared to no treatment/placebo
Outcomes and prioritisation	**Critical:** 1. Quality of life (any validated measure) 2. Cure (resolution of symptoms related to Lyme arthritis) 3. Reduction of clinical symptoms related to Lyme arthritis 4. Relapse of symptoms related to Lyme arthritis **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 specific symptoms 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, steroid or NSAID 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).

Field	Content
	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 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 critically appraise individual studies. 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.

Field	Content
	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.
PROSPERO registration number	Not registered

1 **Table 11: 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).[116] **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 selectively exclude the remaining studies. All studies excluded on the basis of 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 from 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.

1

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 12: 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

1 **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

2 **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 13: 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

1 **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

1 **NHS EED and HTA (CRD) search terms**

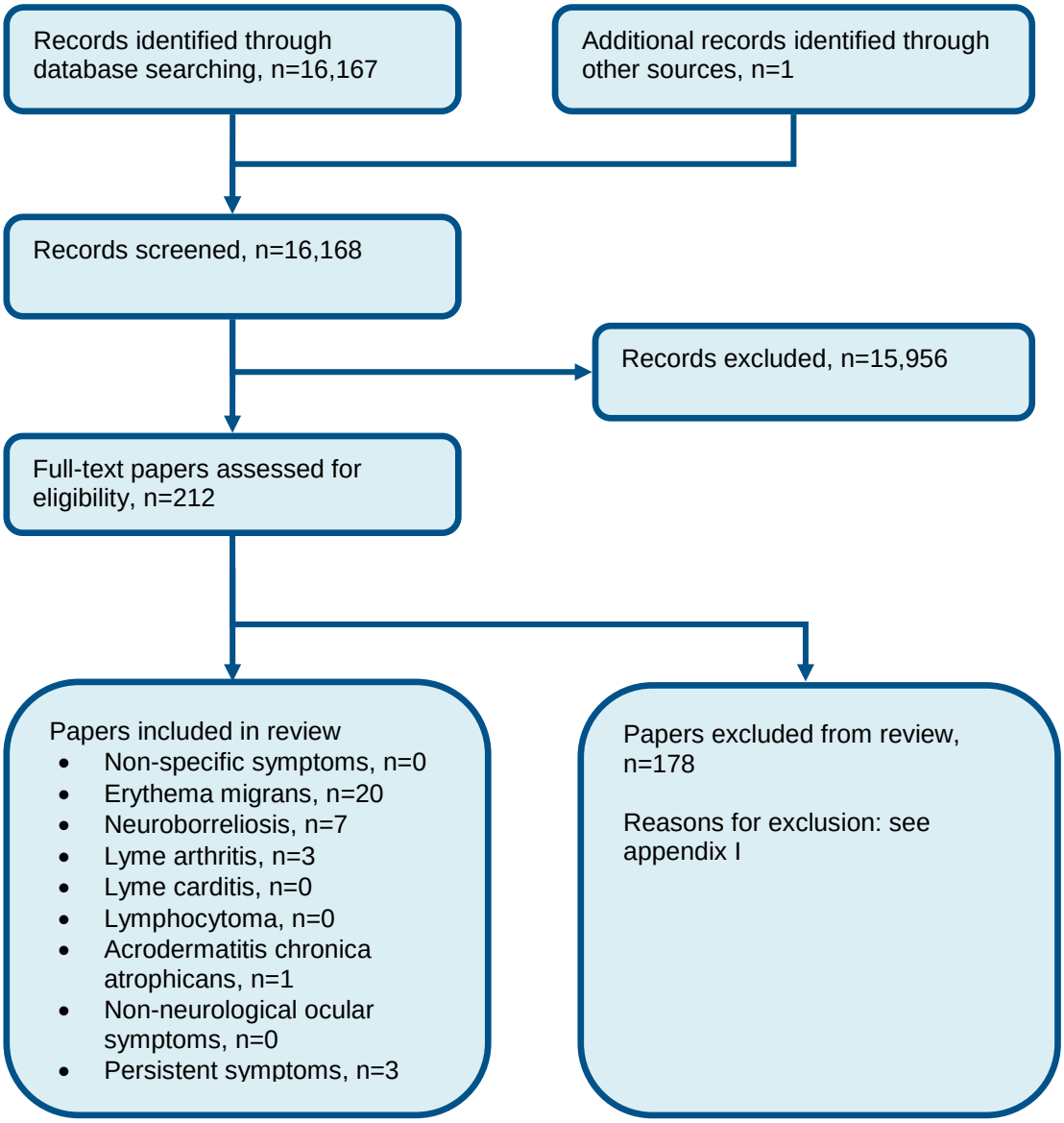
#1.	MeSH DESCRIPTOR Borrelia Infections EXPLODE ALL TREES IN NHSEED,HTA
#2.	MeSH DESCRIPTOR Erythema Chronicum Migrans EXPLODE ALL TREES IN NHSEED,HTA
#3.	((erythema adj3 migrans)) IN NHSEED, HTA
#4.	(lyme*) IN NHSEED, HTA
#5.	((tick* adj2 (bite* or bitten or biting or borne))) IN NHSEED, HTA
#6.	(acrodermatitis 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

