National Institute for Health and Care Excellence

Draft for Consultation

Lyme disease: diagnosis and management

[L] Evidence review for the management of persistent symptoms related to Lyme disease

NICE guideline

Evidence review

September 2017

Draft for Consultation

This evidence review was developed by the National Guideline Centre

1

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ISBN:

Contents

1

1 Management (persistent symptoms)

1.1 Review question: What is the most clinically and cost-effective treatment for seropositive people, who have non-specific symptoms that may be related to Lyme disease?

1.2 Introduction

If Lyme disease is treated early, most people recover completely, but studies show that some people have persistent symptoms following antibiotic treatment. It is not known whether these symptoms are due to persisting infection, tissue damage, autoimmune reaction or some other process. There is currently no test that helps determine this. It is important to assess whether repeat or longer courses of antibiotics might help.

A number of treated people have a slow recovery and may need support and access to social services. It is important that clinical practitioners consider these when managing people with long-term symptoms related to Lyme disease.

This section includes an evidence report and committee discussion on antibiotic management of persisting symptoms as well as a separate section with recommendations and committee discussion about the importance of provision of longer-term support.

1.3 PICO table

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

Table 1: PICO characteristics of review question

Population	People with Lyme disease determined by a diagnostic tests or clinical diagnosis who have non-specific symptoms that may be related to Lyme disease. This includes symptoms such as: • disturbed cognitive function, for example, memory loss • dizziness • fatigue • fever and sweats • headache • lymphadenopathy • myalgia and muscle stiffness • neck pain or stiffness • paraesthesia • photophobia

Interventions	Antimicrobials, including but not limited to:
	• Penicillins
	  ○ Amoxicillin (oral, IV)
	  ○ Ampicillin (oral, IV)
	  ○ Benzylpenicillin sodium / Penicillin G (IV)
	  - Including Augmentin (Amoxicillin and clavulanic acid; oral, IV)
	  ○ Phenoxymethylpenicillin / Penicillin V (oral)
	• Tetracyclines
	  ○ Doxycycline (oral)
	  ○ Minocycline (oral)
	• Cephalosporins

	○ Cefotaxime (IV) ○ Ceftriaxone (IV) ○ Cefuroxime axetil (oral) • Macrolides ○ Azithromycin (oral) ○ Clarithromycin (oral, IV) • Fluoroquinolones ○ Ciprofloxacin (oral, IV) ○ Levofloxacin (oral, IV) ○ Moxifloxacin (oral, IV) ○ Nalidixic acid (oral) ○ Norfloxacin (oral) ○ Ofloxacin (oral, IV) • Rifampicin (oral, IV)
Comparisons	• Antimicrobial agents compared with each other ○ If data are available, consider: - Type of antimicrobial agent (within class or between class) - Route of administration - Duration of treatment: 1 month versus longer • Monotherapy versus polytherapy (any combination) • Antimicrobial agents compared to no treatment / placebo
Outcomes	**Critical:** 1. Quality of life (any validated measure) 2. Cure (resolution of symptoms) 3. Reduction of clinical symptoms 4. Symptom relapse **Important:** 5. Adverse events
Study design	• Randomised control studies (RCT) • Cohort studies (if no RCT evidence is found)

1.4 Clinical evidence

1.4.1 Included studies

The evidence reviews conducted for antibiotic management of Lyme disease did not pre-specify for how long a person with symptoms related to Lyme disease had those symptoms but was organised by symptom or symptom complex. The review question on the management of non-specific symptoms related to Lyme disease did not identify any studies in people with non-specific symptoms in the early stages of Lyme disease. Three studies identified[15 ,80 ,85] were in adults where a significant proportion of the people in these studies had received antibiotic treatment prior to enrolment. The committee agreed that these studies would inform recommendations about treating people with symptoms persisting after treatment.

All participants in the PLEASE trial[15] received 2 grams intravenous ceftriaxone for 14 days prior to the study interventions. One treatment arm in this trial also used an indirect intervention as people received hydroxychloroquine in addition to clarithromycin.

The included studies are summarised in Table 2 below. 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.

1.4.2 Excluded studies

See the excluded studies list in appendix I.

1.4.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Berende 2016 (PLEASE trial)[15]	Doxycycline (n=86): 100 mg oral twice daily. Duration 12 weeks. Concurrent medication/care: Placebo combined with study intervention. Clarithromycin (n=96): 500 mg clarithromycin orally twice daily plus 200 mg hydroxychloroquine orally twice daily. Duration 12 weeks. Concurrent medication/care: none Placebo (n=98): Two different placebo capsules orally twice daily. Duration 12 weeks. Concurrent medication/care: none	n=281 Diagnosis: persistent symptoms attributed to Lyme disease temporarily related to an EM or an otherwise proven case of symptomatic Lyme disease or accompanied by *B burgdorferi* IgM or IgG antibodies	Quality of life Adverse events	People in the clarithromycin group also received hydroxychloroquine All people received open-label intravenous ceftriaxone (2,000 mg daily) for 14 days prior to study intervention. Majority of people (87-91%) had received previous antibiotic treatment
Klempner 2001[80]	Polytherapy (n=64): 2 g ceftriaxone per day intravenous for 30 days followed by 100 mg doxycycline orally twice per day for 60 days. Duration 90 days. Concurrent medication/care: Not reported Placebo (n=65): Dextrose solution intravenous for 30 days followed by oral capsules for 90 days. Duration 90 days. Concurrent medication/care: Not reported	n=129 Diagnosis: history of acute Lyme disease acquired in the US and at least 1 of the following: history of single or multiple EM, early neurologic or cardiac symptoms attributed to Lyme disease, radiculoneuropathy, or Lyme arthritis	Quality of life Adverse events	33% had previously received intravenous antibiotic treatment for mean (±SD) 30 ± 12 days, all other previous treatment consisted of oral antibiotics (mean 3 ± 1.4 courses in the antibiotic group; 2.7 ± 1.3 in the placebo group)

Study	Intervention and comparison	Population	Outcomes	Comments
Krupp 2003[85]	Ceftriaxone (n=28): 2 g per day, intravenous. Duration 28 days. Concurrent medication/care: Not reported Placebo (n=27): Placebo intravenous. Duration 28 days. Concurrent medication/care: Not reported	n=56 Diagnosis: history of physician-documented EM or CDC-defined late manifestation of Lyme disease confirmed by positive ELISA and WB serology, current severe fatigue defined by an elevated score (4 or more) on a modified version of the Fatigue Severity Scale	Reduction of symptoms	Eligibility criteria included completion (6 months before study entry) of standard antibiotic therapy for Lyme disease as defined by at least a 3 week course of oral antibiotic therapy or 3 weeks of IV ceftriaxone

1 See appendix D for full evidence tables.

1.4.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: Ceftriaxone (IV) followed by doxycycline (PO) 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 and doxycycline (95% CI)
Improvement in quality of life at 180 days	115 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 1.11 (0.7 to 1.77)	362 per 1,000	40 more per 1,000 (from 109 fewer to 279 more)
Improvement in SF-36 (physical component) at 180 days; 0-100, higher values are beneficial	115 (1 study)	LOW[1,2] due to risk of bias, imprecision	RR 1.36 (0.77 to 2.38)	259 per 1,000	93 more per 1,000 (from 59 fewer to 357 more)
Improvement in SF-36 (mental component) at 180 days; 0-100, higher values are beneficial	115 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.88 (0.54 to 1.44)	379 per 1,000	46 fewer per 1,000 (from 174 fewer to 167 more)
Adverse events at 90 days	129 (1 study)	LOW[2] due to imprecision	RR 1.48 (0.74 to 2.93)	169 per 1,000	81 more per 1,000 (from 44 fewer to 327 more)

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

Table 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)
Improvement in fatigue at 6 months	55 (1 study)	HIGH	RR 3.47 (1.5 to 8.02)	185 per 1,000	457 more per 1,000 (from 93 more to 1,000 more)
FSS-11 score (final values) at 6 months; 0-77, lower values are beneficial	48 (1 study)	LOW[1,2] due to risk of bias, imprecision	Not applicable	The mean FSS-11 score in the control group was 5.5	The mean FSS-11 score in the intervention group was 1.1 lower (1.89 to 0.31 lower)
Change in FSS-11 score from baseline at 6 months; 0-77, lower values are beneficial	48 (1 study)	LOW[1,2] due to risk of bias, imprecision	Not applicable	The mean change in FSS-11 score from baseline in the control group was -0.5	The mean change in FSS-11 score from baseline in the intervention group was 0.8 lower (1.46 to 0.14 lower)
Improvement in cognitive measure at 6 months	48 (1 study)	LOW[2] due to imprecision	RR 0.85 (0.13 to 5.52)	91 per 1,000	14 fewer per 1,000 (from 79 fewer to 411 more)
A-A score (final values) at 6 months; cognitive processing speed measured in milliseconds, lower values are beneficial	48 (1 study)	MODERATE[2] due to imprecision	Not applicable	The mean A-A score in the control group was 3.4	The mean A-A score in the intervention group was 0.4 higher (0.38 lower to 1.18 higher)
Change in A-A score from baseline at 6 months; cognitive processing speed measured in milliseconds, lower values are beneficial	47 (1 study)	MODERATE[2] due to imprecision	Not applicable	The mean change in A-A score from baseline in the control group was -0.5	The mean change in A-A score from baseline in the intervention group was 0.2 higher (0.32 lower to 0.72 higher)

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

Table 5: Clinical evidence summary: Ceftriaxone (IV) followed by doxycycline (PO) versus ceftriaxone (IV) followed by clarithromycin (PO) plus hydroxychloroquine

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ceftriaxone plus clarithromycin plus hydroxychloroquine	Risk difference with ceftriaxone plus doxycycline (95% CI)
SF-36 (physical component – final values) at 14 weeks; 15-61 (norm-based T-score), general population score 50 (SD 10), higher values are beneficial	182 (1 study)	LOW[1,2] due to indirectness, imprecision	Not applicable	The mean SF-36 (physical component) in the control group was 35.6	The mean SF-36 (physical component) in the intervention group was 0.6 lower (2.62 lower to 1.42 higher)
Adverse events at 14 weeks	182 (1 study)	LOW[1,2] due to indirectness, imprecision	RR 1.12 (0.82 to 1.53)	438 per 1,000	53 more per 1,000 (from 79 fewer to 232 more)
Discontinued treatment due to adverse events at 14 weeks	182 (1 study)	VERY LOW[1,2] due to indirectness, imprecision	RR 0.48 (0.13 to 1.79)	73 per 1,000	38 fewer per 1,000 (from 63 fewer to 58 more)

[1] People in the clarithromycin group also received hydroxychloroquine
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 6: Clinical evidence summary: Ceftriaxone (IV) followed by doxycycline (PO) versus ceftriaxone (IV)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ceftriaxone	Risk difference with ceftriaxone plus doxycycline (95% CI)
SF-36 (physical component – final values) at 14 weeks; 15-61 (norm-based T-score), general population score 50 (SD 10), higher	184 (1 study)	MODERATE[1] due to imprecision	Not applicable	The mean SF-36 (physical component) in the control group was	The mean SF-36 (physical component) in the intervention group was 0.2 higher (1.82 lower to 2.22 higher)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ceftriaxone	Risk difference with ceftriaxone plus doxycycline (95% CI)
values are beneficial				34.8	
Adverse events at 14 weeks	184 (1 study)	MODERATE[1] due to imprecision	RR 1.41 (0.99 to 1.99)	347 per 1,000	142 more per 1,000 (from 3 fewer to 343 more)
Discontinued treatment due to adverse events at 14 weeks	184 (1 study)	LOW[1] due to imprecision	RR 0.85 (0.2 to 3.71)	41 per 1,000	6 fewer per 1,000 (from 33 fewer to 111 more)

[1] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 7: Clinical evidence summary: Ceftriaxone (IV) followed by clarithromycin (PO) plus hydroxychloroquine versus ceftriaxone (IV)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ceftriaxone	Risk difference with ceftriaxone plus clarithromycin plus hydroxychloroquine (95% CI)
SF-36 (physical component – final values) at 14 weeks; 15-61 (norm-based T-score), general population score 50 (SD 10), higher values are beneficial	194 (1 study)	LOW[1,2] due to indirectness, imprecision	Not applicable	The mean SF-36 (physical component) in the control group was 34.8	The mean SF-36 (physical component) in the intervention group was 0.8 higher (1.15 lower to 2.75 higher)
Adverse events at 14 weeks	194 (1 study)	LOW[1,2] due to indirectness, imprecision	RR 1.26 (0.89 to 1.8)	347 per 1,000	90 more per 1,000 (from 38 fewer to 278 more)
Discontinued treatment due to adverse events at 14 weeks	194 (1 study)	VERY LOW[1,2] due to indirectness, imprecision	RR 1.79 (0.54 to 5.91)	41 per 1,000	32 more per 1,000 (from 19 fewer to 200 more)

[1] People in the clarithromycin group also received hydroxychloroquine
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

See appendix F for full GRADE tables.

1.5 Economic evidence

1.5.1 Included studies

No relevant health economic studies were identified.

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

1.5.2 Excluded studies

No relevant health economic studies were identified and excluded.

1.5.3 Unit costs

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

Table 8: 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: intravenously.

Sources: Unit costs from NHS Electronic Drug Tariff January 2017,[120] except cefotaxime from BNF, January 2017[21] and ceftriaxone from EMIT March 2017;[38] dosage from BNF and BNF for Children January 2017,[21,22] exceptions below:

(a) Source of dosage from RCT in adults with EM: Steere 1983,[167] dosage for Lyme disease not available from BNF or BNF for children.

(b) Source of dosage from RCT in adults with neuroborreliosis: Pfister 1989[132] and Pfister 1991,[133] dosage for Lyme disease not available from BNF or BNF for children.[21,22]

(c) For disseminated Lyme borreliosis.

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

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

(f) Source of dosage from RCT in adults with Lyme arthritis: Steere 1985:[166] 1.2 million U injected in each buttock weekly intramuscularly. Duration 3 weeks. Dosage for Lyme disease not available from BNF or BNF for children. [21,22]

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

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

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

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

- antibiotic
- nursing time (for example, Band 6 nurse, £44 per hour, PSSRU 2016[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).[117] 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 9: 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 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 9, 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:

- Low to Very Low quality evidence from 1 RCT did not find any clinical difference between intravenous ceftriaxone followed by oral doxycycline versus placebo.
- High quality evidence from 1 RCT found a clinical benefit of intravenous ceftriaxone over placebo regarding the improvement in fatigue. Low quality evidence from 1 RCT found a clinical benefit of intravenous ceftriaxone over placebo for the improvement in fatigue as measured by the FSS-11 score. There was no difference between intravenous ceftriaxone and placebo regarding the improvement in cognitive function.
- Low to Very Low quality evidence from 1 RCT did not find any difference between intravenous ceftriaxone followed by oral doxycycline and intravenous ceftriaxone followed by oral clarithromycin and hydroxychloroquine.
- Moderate quality evidence from 1 RCT did not find any difference in quality of life between intravenous ceftriaxone followed by oral doxycycline and intravenous ceftriaxone alone. Moderate quality evidence from 1 RCT showed a higher rate of adverse events for intravenous ceftriaxone followed by oral doxycycline. Low quality evidence from 1 RCT did not find any difference in the number of people discontinuing treatment due to adverse events between the treatment arms.
- Low to Very Low quality evidence did not find any difference between intravenous ceftriaxone followed by oral clarithromycin plus hydroxychloroquine and intravenous ceftriaxone alone.

Children:

- No evidence was found.

1.7.2 Health economic evidence statements

No relevant economic evaluations were identified.

1.8 Recommendations

L1. If symptoms that may be related to Lyme disease persist or worsen after antibiotic treatment, review the person's history and examination to explore:

- any possible alternative causes of the symptoms
- if re-infection may have occurred
- details of any previous treatment, including whether the course of antibiotics was completed without interruption
- if symptoms may be related to organ damage caused by Lyme disease, for example, nerve palsy.

L2. If the person’s history suggests re-infection, offer antibiotic treatment according to their symptoms (see recommendations A1-A2 in evidence report D).

L3. Consider a second course of antibiotics for people with persisting symptoms if treatment may have failed. Use an alternative antibiotic to that used for initial treatment, for example for adults with Lyme disease and arthritis, offer amoxicillin if the person has completed an initial course of doxycycline.

L4. Do not routinely offer further antibiotics if a person has persisting symptoms following 2 courses of antibiotics (see table 30 and table 31 in evidence report D). Consider discussion with or referral to a specialist as outlined in recommendation C10.

L5. Explain to people with persisting symptoms following antibiotic treatment that:

- symptoms of Lyme disease may take months to resolve even after treatment
- continuing symptoms does not necessarily mean they still have an active infection
- symptoms may be a consequence of damage from infection
- there may be an alternative diagnosis.

L6. Support people who have a slow recovery from Lyme disease by:

- encouraging and helping them to access additional services, including referring to adult social care for a care and support needs assessment, if they would benefit from these
- communicating with social services, educational services and employers about the person's need for gradual return to activities, if relevant.

1.8.1 Research recommendations

RR1. What are the incidence, presenting features, management and outcome of Lyme disease, including in women with Lyme disease who are pregnant, in the UK?

See also rationale in appendix J of evidence report A.

RR2. Can a core outcome set be developed for clinical trials of management of Lyme disease?

RR3. What are the most clinically and cost-effective treatment options for different clinical presentations of Lyme disease in the UK?

See also rationale in appendix J of evidence report D.

1.9 Rationale and impact

1.9.1 Why the committee made the recommendations

People who have had treatment for Lyme disease sometimes report persisting symptoms. These may be caused by re-infection, insufficient initial treatment or lack of adherence to treatment, or organ damage caused by Lyme disease, which may take a long time to heal or may even be permanent.

The evidence available did not show benefit from prolonged treatment with antibiotics, but the committee agreed that treatment failure could occur and that a second course of antibiotics might sometimes be appropriate. The committee noted the importance of considering alternative diagnoses to prevent inappropriate antibiotic treatment and misdiagnosis.

The committee recommended that people with persisting symptoms should not routinely be offered more than 2 courses of antibiotics because of lack of evidence of benefit. However, discussion with a specialist or referral should be considered in some cases.

People who have a slow recovery from Lyme disease may need additional support and access to social services. The committee felt that it was important to recommend that healthcare professionals help people with long-term symptoms related to Lyme disease to access support if needed.

1.9.2 Impact of the recommendations on practice

Current treatment for Lyme disease is a single course of antibiotics. Treatment for persisting symptoms is unclear and practice varies. Further antibiotic treatment is now recommended as an option if persisting infection is a possibility. This will standardise practice but may cause an increase in antibiotic prescribing in a small number of patients. The committee agreed that this change in practice would not result in a significant resource impact given the small number of people with recurrent symptoms.

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 evidence included in this chapter was identified through the review on the management of non-specific symptoms associated with Lyme disease. The identified evidence was in people with Lyme disease who had persistent, non-specific symptoms despite having previous antibiotic treatment. The committee acknowledged that the included studies provided some limited evidence on the effectiveness of long-term antibiotic treatment for Lyme disease.

The guideline committee considered quality of life, cure or the resolution of Lyme disease symptoms, the reduction of Lyme disease symptoms, and the relapse of Lyme disease symptoms to be critical outcomes. Adverse events as a result of treatment were considered to be an important outcome.

This review only found evidence for the outcomes quality of life, reduction of clinical symptoms and adverse events. No evidence was found for the outcomes cure or resolution of symptoms and symptom relapse.