1
2

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	Caperton 1990[29]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in USA; Setting: Not reported
Line of therapy	first line
Duration of study	
Method of assessment of guideline condition	Adequate method of assessment or diagnosis: Clinical diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults, chronic inflammatory arthritis, 2 reactive antibody titres to *B. burgdorferi* in a titre at 1:64 or greater within 6 months of enrolment including a positive test within 2 weeks of starting therapy
Exclusion criteria	Not reported
Recruitment or selection of patients	Not reported
Age, gender and family origin	Age - Mean (SD): Ceftriaxone group: 46.7 years (13.9); placebo group: 42.7 years (13.7). Gender (M:F): 22:37. Family origin: Not reported
Further population details	1. Immunosuppression: Not applicable 2. Pregnancy: Not applicable 3. Previous treatment failure: Not applicable
Indirectness of population	Very serious indirectness: Rheumatoid arthritis, psoriatic arthritis, vasculitis (with arthritis) and atypical arthritis with a *B. burgdorferi* titre; most people had been treated with antibiotics before
Interventions	(n=40) Intervention 1: Antibiotics - Ceftriaxone. 2 g intravenously in a 30-minute infusion daily. Vitamin preparation added to prevent people from detecting their treatment group by appearance or taste of solution. Duration 14 days. Concurrent medication or care: Not reported (n=20) Intervention 2: Placebo. Placebo. Duration 14 days. Concurrent medication or care: Not reported
Funding	Study funded by industry (Grant from Hoffmann-LaRoche Inc.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CEFTRIAXONE versus PLACEBO	

Study	Caperton 1990[29]
Protocol outcome 1: Reduction of symptoms - Actual outcome: Improvement at 1 month; Group 1: 19/39, Group 2: 2/20 Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Very high, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 1; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life; Cure (resolution of symptoms); Symptom relapse; Adverse events

Study	Steere 1985[164]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in USA; Setting: Lyme disease clinic, Yale University, USA
Line of therapy	Unclear
Duration of study	Intervention + follow up: 3 weeks + 3-12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	living in an area endemic for Lyme disease; history of EM, meningitis, or Bell's palsy during the summer followed within 1 year by arthritis; or to have short recurrent attacks of oligoarticular arthritis not due to other known causes; onset of infection >1 year earlier; at least 1 actively inflamed joint
Exclusion criteria	history of penicillin allergy or atopy; children younger than 8 years
Recruitment/selection of patients	consecutive people meeting the inclusion criteria during the recruitment period
Age, gender and family origin	Age - Mean (SD): penicillin group 30 (17); placebo group 31 (15) years. Gender (M:F): 28/12. 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: NA
Interventions	(n=20) Intervention 1: Antibiotics - Benzylpenicillin sodium or Penicillin G. 1.2 million U injected in each buttock weekly intramuscularly. Duration 3 weeks. Concurrent medication or care: other anti-inflammatory medications continued according to clinical indications

Study	Steere 1985[164]
	(n=20) Intervention 2: Placebo. 2 ml saline injected in each buttock weekly. Duration 3 weeks. Concurrent medication/care: other anti-inflammatory medications continued according to clinical indications
Funding	Academic or government funding (grants from the National Institutes of Health and the Arthritis Foundation and its Connecticut Chapter)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BENZYLPENICILLIN SODIUM / PENICILLIN G versus PLACEBO Protocol outcome 1: Cure (resolution of symptoms) - Actual outcome for Adults: complete resolution of arthritis at mean 33 months ; Group 1: 7/20, Group 2: 0/20 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: more people in the placebo group used intraarticular steroids; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life; Reduction of symptoms; Symptom relapse; Adverse events

Study	Steere 1994[166]
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in USA; Setting: 3 study sites (private practices or Lyme disease clinics)
Line of therapy	first line
Duration of study	Intervention + follow up: 30 days + up to 12 months
Method of assessment of guideline condition	Partially adequate method of assessment or diagnosis: arthritis, inflamed joint and positive response to B burgdorferi by ELISA
Stratum	Adults
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	13 years or older; initial attack or intermittent episodes of arthritis in 1 or a few joints; at least 1 actively inflamed joint at the time of study entry; positive antibody response to *B. burgdorferi* determined by ELISA
Exclusion criteria	12 years or younger; pregnant or nursing; active neuroborreliosis; allergic to study medications; already failed to respond to a 30-day course of oral doxycycline or amoxicillin for Lyme arthritis
Recruitment/selection of patients	unclear
Age, gender and family origin	Age - Median (range): doxycycline group 40 (13-72); amoxicillin + probenecid group 45.5 (14-67) years.

Study	Steere 1994[166]
	Gender (M:F): 28/12. Family origin: not reported
Further population details	1. Immunosuppression: Not stated or unclear 2. Pregnancy: No pregnancy 3. Previous treatment failure: No previous treatment
Indirectness of population	No indirectness: NA
Interventions	(n=23) Intervention 1: Antibiotics - Amoxicillin. 500 mg + probenecid 500 mg 4 times per day. Duration 30 days. Concurrent medication/care: NSAIDs taken by people with marked joint inflammation, steroid infections were not allowed during antibiotic therapy (n=25) Intervention 2: Antibiotics - Doxycycline. 100 mg twice per day. Duration 30 days. Concurrent medication/care: NSAIDs taken by people with marked joint inflammation, steroid infections not allowed during antibiotic treatment
Funding	Academic or government funding (supported by NIH grants and by the Eshe fund)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AMOXICILLIN versus DOXYCYLINE

Protocol outcome 1: Cure (resolution of symptoms)

- Actual outcome: resolution of arthritis at 3 months; Group 1: 16/18, Group 2: 18/20

Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 2, Reason: 23 originally randomised, 3 excluded from analysis, 2 switched to doxycycline due to drug eruption; Group 2 Number missing: 0, Reason: 25 originally randomised, 5 excluded from analysis

Protocol outcome 2: Symptom relapse

- Actual outcome: subsequent complications at mean 3.3 years; Group 1: 5/16, Group 2: 2/18

Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 2, Reason: 23 originally randomised, 3 excluded from analysis, 2 switched to doxycycline due to drug eruption; Group 2 Number missing: 0, Reason: 25 originally randomised, 5 excluded from analysis

Protocol outcome 3: Adverse events

- Actual outcome: side effects at during antibiotic treatment ; Group 1: 7/20, Group 2: 0/20

Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 3, Reason: 23 originally randomised, 3 excluded from analysis; Group 2 Number missing: 5, Reason: 25 originally randomised, 5 excluded from analysis

Study	Steere 1994[166]
Protocol outcomes not reported by the study	Quality of life; Reduction of symptoms