1.10.1.2 The quality of the evidence

The evidence was generally of Moderate to Very Low quality due to risk of bias, indirectness and imprecision. There were particular concerns around a lack of outcome assessor blinding for subjective outcomes, such as quality of life. One treatment arm in the PLEASE trial also used an indirect intervention as people received hydroxychloroquine in addition to clarithromycin.

One outcome, improvement in fatigue for the comparison of intravenous ceftriaxone versus placebo, was of High quality.

There were no concerns regarding the risk of bias for any of the outcome reported by the PLEASE trial. However, all participants in the trial received a 2-week course of open-label intravenous ceftriaxone before their assigned study drug. This antibiotic treatment might have resulted in people experiencing a quality of life improvement.

There was a general lack of evidence with only single, small studies identified for each comparison. The committee agreed that while the evidence had to be interpreted with caution, there was a trend suggesting that continuous long-term treatment did not provide an additional benefit.

1.10.1.3 Benefits and harms

The evidence identified was in people with Lyme disease who had persistent non-specific symptoms despite having undergone antibiotic treatment. The majority of the people included in the studies received oral or intravenous antibiotic treatment for their Lyme disease symptoms prior to enrolment in the study.

All 3 included studies assessed the effectiveness of intravenous ceftriaxone, alone or in combination with oral doxycycline or oral clarithromycin.

The evidence showed a clear benefit of intravenous ceftriaxone (2 grams once daily for 28 days) compared to placebo in the improvement of fatigue and quality of life as measured by the FSS-11 score. There was no difference between intravenous ceftriaxone and placebo regarding changes in cognitive function.

Two RCTs assessed the effectiveness of intravenous ceftriaxone followed by long-term oral doxycycline or clarithromycin in people with persistent symptoms associated with Lyme disease. In the PLEASE trial, all participants received 2 grams of open-label intravenous ceftriaxone once daily for 14 days before their assigned masked study intervention; either 12 weeks of oral doxycycline (100 milligrams twice daily) or 12 weeks of oral clarithromycin (500 milligrams clarithromycin plus 200 milligrams hydroxychloroquine twice daily). In the other study, people were randomly assigned 2 grams of intravenous ceftriaxone once daily for 30 days followed by 100 milligrams oral doxycycline twice daily for 60 days or a 90-day course of placebo. People with a presumed diagnosis of neuroborreliosis as indicated by a CSF pleocytosis were excluded from this study.

Evidence from these 2 RCTs found that the addition of long-term oral doxycycline or oral clarithromycin increased the number of adverse events and led to a significantly higher treatment discontinuation rate due to adverse events. There was, however, no additional benefit of taking long-term oral dosages of doxycycline or clarithromycin after intravenous ceftriaxone on quality of life.

1.10.2 Cost effectiveness and resource use

No relevant health economic evidence was identified. The unit costs of different oral and intravenous antimicrobials were presented to the committee. The committee agreed it was important to establish if persisting symptoms are related to Lyme disease. This may require additional healthcare practitioner time to allow for a review of history and examination. The committee noted that establishing if a re-infection has occurred would be done clinically not through further testing. Although no cost-effectiveness evidence was identified, it is considered good clinical practice to assess a person with persisting symptoms. Treating people who have been re-infected is considered standard practice for all infections. A recommendation to offer a second course of antibiotics to people with persisting symptoms, who may have treatment failure, was based on the clinical evidence identified and committee discussion as described below. This additional treatment cost is unlikely to apply to a large population and therefore not expected to have a significant resource impact.

1.10.3 Other factors the committee took into account

The committee considered it important to acknowledge that recovery from infection can take time and this occurs in many infections including Lyme disease.

The committee considered evidence from the PLEASE trial to be particularly relevant when developing clinical recommendations for people with persistent symptoms related to Lyme disease. In the study, all participants received open-label intravenous ceftriaxone for 2 weeks followed by their randomly assigned study drug; 12 weeks of oral doxycycline, 12 weeks of oral clarithromycin, or 12 weeks of oral placebo. Although the PLEASE trial showed a quality of life improvement in all treatment arms, there was no difference between treatment arms.

The committee considered that any quality of life improvements could be due to the initial 2-week treatment of intravenous ceftriaxone with no clear additional benefit from long-term treatment with oral doxycycline or clarithromycin. To determine the effectiveness of long-term antibiotic treatment, study participants should have also been blinded to the intravenous ceftriaxone treatment, and a fourth treatment arm consisting of only placebo should have been introduced. The committee considered that the evidence did not provide support for long-term antibiotic treatment.

The committee also discussed the possibility of treatment failure. Evidence for management of different presentations of Lyme disease all indicated some treatment failures. People respond to treatments differently for various reasons and this is not specific to Lyme disease. The committee agreed that the emphasis on higher doses and 3- or 4-week treatment courses in this guideline should reduce treatment failure but recognised that this can still occur.

The committee therefore recommended the consideration of a second course of antibiotic treatment using an alternative antibiotic to the antibiotic initially prescribed if a person has persistent symptoms and treatment failure is suspected.

The committee agreed that there was no evidence for further antibiotic treatment beyond this. People with persisting symptoms attributed to Lyme disease despite 2 adequate courses of antibiotics should have their care discussed with a specialist appropriate to their symptoms, for example a rheumatologist if they have joint problems. The committee was concerned about both missing alternate diagnoses and problems caused by inappropriate treatment with antibiotics.

The committee also acknowledged that the antibiotic treatment might result in an eradication of the bacteria but may not have any immediate effect on the organ damage. Symptoms associated with organ damage may take a long time to heal or even remain permanent. These symptoms are therefore not necessarily indicative of treatment failure.

The committee made a number of high priority research recommendations which include the clinical epidemiology of Lyme disease, the development of a core outcome set for studies of management of Lyme disease, the evaluation of antibiotic regimens for management of Lyme disease. Research in these areas would ensure improved understanding of presentations and treatments for people with persisting symptoms. These research recommendations are outlined in more detail in appendix J of evidence report A and appendix J of evidence report D.

1.11 Recommendations

L7. Assess and offer additional treatment if needed for symptoms of Lyme disease following usual clinical practice (for example, heart block).

L8. Be alert to the possibility of symptoms related to Lyme disease that may need assessment and management including:

- depression and anxiety (see NICE's guideline on common mental health disorders)
- chronic pain
- sleep disturbance
- fatigue.

1.12 Rationale and impact

1.12.1 Why the committee made the recommendations

No specific evidence review was carried out to inform recommendations on support, referral to social services or the need to consider assessing and managing other symptoms related to Lyme disease, such as chronic pain, fatigue or depression. The committee, however, acknowledged that some people with Lyme disease experience a slow recovery and may require professional support. Some people with Lyme disease feel that their needs are not considered in an appropriate way and the committee therefore decided to recommend that physicians consider the possibility of such needs.

1.12.2 Impact of the recommendations on practice

Some people with Lyme disease may require support or social services, especially when they have a slow recovery. Social services needs assessments are carried out by local authorities and will not affect NHS practice.

Some people with Lyme disease may also present with related symptoms, such as chronic pain, depression or fatigue. Guidance for managing these symptoms already exists and therefore there will be no change to existing clinical practice.

1.13 The committee's discussion of the evidence

1.13.1 Interpreting the evidence

1.13.1.1 The outcomes that matter most

No specific evidence review was undertaken for the assessment and management of persistent symptoms related to Lyme disease and support of people who have a slow recovery from Lyme disease. The recommendations are based on consensus with regard for the long-term difficulties people with Lyme disease often face.

1.13.1.2 The quality of the evidence

No specific evidence review was undertaken.

1.13.1.3 Benefits and harms

No specific evidence review was undertaken.

1.13.2 Cost effectiveness and resource use

No health economic review was undertaken. Providing information and support towards access to further services such as social care is considered good patient care, particularly in people who experience a slow recovery from illness. In addition, it is considered current practice to assess and manage people for all their presenting symptoms.

These recommendations are not expected to apply to all people with Lyme disease and so are not anticipated to have a significant resource impact.

1.13.3 Other factors the committee took into account

The committee discussed the difficulties people with Lyme disease often face, particularly in the absence of a speedy recovery. Although long-term support and the referral to social care services were not part of the scope of this guideline, the committee emphasized that some people may require support, access to social services or a gradual return to work. This is similar to other conditions where recovery is slow, but the committee considered it appropriate to emphasise the need for this in people with Lyme disease.

People who have a slow recovery or who experience a significant impact on their personal and professional life may benefit from access to addition services, such as a social services needs assessment.

The committee also wished to emphasise the needs of people with Lyme disease for management of symptoms that may need further assessment and management. These symptoms include depression and anxiety, chronic pain, sleep disturbance and fatigue. The committee agreed that these symptoms were not specific to Lyme disease and that guidance on the assessment and management for these already exist. It was therefore decided to highlight the need to consider these symptoms and refer to relevant existing guidance.

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Appendices

Appendix A: Review protocols

No separate review was undertaken to assess the effectiveness of treatment in people with persistent symptoms. People with persistent symptoms were included in the review population for the review question on the management of non-specific symptoms related to Lyme disease.