Appendix E: Forest plots

E.1 Doxycycline (PO) versus amoxicillin (PO) plus probenecid

E.1.1 Lyme arthritis

Figure 2: Cure (at 3 months)

Study or Subgroup	Doxycycline Events	Total	Amoxicillin + Probenecid Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Steere 1994	18	20	16	18	100.0%	1.01 [0.81, 1.26]
Total (95% CI)		**20**		**18**	**100.0%**	**1.01 [0.81, 1.26]**
Total events	18		16			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.11 (P = 0.91)

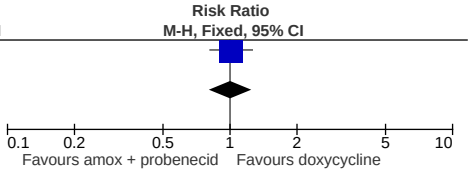


Figure 3: Symptom relapse (subsequent complications at a mean of 3.3 years)

Study or Subgroup	Doxycycline Events	Total	Amoxicillin + Probenecid Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Steere 1994	2	18	5	16	100.0%	0.36 [0.08, 1.59]
Total (95% CI)		**18**		**16**	**100.0%**	**0.36 [0.08, 1.59]**
Total events	2		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.36 (P = 0.18)

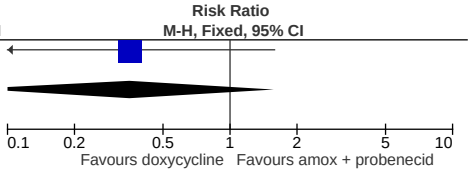
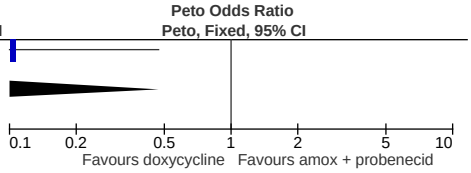


Figure 4: Adverse events (side effects during treatment)

Study or Subgroup	Doxycycline Events	Total	Amoxicillin + Probenecid Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Steere 1994	0	20	7	20	100.0%	0.09 [0.02, 0.47]
Total (95% CI)		**20**		**20**	**100.0%**	**0.09 [0.02, 0.47]**
Total events	0		7			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.88 (P = 0.004)



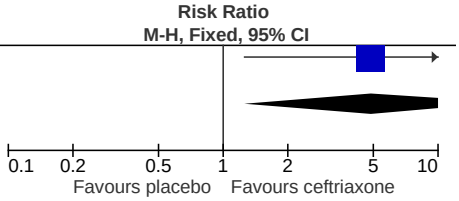
E.2 Ceftriaxone (IV) versus placebo

E.2.1 Lyme arthritis

Figure 5: Reduction in symptoms (at 1 month)

Study or Subgroup	Ceftriaxone Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Caperton 1990	19	39	2	20	100.0%	4.87 [1.26, 18.86]
Total (95% CI)		**39**		**20**	**100.0%**	**4.87 [1.26, 18.86]**
Total events	19		2			

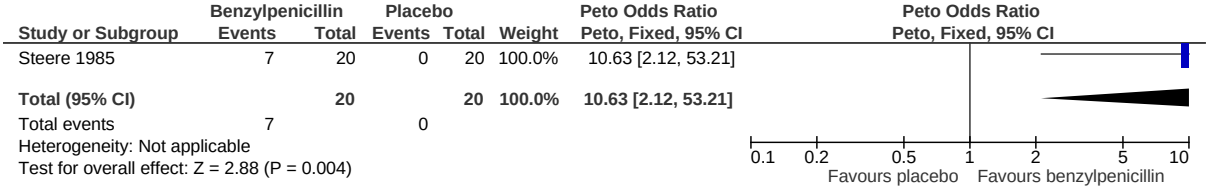
Heterogeneity: Not applicable
Test for overall effect: Z = 2.29 (P = 0.02)



E.3 Benzylpenicillin (IM) versus placebo

E.3.1 Lyme arthritis

Figure 6: Cure (complete resolution of symptoms at a mean of 33 months)



Appendix F:GRADE tables

Table 14: Clinical evidence profile: doxycycline (PO) versus amoxicillin (PO) plus probenecid

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Doxycycline	Amoxicillin plus probenecid	Relative (95% CI)	Absolute		
Cure (resolution of arthritis at 3 months)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	18/20 (90%)	16/18 (88.9%)	RR 1.01 (0.81 to 1.26)	9 more per 1,000 (from 169 fewer to 231 more)	⊕OOO VERY LOW	CRITICAL
Symptom relapse (subsequent complications at mean 3.3 years)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	2/18 (11.1%)	5/16 (31.3%)	RR 0.36 (0.08 to 1.59)	200 fewer per 1,000 (from 287 fewer to 184 more)	⊕OOO VERY LOW	CRITICAL
Adverse events (side effects during treatment)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	0/20 (0%)	7/20 (35%)	OR 0.09 (0.02 to 0.47)[4]	304 fewer per 1,000 (from 148 fewer to 339 fewer)	⊕OOO VERY LOW	IMPORTANT

[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 because of a serious intervention indirectness
[3] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
[4] The Peto odds ratio method was used due to a zero event rate in the intervention arm

Table 15: Clinical evidence profile: ceftriaxone (IV) versus placebo

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ceftriaxone	Placebo	Relative (95% CI)	Absolute		
Reduction of symptoms (improvement at 1 month)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	19/39 (48.7%)	2/20 (10%)	RR 4.87 (1.26 to 18.86)	387 more per 1,000 (from 26 more to 1,000 more)	⊕⊕OO 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

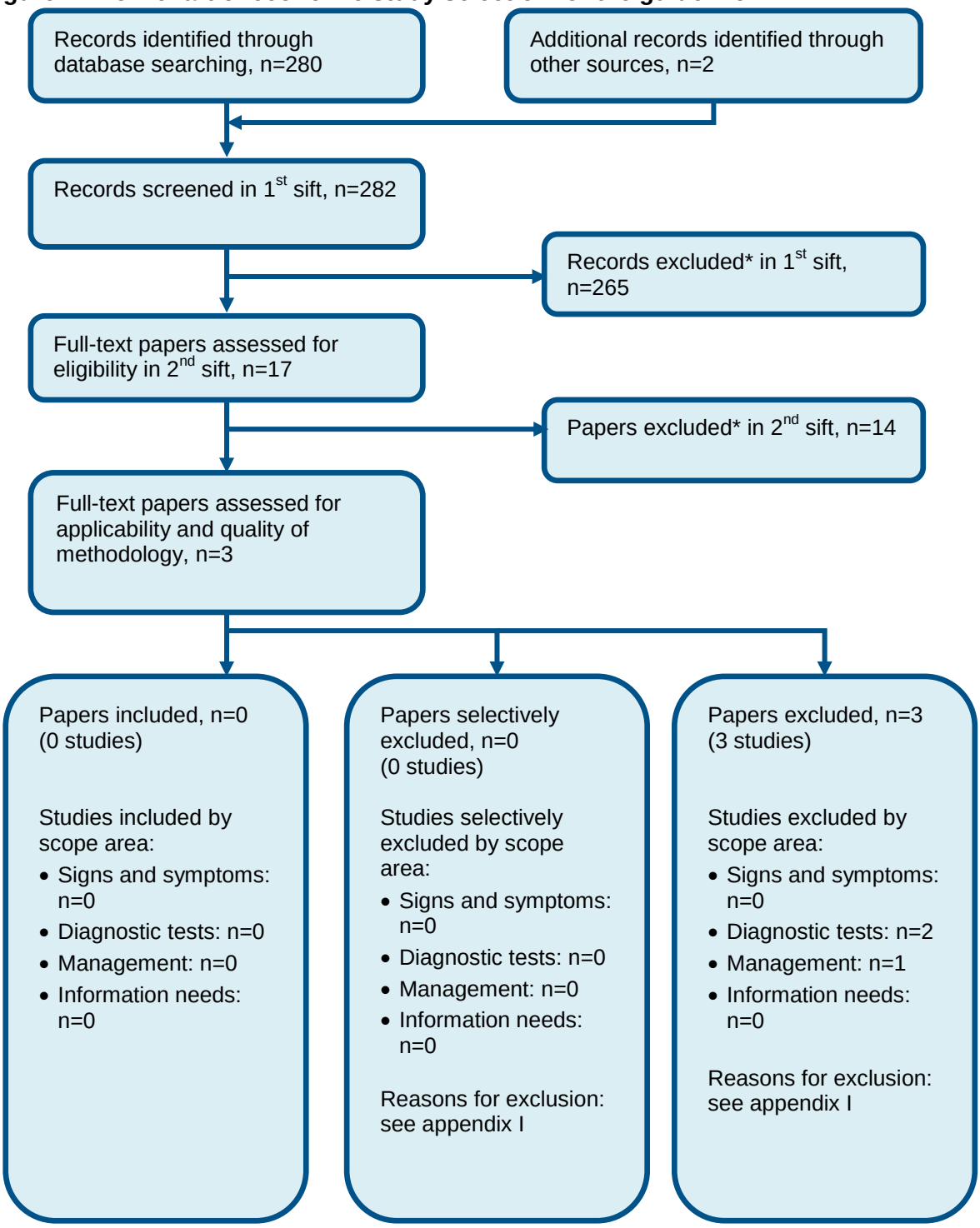
Table 16: Clinical evidence profile: benzylpenicillin (IM) versus placebo