Table 10: Review protocol for the management of non-specific symptoms

Question number: 4.1

Relevant section of Scope: management

Field	Content
Review question	What is the most clinically and cost-effective treatment for seropositive people, who have non-specific symptoms that may be 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 a seropositive test result for Lyme disease, who have non-specific symptoms that may be related to Lyme disease.
Eligibility criteria – population / disease / condition / issue / domain	People with Lyme disease determined by a diagnostic tests or clinical diagnosis who have non-specific symptoms that may be related to Lyme disease. This includes symptoms such as: • disturbed cognitive function, for example, memory loss • dizziness • fatigue • fever and sweats • headache • lymphadenopathy • myalgia and muscle stiffness • neck pain or stiffness • paraesthesia • photophobia

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 and clavulanic acid; oral, IV)
	  ○ Phenoxymethylpenicillin / Penicillin V (oral)
	• Tetracyclines

Field	Content
	○ 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)
Eligibility criteria – comparator(s) / control or reference (gold) standard	• Antimicrobial agents compared with each other ○ If data are available, consider: - Type of antimicrobial agent (within class or between class) - Route of administration - Duration of treatment: 1 month versus longer • Monotherapy versus polytherapy (any combination) • Antimicrobial agents compared to no treatment / placebo
Outcomes and prioritisation	**Critical:** 1. Quality of life (any validated measure) 2. Cure (resolution of symptoms) 3. Reduction of clinical symptoms 4. Symptom relapse **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 has

Field	Content
	failed
Selection process – duplicate screening / selection / analysis	Studies will be sifted by title and abstract. Potentially significant publications obtained in full text will then be assessed against the inclusion criteria specified in this protocol.
Data management (software)	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). GRADEpro will be used to assess the quality of evidence for each outcome Bibliographies, citations, study sifting and reference management will be managed using EndNote. Data extractions will be performed using EviBase, a platform designed and maintained by the National Guideline Centre (NGC)
Information sources – databases and dates	Clinical searches Medline, Embase, The Cochrane Library all years Health economic searches Medline, Embase, NHS Economic Evaluation Database (NHS EED), Health Technology Assessment (HTA) all years
Identify if an update	Not applicable
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10007
Highlight if amendment to previous protocol	For details, please see section 4.5 of Developing NICE guidelines: the manual.
Search strategy – for one database	For details, please see appendix B
Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as appendix D of the evidence report.
Data items – define all variables to be collected	For details, please see evidence tables in appendix D (clinical evidence tables) or H (health economic evidence tables).
Methods for assessing bias at outcome / study level	Standard study checklists were used to appraise individual studies critically. For details, please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details, please see section 6.4 of Developing NICE guidelines: the manual. Meta-analysis will be conducted wherever possible (that is, where similar studies can be combined) In the absence of clinically established MIDs, standard MIDs for dichotomous (25% risk reduction or risk increase) and continuous outcomes (+/-0.5 standard deviation) will be used If heterogeneity is found, the influence of subgroups will be examined
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details, please see the separate Methods report for this guideline.
Meta-bias assessment – publication bias, selective reporting bias	For details, please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative	For details, please see sections 6.4 and 9.1 of Developing NICE

Field	Content
evidence	guidelines: the manual.
Rationale / context – what is known	For details, please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the NGC and chaired by Saul Faust in line with section 3 of Developing NICE guidelines: the manual. Staff from the NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details, please see Developing NICE guidelines: the manual.
Sources of funding / support	The NGC is funded by NICE and hosted by the Royal College of Physicians.
Name of sponsor	The NGC is funded by NICE and hosted by the Royal College of Physicians.
Roles of sponsor	NICE funds the NGC to develop guidelines for those working in the NHS, public health and social care in England.
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).[118] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations', then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations', then it will usually be excluded from the guideline. If it is excluded, then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or

both, then there is discretion over whether it should be included.

Where there is discretion

The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to exclude the remaining studies selectively. All studies excluded based on applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.

The health economist will be guided by the following hierarchies.

Setting:

- UK NHS (most applicable).
- OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).
- OECD countries with predominantly private health insurance systems (for example, Switzerland).
- Studies set in non-OECD countries or in the US will be excluded before being assessed for applicability and methodological limitations.

Health economic study type:

- Cost–utility analysis (most applicable).
- Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).
- Comparative cost analysis.
- Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.

Year of analysis:

- The more recent the study, the more applicable it will be.
- Studies published in 2001 or later but that depend on unit costs and resource data entirely or predominantly before 2001 will be rated as 'Not applicable'.
- Studies published before 2001 will be excluded before being assessed for applicability and methodological limitations.

Quality and relevance of effectiveness data used in the health economic analysis:

- The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

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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

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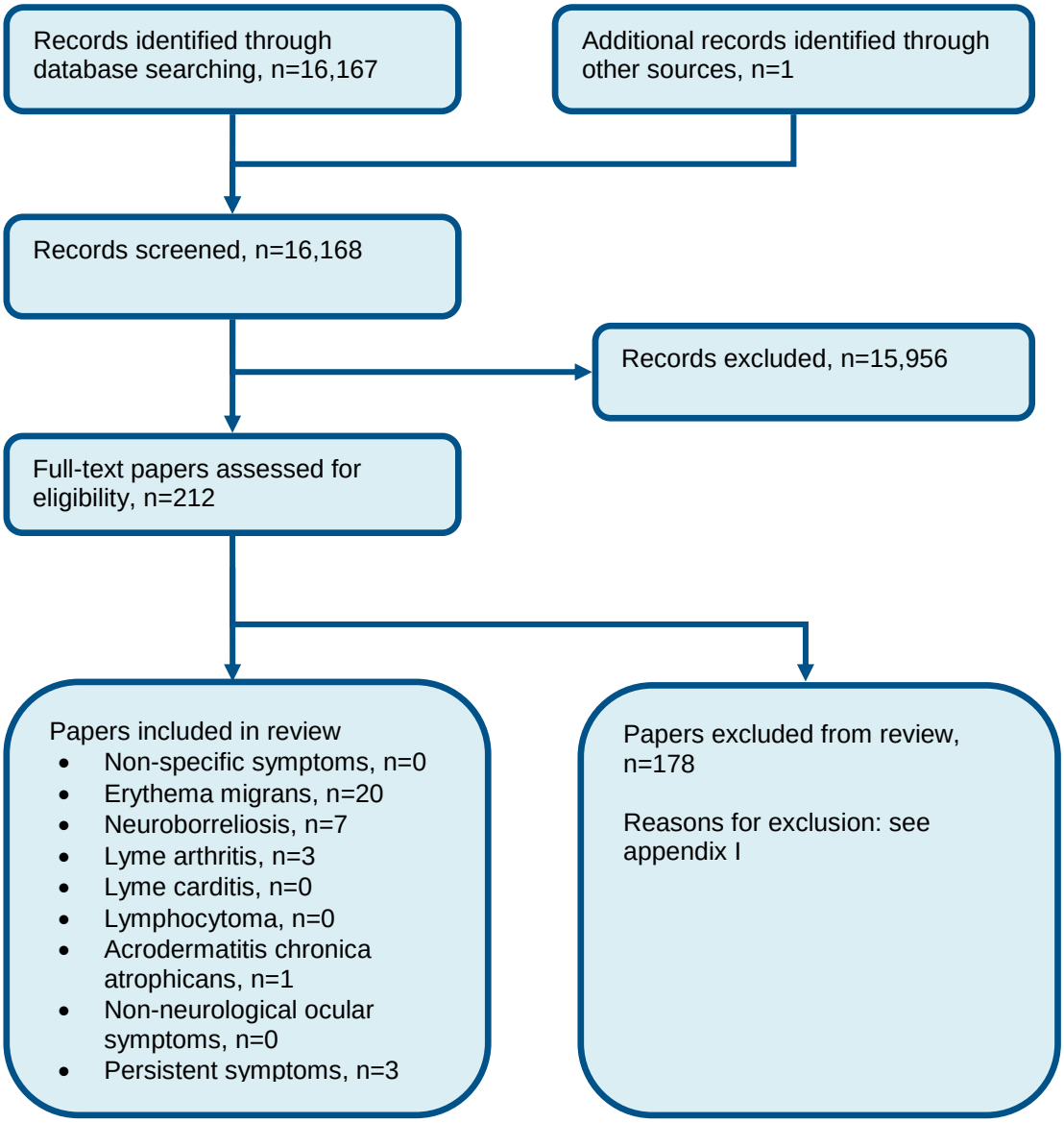
Appendix C: Clinical evidence selection

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



Appendix D: Clinical evidence tables

Study	Klempner 2001[80]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=129)
Countries and setting	Conducted in USA; Setting: Dual-centre
Line of therapy	first line
Duration of study	Follow up (post intervention): 180 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinical diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	18 years or older, history of acute Lyme disease acquired in the US, at least 1 of the following: history of single or multiple EM, early neurologic or cardiac symptoms attributed to Lyme disease, radiculoneuropathy, or Lyme arthritis
Exclusion criteria	Hypersensitivity to the study medications, previous parenteral antibiotic treatment for 60 days or more for their current symptoms, active inflammatory synovitis, coexisting condition that could have accounted for their symptoms, unable to discontinue medications that could interfere with the evaluation of their response to the treatment regimen
Recruitment or selection of people	Not reported
Age, gender and family origin	Age - Mean (SD): Antibiotic group: 54 years (14); placebo group: 53 years (13). Gender (M:F): Define. Family origin: 92% white Previous course of antibiotic treatment: 42 people (33%) received intravenous antibiotics, 87 people (67%) received oral antibiotics; mean number of previous antibiotic courses: 2.7 (SD 1.3)
Further population details	1. Immunocompromised people: Not applicable 2. Pregnant women: Not applicable
Indirectness of population	Serious indirectness: People were eligible if they had any specific symptoms (such as EM, neurological symptoms)
Interventions	(n=64) Intervention 1: Polytherapy. 2 g ceftriaxone per day intravenous for 30 days followed by 100 mg doxycycline orally twice per day for 60 days. Duration 90 days. Concurrent medication/care: Not reported (n=65) Intervention 2: Placebo. Dextrose solution intravenous for 30 days followed by oral capsules for 90

Study	Klempner 2001[80]
	days. Duration 90 days. Concurrent medication/care: Not reported
Funding	Equipment / drugs provided by industry
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: POLYTHERAPY versus PLACEBO Protocol outcome 1: Quality of life - Actual outcome: Improvement in SF-36 total score at 180 days; Group 1: 23/57, Group 2: 21/58 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 7; Group 2 Number missing: 7 - Actual outcome: Improvement in SF-36 physical component at 180 days; Group 1: 20/57, Group 2: 15/58 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 7; Group 2 Number missing: 7 - Actual outcome: Improvement in SF-36 mental component at 180 days; Group 1: 19/57, Group 2: 22/58 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 7; Group 2 Number missing: 7 Protocol outcome 2: Adverse events - Actual outcome: Adverse events at 90 days; Group 1: 16/64, Group 2: 11/65 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Cure (resolution of symptoms); Reduction of symptoms; Symptom relapse

Study	Krupp 2003[85]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=56)
Countries and setting	Conducted in USA; Setting: Multi-centre
Line of therapy	first line
Duration of study	Follow up (post intervention): 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinical diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 18-70 years, history of physician-documented EM or CDC-defined late manifestation of Lyme disease confirmed by positive ELISA and WB serology, completion (6 months before study entry) of standard antibiotic treatment for Lyme disease as defined by at least a 3-week course of oral antibiotic therapy or 3 weeks of IV ceftriaxone, current severe fatigue defined by an elevated score (4 or more) on a modified version of the Fatigue Severity Scale
Exclusion criteria	Mental disorder, medical disorder that confounded the assessment of severe fatigue or cognitive loss, cephalosporin allergy, severe psychiatric disorders
Recruitment or selection of people	Not reported
Age, gender and family origin	Age - Mean (SD): Ceftriaxone group: 48.0 years (11.8); placebo group: 47.0 years (9.7). Gender (M:F): 37:19. Family origin: 52 white
Further population details	1. Immunocompromised people: Not stated / Unclear 2. Pregnant women: Not stated / Unclear
Indirectness of population	Serious indirectness: People previously had either EM or late Lyme manifestations
Interventions	(n=28) Intervention 1: Antibiotics - Ceftriaxone. 2 g per day, intravenous. Duration 28 days. Concurrent medication/care: Not reported (n=27) Intervention 2: Placebo. Placebo intravenous. Duration 28 days. Concurrent medication/care: Not reported
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CEFTRIAXONE versus PLACEBO Protocol outcome 1: Reduction of symptoms at Define - Actual outcome: Improvement in fatigue at 6 months; Group 1: 18/28, Group 2: 5/27	

Study	Krupp 2003[85]
	Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: FSS-11 score at 6 months; Group 1: mean 4.4 (SD 1.5); n=26, Group 2: mean 5.5 (SD 1.3); n=22; Fatigue Severity Scale 0-77 Top equals High is poor outcome Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2; Group 2 Number missing: 5 - Actual outcome: Change in FSS-11 score from baseline at 6 months; Group 1: mean -1.3 (SD 1.4); n=26, Group 2: mean -0.5 (SD 0.93); n=22; Fatigue Severity Scale 0-77 Top equals High is poor outcome Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2; Group 2 Number missing: 5 - Actual outcome: Improvement in cognitive measure at 6 months; Group 1: 2/26, Group 2: 2/22 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 3; Group 2 Number missing: 5 - Actual outcome: A-A score at 6 months; Group 1: mean 3.8 Seconds (SD 1.7); n=26; Group 2: mean 3.4 Seconds (SD 1); n=22 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 3; Group 2 Number missing: 5 - Actual outcome: Change in A-A test score from baseline at 6 months; Group 1: mean -0.3 Seconds (SD 1); n=25; Group 2: mean -0.5 Seconds (SD 0.8); n=22 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 3; Group 2 Number missing: 5
Protocol outcomes not reported by the study	Quality of life; Cure (resolution of symptoms); Symptom relapse; Adverse events

Study	PLEASE trial: Berende 2016[15]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=281)
Countries and setting	Conducted in Netherlands; Setting: Single centre
Line of therapy	first line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinical diagnosis
Stratum	Overall

Study	PLEASE trial: Berende 2016[15]
Subgroup analysis within study	Not applicable
Inclusion criteria	Persistent symptoms attributed to Lyme disease temporarily related to an EM or an otherwise proven case of symptomatic Lyme disease or accompanied by *B burgdorferi* IgM or IgG antibodies
Exclusion criteria	allergy or intolerance to study drugs or ceftriaxone, more than 5 days of antimicrobial therapy with activity against B burgdorferi within previous 4 weeks, presumed diagnosis of neuroborreliosis, known diagnosis of HIV-seropositivity or other immune disorders, positive syphilis serology, liver disease, enrolled in other trials, previously randomised into this study, comorbidity that could account for symptoms of the subject
Recruitment or selection of people	Not reported
Age, gender and family origin	Age - Mean (SD): Doxycycline group: 48.1 years (12.8); clarithromycin group: 48.2 years (13.0); placebo group: 50.0 years (9.7). Gender (M:F): 151:129. Family origin: Doxycycline group: 98% white; clarithromycin group: 96% white; placebo group: 98% white
Further population details	1. Immunocompromised people: Not applicable 2. Pregnant women: Not applicable
Indirectness of population	No indirectness
Interventions	(n=86) Intervention 1: Antibiotics - Doxycycline. 100 mg oral twice daily. Duration 12 weeks. Concurrent medication/care: Open-label intravenous ceftriaxone (2000 mg daily) for 14 days prior to study intervention. Placebo combined with study intervention. (n=96) Intervention 2: Antibiotics - Clarithromycin. 500 mg clarithromycin orally twice daily plus 200 mg hydroxychloroquine orally twice daily. Duration 12 weeks. Concurrent medication/care: Open-label intravenous ceftriaxone (2000 mg daily) for 14 days prior to study intervention. (n=98) Intervention 3: Placebo. Two different placebo capsules orally twice daily. Duration 12 weeks. Concurrent medication/care: Open-label intravenous ceftriaxone (2000 mg daily) for 14 days prior to study intervention.
Funding	Academic or government funding (Netherlands Health Research grant)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DOXYCYCLINE versus CLARITHROMYCIN Protocol outcome 1: Quality of life - Actual outcome for Adults: SF-36 physical component summary score at 14 weeks; 35.0 (95% CI 33.5 to 36.5) versus 35.6 (95% CI 34.2 to 37.1) Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Adverse events	

Study	PLEASE trial: Berende 2016[15]
- Actual outcome for Adults: Any drug-related adverse event at 14 weeks; Group 1: 42/86, Group 2: 42/96 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Adults: Discontinued treatment due to adverse events at 14 weeks; Group 1: 3/86, Group 2: 7/96 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DOXYCYCLINE versus PLACEBO Protocol outcome 1: Quality of life - Actual outcome for Adults: SF-36 physical component summary score at 14 weeks; 35.0 (95% CI 33.5 to 36.5) versus 34.8 (95% CI 33.4 to 36.2) Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Adverse events - Actual outcome for Adults: Any drug-related adverse event at 14 weeks; Group 1: 42/86, Group 2: 34/98 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Adults: Discontinued treatment due to adverse events at 14 weeks; Group 1: 3/86, Group 2: 4/98 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CLARITHROMYCIN versus PLACEBO Protocol outcome 1: Quality of life at Define - Actual outcome for Adults: SF-36 physical component summary score at 14 weeks; 35.6 (95% CI 34.2 to 37.1) versus 34.8 (95% CI 33.4 to 36.2) Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Adverse events at Define - Actual outcome for Adults: Any drug-related adverse event at 14 weeks; Group 1: 42/96, Group 2: 34/98 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

Study	PLEASE trial: Berende 2016[15]
- Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Adults: Discontinued treatment due to adverse events at 14 weeks; Group 1: 7/96, Group 2: 4/98 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Cure (resolution of symptoms); Reduction of symptoms; Symptom relapse

Appendix E: Forest plots

E.1 Ceftriaxone (IV) followed by doxycycline (PO) versus placebo

E.1.1 Persistent Lyme disease symptoms

Figure 2: Improvement in quality of life

Study or Subgroup	Polytherapy Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Klempner 2001	23	57	21	58	100.0%	1.11 [0.70, 1.77]
Total (95% CI)		**57**		**58**	**100.0%**	**1.11 [0.70, 1.77]**
Total events	23		21			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.46 (P = 0.65)

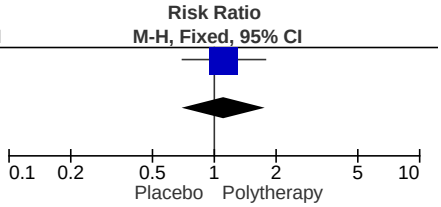


Figure 3: Improvement in SF-36 (physical component)

Study or Subgroup	Polytherapy Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Klempner 2001	20	57	15	58	100.0%	1.36 [0.77, 2.38]
Total (95% CI)		**57**		**58**	**100.0%**	**1.36 [0.77, 2.38]**
Total events	20		15			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.07 (P = 0.29)

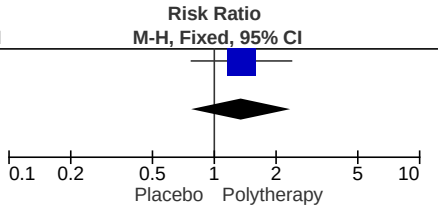


Figure 4: Improvement in SF-36 (mental component)

Study or Subgroup	Polytherapy Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Klempner 2001	19	57	22	58	100.0%	0.88 [0.54, 1.44]
Total (95% CI)		**57**		**58**	**100.0%**	**0.88 [0.54, 1.44]**
Total events	19		22			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.51 (P = 0.61)

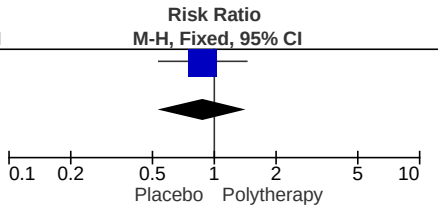
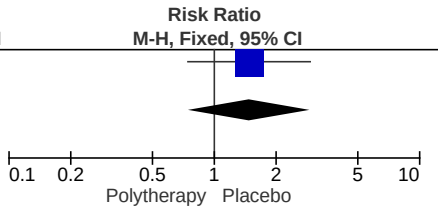