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Benzylpenicillin	Placebo	Relative (95% CI)	Absolute		
Cure (complete resolution at mean 33 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	7/20 (35%)	0/20 (0%)	OR 10.63 (2.12 to 53.21)[2]	350 more per 1,000 (from 141 more to 559 more)	⊕⊕OO 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] The Peto odds ratio method was used due to a zero event rate in one of the treatment arms

Appendix G: Health economic evidence selection

Figure 7: 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 17: Studies excluded from the clinical management reviews

Reference	Reason for exclusion
Aberer 2006[1]	Excluded due to an incorrect intervention
Abrutyn 1989[2]	Excluded due to an incorrect study design
Agger 1992[3]	Excluded due to an incorrect study design
Agus 1995[4]	Excluded due to an incorrect study design
Agwuh 2006[5]	Excluded due to an incorrect study design
Ahmed 2005[6]	Excluded due to an incorrect study design
Ahmed 2013[7]	Excluded due to an incorrect study design
Alarcon 1994[8]	Excluded due to an incorrect study design
Andiman 1986[9]	Excluded due to an incorrect study design
Anonymous 1991[10]	Excluded due to an incorrect study design
Arvikar 2015[11]	Excluded due to an incorrect study design
Auwaerter 2004[12]	Excluded due to an incorrect study design
Bennet 2003[13]	Excluded due to an incorrect study design
Berende 2014[14]	Excluded due to an incorrect study design
Berger 1988[16]	Excluded due to an incorrect study design
Berger 1986[15]	Excluded due to an incorrect study design
Bernardino 2009[17]	Excluded due to an incorrect study design
Bhate 2011[18]	Excluded due to an incorrect study design
Bjark 2016[19]	Not available
Borg 2005[22]	Excluded due to an incorrect study design
Bratton 2008[23]	Excluded due to an incorrect study design
Bremell 2014[24]	Excluded due to an incorrect study design
British Infection Association 2011[25]	Excluded due to an incorrect study design
Butler 1978[26]	Excluded due to an incorrect population
Cadavid 2016[27]	Excluded due to an incorrect study design
Canadian Paediatric Society 1992[28]	Excluded due to an incorrect study design
Chen 1999[31]	Excluded due to an incorrect outcome
Choo-Kang 2010[32]	Excluded due to an incorrect study design
Christian 1992[33]	Excluded due to an incorrect study design
Cimmino 1992[35]	Excluded due to an incorrect study design
Cimmino 1997[34]	Excluded due to an incorrect study design
Cimperman 1999[36]	Excluded due to an incorrect study design
Coblyn 1981[37]	Excluded due to an incorrect study design
Committee on Infectious Diseases 1991[39]	Excluded due to an incorrect study design
Cuisset 2008[40]	Excluded due to an incorrect study design
Dattwyler 1996[42]	Excluded due to an incorrect comparison
Dattwyler 1987[43]	Excluded due to an incorrect study design
Dattwyler 1988[44]	Excluded due to an incorrect population
Dattwyler 2005[45]	Excluded due to an incorrect population
Dersch 2015[47]	Excluded due to an incorrect study design