Figure 5: Adverse events

Study or Subgroup	Polytherapy Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Klempner 2001	16	64	11	65	100.0%	1.48 [0.74, 2.93]
Total (95% CI)		**64**		**65**	**100.0%**	**1.48 [0.74, 2.93]**
Total events	16		11			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.12 (P = 0.26)



1 E.2 Ceftriaxone (IV) versus placebo

2 E.2.1 Persistent Lyme disease symptoms

Figure 6: Improvement in fatigue

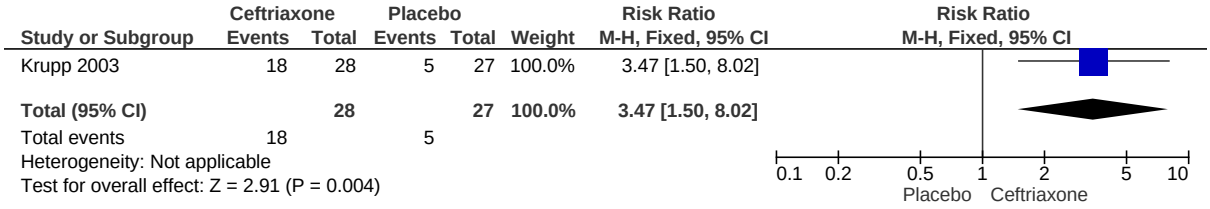


Figure 7: FS-11 score (final values)

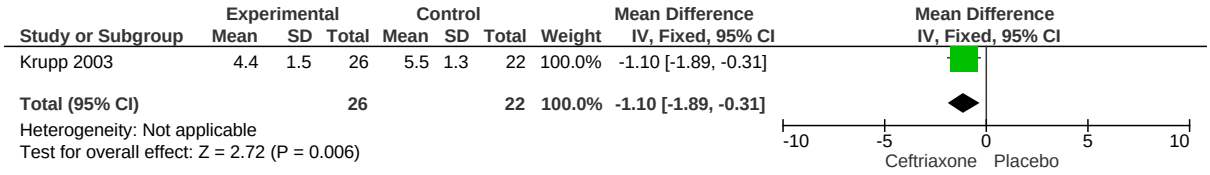


Figure 8: Change in FSS-11 score from baseline

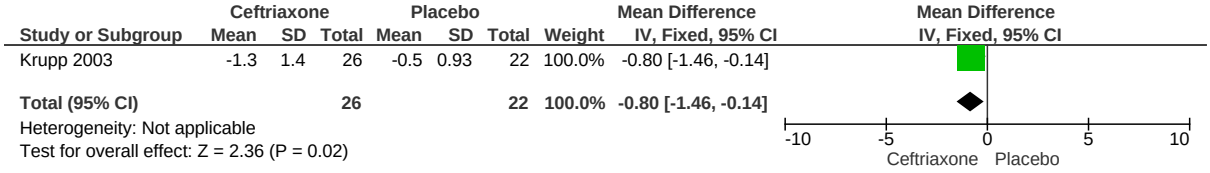


Figure 9: Improvement in cognitive measure

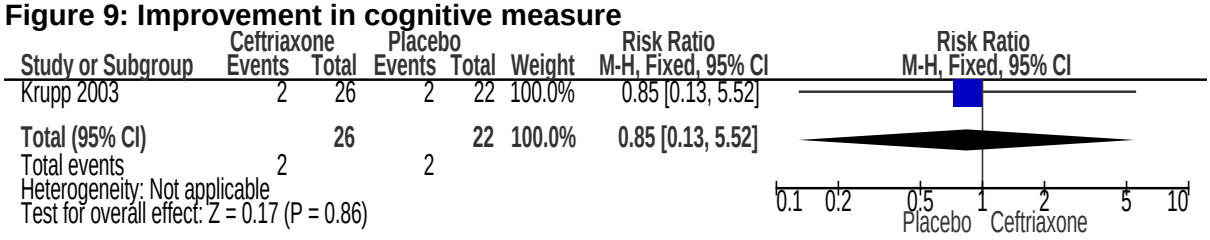


Figure 10: A-A score (final values)

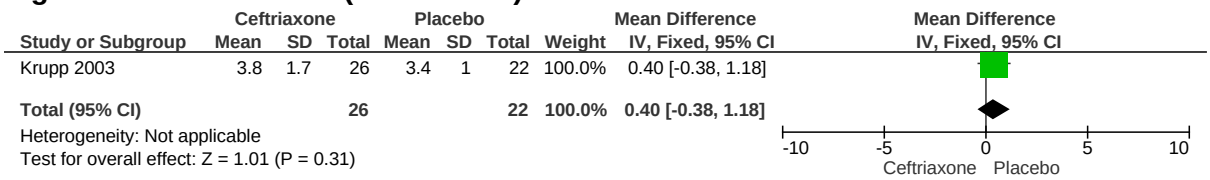
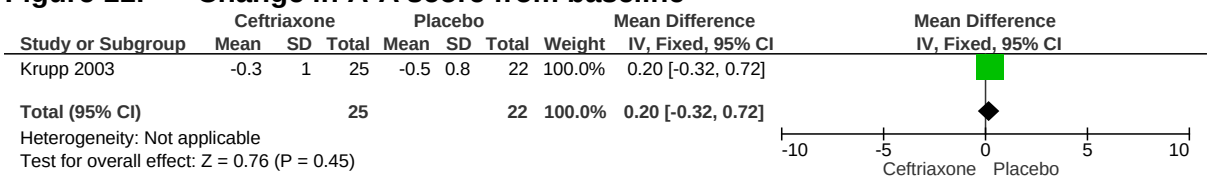


Figure 11: Change in A-A score from baseline



E.3 Ceftriaxone (IV) followed by doxycycline (PO) versus ceftriaxone (IV) followed by clarithromycin (PO) plus hydroxychloroquine

E.3.1 Persistent Lyme disease symptoms

Figure 12: SF-36 (physical component – final values)

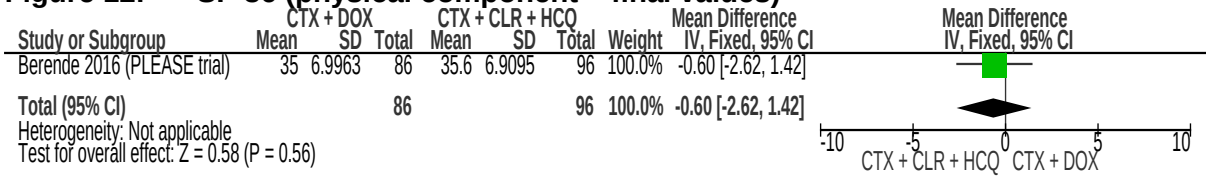


Figure 13: Adverse events

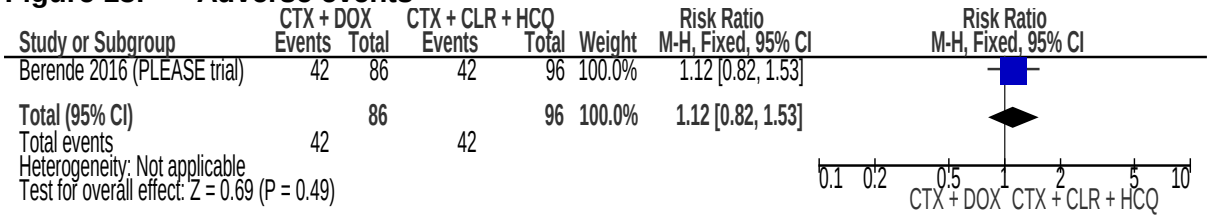
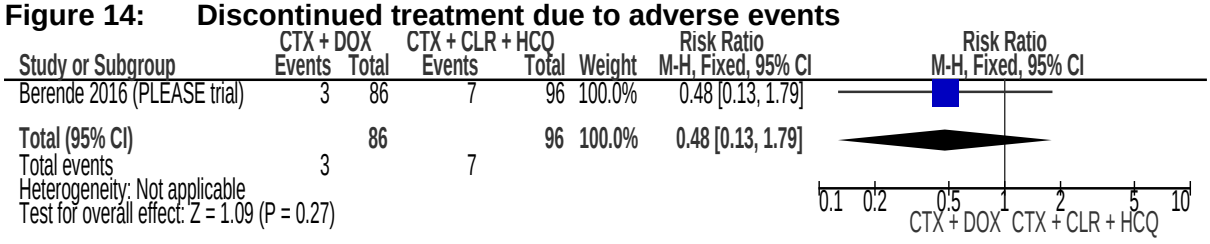


Figure 14: Discontinued treatment due to adverse events



E.4 Ceftriaxone (IV) followed by doxycycline (PO) versus ceftriaxone (IV)

E.4.1 Persistent Lyme disease symptoms

Figure 15: SF-36 (physical component – final values)

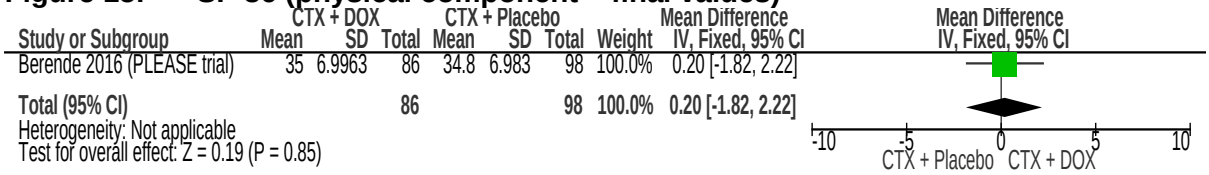


Figure 16: Adverse events

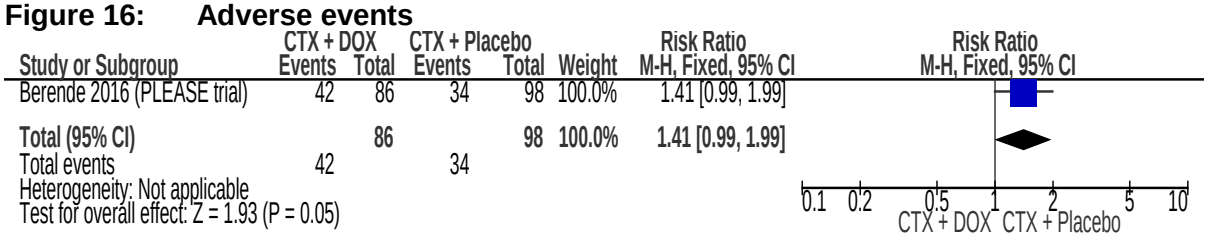
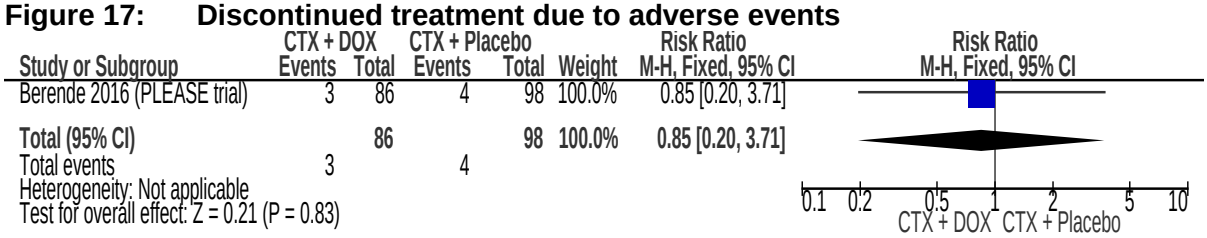


Figure 17: Discontinued treatment due to adverse events



E.5 Ceftriaxone (IV) followed by clarithromycin (PO) plus hydroxychloroquine versus ceftriaxone (IV)

E.5.1 Persistent Lyme disease symptoms

Figure 18: SF-36 (physical component – final values)

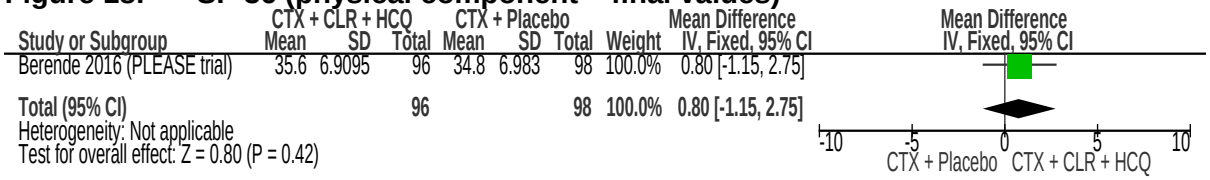


Figure 19: Adverse events

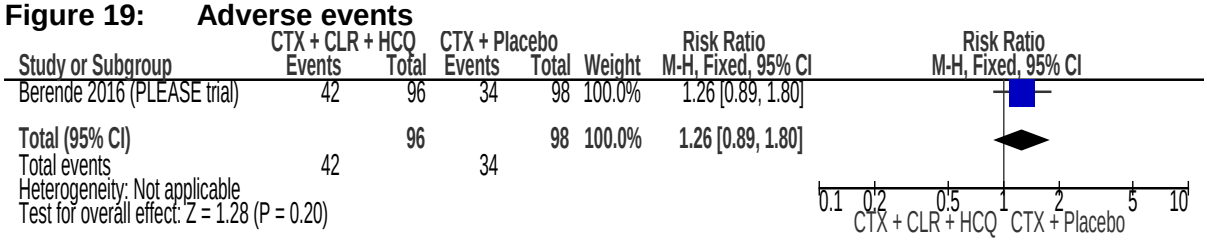
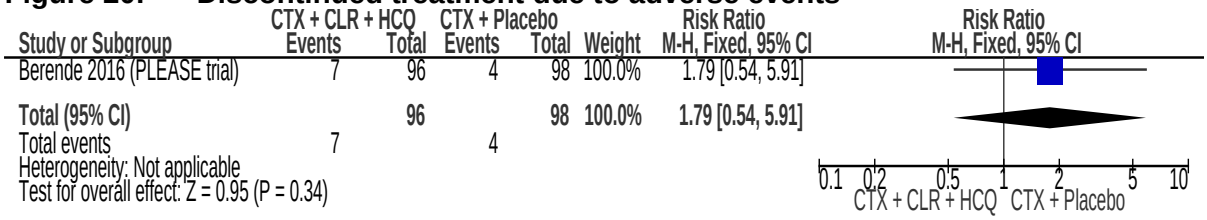


Figure 20: Discontinued treatment due to adverse events



Appendix F:GRADE tables

Table 14: Clinical evidence profile: Ceftriaxone (IV) followed by doxycycline (PO) versus placebo

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ceftriaxone plus doxycycline	Placebo	Relative (95% CI)	Absolute		
Improvement in quality of life at 180 days												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	23/57 (40.4%)	21/58 (36.2%)	RR 1.11 (0.7 to 1.77)	40 more per 1000 (from 109 fewer to 279 more)	⊕OOO VERY LOW	CRITICAL
Improvement in SF-36 (physical component) at 180 days; 0-100, higher values are beneficial												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	20/57 (35.1%)	15/58 (25.9%)	RR 1.36 (0.77 to 2.38)	93 more per 1000 (from 59 fewer to 357 more)	⊕⊕OO LOW	CRITICAL
Improvement in SF-36 (mental component) at 180 days; 0-100, higher values are beneficial												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	19/57 (33.3%)	22/58 (37.9%)	RR 0.88 (0.54 to 1.44)	46 fewer per 1000 (from 174 fewer to 167 more)	⊕OOO VERY LOW	CRITICAL
Adverse events at 90 days												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	16/64 (25%)	11/65 (16.9%)	RR 1.48 (0.74 to 2.93)	81 more per 1000 (from 44 fewer to 327 more)	⊕⊕OO 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 if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

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**		
Improvement in fatigue at 6 months												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	18/28 (64.3%)	5/27 (18.5%)	RR 3.47 (1.5 to 8.02)	457 more per 1000 (from 93 more to 1000 more)	⊕⊕⊕⊕ HIGH	CRITICAL
FSS-11 score at 6 months; 0-77, lower values are beneficial												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	26	22	Not applicable	MD 1.1 lower (1.89 to 0.31 lower)	⊕⊕OO LOW	CRITICAL
Change in FSS-11 score from baseline at 6 months; 0-77, lower values are beneficial												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	26	22	Not applicable	MD 0.8 lower (1.46 to 0.14 lower)	⊕⊕OO LOW	CRITICAL
Improvement in cognitive measure at 6 months												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	2/26 (7.7%)	2/22 (9.1%)	RR 0.85 (0.13 to 5.52)	14 fewer per 1000 (from 79 fewer to 411 more)	⊕⊕OO LOW	CRITICAL
A-A score at 6 months; cognitive processing speed measured in milliseconds, lower values are beneficial												
1	randomised	no serious	no serious	no serious	serious[2]	none	26	22	Not	MD 0.4 higher (0.38	⊕⊕⊕O	CRITICAL

	trials	risk of bias	inconsistency	indirectness					applicable	lower to 1.18 higher)	MODERATE	
Change in A-A score from baseline at 6 months; cognitive processing speed measured in milliseconds, lower values are beneficial												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	25	22	Not applicable	MD 0.2 higher (0.32 lower to 0.72 higher)	⊕⊕⊕O MODERATE	CRITICAL

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

Table 16: Clinical evidence profile: Ceftriaxone (IV) followed by doxycycline (PO) versus ceftriaxone (IV) followed by clarithromycin (PO) plus hydroxychloroquine

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ceftriaxone plus doxycycline**	**Ceftriaxone plus clarithromycin plus hydroxychloroquine**	**Relative (95% CI)**	**Absolute**		
SF-36 (physical component) at 14 weeks; 15-61 (norm-based T-score), general population score 50 (SD 10), higher values are beneficial												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious imprecision[2]	none	86	96	Not applicable	MD 0.6 lower (2.62 lower to 1.42 higher)	⊕⊕OO LOW	CRITICAL
Adverse events at 14 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	Serious[2]	none	42/86 (48.8%)	42/96 (43.8%)	RR 1.12 (0.82 to 1.53)	53 more per 1000 (from 79 fewer to 232 more)	⊕⊕OO LOW	IMPORTANT
Discontinued treatment due to adverse events at 14 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	3/86 (3.5%)	7/96 (7.3%)	RR 0.48 (0.13 to 1.79)	38 fewer per 1000 (from 63 fewer to 58 more)	⊕OOO VERY LOW	IMPORTANT

[1] People in the clarithromycin group also received hydroxychloroquine
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 17: Clinical evidence profile: Ceftriaxone (IV) followed by doxycycline (PO) versus ceftriaxone (IV)

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ceftriaxone plus doxycycline	Ceftriaxone	Relative (95% CI)	Absolute		
SF-36 (physical component) at 14 weeks; 15-61 (norm-based T-score), general population score 50 (SD 10), higher values are beneficial												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[1]	none	86	98	Not applicable	MD 0.2 higher (1.82 lower to 2.22 higher)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events at 14 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	42/86 (48.8%)	34/98 (34.7%)	RR 1.41 (0.99 to 1.99)	142 more per 1000 (from 3 fewer to 343 more)	⊕⊕⊕O MODERATE	IMPORTANT
Discontinued treatment due to adverse events at 14 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	3/86 (3.5%)	4/98 (4.1%)	RR 0.85 (0.2 to 3.71)	6 fewer per 1000 (from 33 fewer to 111 more)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 18: Clinical evidence profile: Ceftriaxone (IV) followed by clarithromycin (PO) plus hydroxychloroquine versus ceftriaxone (IV)