Reference	Reason for exclusion
Dersch 2016[50]	Excluded due to an incorrect study design
Dersch 2014[48]	Excluded due to an incorrect study design
Dersch 2017[49]	Not available
Dhoot 2011[51]	Excluded due to an incorrect study design
Dinser 2005[52]	Excluded due to an incorrect study design
Dotevall 1988[53]	Excluded due to an incorrect study design
Eliassen 2017[54]	Excluded due to an incorrect study design
Eliassen 2017[55]	Excluded due to an incorrect intervention
Eppes 2003[56]	Excluded due to an incorrect study design
Esposito 2013[57]	Excluded due to an incorrect study design
Fallon 1999[59]	Excluded due to an incorrect intervention
Fallon 2008[58]	Excluded due to an incorrect outcome
Galev 2005[60]	Excluded due to an incorrect study design
Garkowski 2017[61]	Systematic review
Gasser 1996[63]	Excluded due to an incorrect not available
Gasser 1995[64]	Excluded due to an incorrect study design
Gasser 1995[62]	Excluded due to an incorrect study design
Gerber 1996[65]	Excluded due to an incorrect intervention
Gillies 2015[66]	Excluded due to an incorrect study design
Goodwin 1990[67]	Excluded due to an incorrect study design
Hansen 1992[68]	Excluded due to an incorrect intervention
Hassler 1990[69]	Excluded due to an incorrect population
Horton 2017[70]	Conference abstract
Hu 2001[71]	Excluded due to an incorrect study design
Inboriboon 2010[72]	Excluded due to an incorrect study design
Kaplan 2003[73]	Excluded due to an incorrect population
Karkkonen 2001[74]	Excluded due to an incorrect study design
Karlsson 1996[75]	Excluded due to an incorrect outcome
Kersten 1995[76]	Excluded due to an incorrect study design
Kilic Muftuoglu 2016[77]	Excluded due to an incorrect study design
Klempner 2013[79]	Excluded due to an incorrect study design
Korenberg 1996[80]	Excluded due to an incorrect intervention
Kowalski 2010[82]	Excluded due to an incorrect outcome
Kowalski 2011[81]	Excluded due to an incorrect study design
Krbkova 1996[83]	Excluded due to an incorrect comparison
Kuhn 2012[84]	Excluded due to an incorrect study design
Laasila 2003[85]	Excluded due to an incorrect population
Lantos 2013[86]	Excluded due to an incorrect study design
Lauhio 1994[87]	Excluded due to an incorrect population
Lauhio 1991[88]	Excluded due to an incorrect population
Lempner 2002[78]	Excluded due to an incorrect study design
Liegner 1992[89]	Excluded due to an incorrect study design
Lipsker 2002[90]	Excluded due to an incorrect study design
Ljostad 2008[91]	Study abstract
Loewen 1999[92]	Excluded due to an incorrect study design

Reference	Reason for exclusion
Loewen 2000[93]	Excluded due to an incorrect study design
Luft 1988[95]	Excluded due to an incorrect outcome
Luft 1989[94]	Excluded due to an incorrect population
Maraspin1995[101]	Excluded due to an incorrect study design
Maraspin 1996[96]	Excluded due to an incorrect study design
Maraspin 1999[97]	Excluded due to an incorrect study design
Maraspin 2002[98]	Excluded due to an incorrect study design
Maraspin 1999[99]	Excluded due to an incorrect study design
Maraspin 2002[100]	Excluded due to an incorrect population
Marks 2016[102]	Excluded due to an incorrect study design
McGill 1965[103]	Excluded due to an incorrect population
Meyerhoff 2002[104]	Excluded due to an incorrect study design
Meyerhoff 2016[105]	Excluded due to an incorrect study design
Millner 1996[106]	Excluded due to an incorrect outcome
Millner 1996[107]	Excluded due to an incorrect outcome
Morales 2000[108]	Excluded due to an incorrect study design
Muellegger 1995[110]	Excluded due to an incorrect study design
Muellegger 1996[109]	Excluded due to an incorrect comparison
Mullegger 1991[111]	Excluded due to an incorrect outcome
Nadelman 1993[113]	Excluded due to an incorrect study design
Nadelman 2001[112]	Excluded due to an incorrect population
Naglo 1989[114]	Excluded due to an incorrect study design
Neumann 1987[117]	Excluded due to an incorrect study design
Nimmrich 2014[119]	Excluded due to an incorrect study design
Nowakowski 2000[120]	Excluded due to an incorrect study design
Nowakowski 1995[121]	Excluded due to an incorrect study design
Ogrinc 2006[122]	Excluded due to an incorrect population
Oksi 1999[123]	Excluded due to an incorrect study design
Oksi 2007[124]	Excluded due to an incorrect population
Oksi 1998[125]	Excluded due to an incorrect population
Peltomaa 1998[126]	Excluded due to an incorrect comparison
Pena 1999[127]	Excluded due to an incorrect study design
Perronne 2015[128]	Not available
Pfister 1988[129]	Excluded due to an incorrect outcome
Pirila 1951[132]	Excluded due to an incorrect study design
Plorer 1993[133]	Excluded due to an incorrect study design
Plotkin 1991[134]	Excluded due to an incorrect study design
Puchalska 1996[135]	Excluded due to an incorrect study design
Puri 2015[136]	Excluded due to an incorrect comparison
Puri 2015[137]	Excluded due to an incorrect study design
Rebman 2015[138]	Excluded due to an incorrect study design
Renaud 2004[139]	Excluded due to an incorrect study design
Rohacova 1996[140]	Excluded due to an incorrect comparison
Rose 1994[141]	Excluded due to an incorrect study design
Rose 1996[142]	Excluded due to an incorrect intervention

Reference	Reason for exclusion
Rubin 1992[143]	Excluded due to an incorrect study design
Salazar 2005[144]	Excluded due to an incorrect intervention
Salazar 1993[145]	Excluded due to an incorrect study design
Sanchez 2016[146]	Excluded due to an incorrect study design
Sandstrom 1989[147]	Excluded due to an incorrect study design
Schmidt 1995[148]	Excluded due to an incorrect study design
Selby 2008[149]	Excluded due to an incorrect study design
Shadick 1994[150]	Excluded due to an incorrect study design
Shadick 1999[151]	Excluded due to an incorrect study design
Shemenski 2016[152]	Excluded due to an incorrect study design
Shoemaker 2006[153]	Excluded due to an incorrect intervention
Sjowall 2012[155]	Excluded due to an incorrect intervention
Sjowall 2011[154]	Excluded due to an incorrect study design
Skogman 2003[157]	Excluded due to an incorrect intervention
Skogman 2008[156]	Excluded due to an incorrect study design
Skoldenberg 1988[158]	Excluded due to an incorrect study design
Smith 2002[159]	Excluded due to an incorrect study design
Solomon 1998[160]	Excluded due to an incorrect intervention
Spathling 1992[161]	Article not in English
Stanek 1999[162]	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[163]	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

Reference	Reason for exclusion
Weissenbacher 2005[191]	Excluded due to an incorrect intervention
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 18: Studies excluded from the health economic review

Reference	Reason for exclusion
None	None