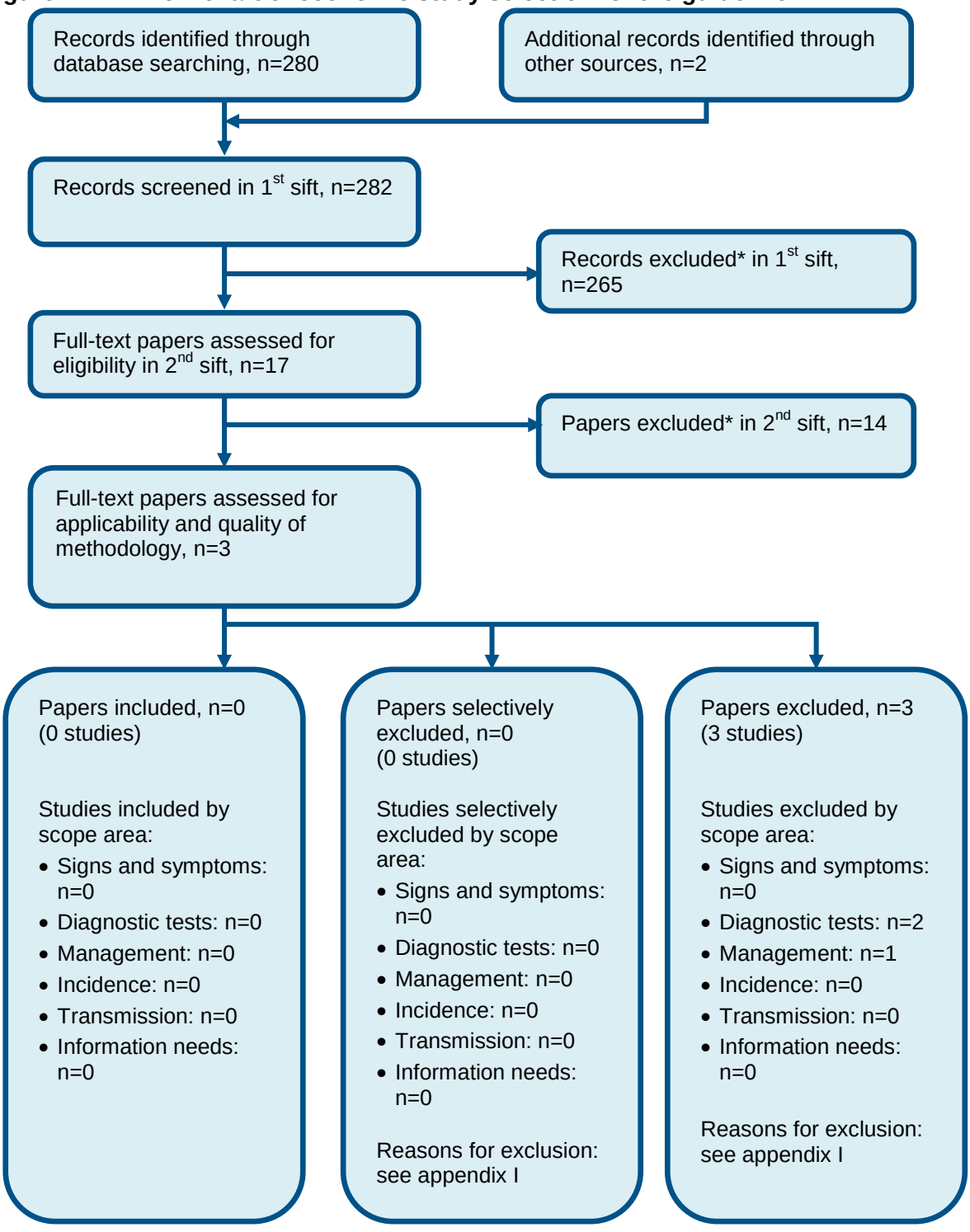
Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ceftriaxone plus clarithromycin plus hydroxychloroquine	Ceftriaxone	Relative (95% CI)	Absolute		

SF-36 (physical component) at 14 weeks; 15-61 (norm-based T-score), general population score 50 (SD 10), higher values are beneficial												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious imprecision[2]	none	96	98	Not applicable	MD 0.8 higher (1.15 lower to 2.75 higher)	⊕⊕OO LOW	CRITICAL
Adverse events at 14 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	Serious[2]	none	42/96 (43.8%)	34/98 (34.7%)	RR 1.26 (0.89 to 1.8)	90 more per 1000 (from 38 fewer to 278 more)	⊕⊕OO LOW	IMPORTANT
Discontinued treatment due to adverse events at 14 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	7/96 (7.3%)	4/98 (4.1%)	RR 1.79 (0.54 to 5.91)	32 more per 1000 (from 19 fewer to 200 more)	⊕OOO VERY LOW	IMPORTANT

[1] People in the clarithromycin group also received hydroxychloroquine
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Appendix G: Health economic evidence selection

Figure 21: 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 19: 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[17]	Excluded due to an incorrect study design
Berger 1986[16]	Excluded due to an incorrect study design
Bernardino 2009[18]	Excluded due to an incorrect study design
Bhate 2011[19]	Excluded due to an incorrect study design
Bjark 2016[20]	Not available
Borg 2005[23]	Excluded due to an incorrect study design
Bratton 2008[24]	Excluded due to an incorrect study design
Bremell 2014[25]	Excluded due to an incorrect study design
British Infection Association 2011[26]	Excluded due to an incorrect study design
Butler 1978[27]	Excluded due to an incorrect population
Cadavid 2016[28]	Excluded due to an incorrect study design
Canadian Paediatric Society 1992[29]	Excluded due to an incorrect study design
Chen 1999[31]	Excluded due to an incorrect outcome
Choo-Kang 2010[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[81]	Excluded due to an incorrect intervention
Kowalski 2010[83]	Excluded due to an incorrect outcome
Kowalski 2011[82]	Excluded due to an incorrect study design
Krbkova 1996[84]	Excluded due to an incorrect comparison
Kuhn 2012[86]	Excluded due to an incorrect study design
Laasila 2003[87]	Excluded due to an incorrect population
Lantos 2013[88]	Excluded due to an incorrect study design
Lauhio 1994[89]	Excluded due to an incorrect population
Lauhio 1991[90]	Excluded due to an incorrect population
Lempner 2002[78]	Excluded due to an incorrect study design
Liegner 1992[91]	Excluded due to an incorrect study design
Lipsker 2002[92]	Excluded due to an incorrect study design
Ljostad 2008[93]	Study abstract
Loewen 1999[94]	Excluded due to an incorrect study design

Reference	Reason for exclusion
Loewen 2000[95]	Excluded due to an incorrect study design
Luft 1988[97]	Excluded due to an incorrect outcome
Luft 1989[96]	Excluded due to an incorrect population
Maraspin 1995[103]	Excluded due to an incorrect study design
Maraspin 1996[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 study design
Maraspin 1999[101]	Excluded due to an incorrect study design
Maraspin 2002[102]	Excluded due to an incorrect population
Marks 2016[104]	Excluded due to an incorrect study design
McGill 1965[105]	Excluded due to an incorrect population
Meyerhoff 2002[106]	Excluded due to an incorrect study design
Meyerhoff 2016[107]	Excluded due to an incorrect study design
Millner 1996[108]	Excluded due to an incorrect outcome
Millner 1996[109]	Excluded due to an incorrect outcome
Morales 2000[110]	Excluded due to an incorrect study design
Muellegger 1995[112]	Excluded due to an incorrect study design
Muellegger 1996[111]	Excluded due to an incorrect comparison
Mullegger 1991[113]	Excluded due to an incorrect outcome
Nadelman 1993[115]	Excluded due to an incorrect study design
Nadelman 2001[114]	Excluded due to an incorrect population
Naglo 1989[116]	Excluded due to an incorrect study design
Neumann 1987[119]	Excluded due to an incorrect study design
Nimmrich 2014[121]	Excluded due to an incorrect study design
Nowakowski 2000[122]	Excluded due to an incorrect study design
Nowakowski 1995[123]	Excluded due to an incorrect study design
Ogrinc 2006[124]	Excluded due to an incorrect population
Oksi 1999[125]	Excluded due to an incorrect study design
Oksi 2007[126]	Excluded due to an incorrect population
Oksi 1998[127]	Excluded due to an incorrect population
Peltomaa 1998[128]	Excluded due to an incorrect comparison
Pena 1999[129]	Excluded due to an incorrect study design
Perronne 2015[130]	Not available
Pfister 1988[131]	Excluded due to an incorrect outcome
Pirila 1951[134]	Excluded due to an incorrect study design
Plorer 1993[135]	Excluded due to an incorrect study design
Plotkin 1991[136]	Excluded due to an incorrect study design
Puchalska 1996[137]	Excluded due to an incorrect study design
Puri 2015[138]	Excluded due to an incorrect comparison
Puri 2015[139]	Excluded due to an incorrect study design
Rebman 2015[140]	Excluded due to an incorrect study design
Renaud 2004[141]	Excluded due to an incorrect study design
Rohacova 1996[142]	Excluded due to an incorrect comparison
Rose 1994[143]	Excluded due to an incorrect study design
Rose 1996[144]	Excluded due to an incorrect intervention

Reference	Reason for exclusion
Rubin 1992[145]	Excluded due to an incorrect study design
Salazar 2005[146]	Excluded due to an incorrect intervention
Salazar 1993[147]	Excluded due to an incorrect study design
Sanchez 2016[148]	Excluded due to an incorrect study design
Sandstrom 1989[149]	Excluded due to an incorrect study design
Schmidt 1995[150]	Excluded due to an incorrect study design
Selby 2008[151]	Excluded due to an incorrect study design
Shadick 1994[152]	Excluded due to an incorrect study design
Shadick 1999[153]	Excluded due to an incorrect study design
Shemenski 2016[154]	Excluded due to an incorrect study design
Shoemaker 2006[155]	Excluded due to an incorrect intervention
Sjowall 2012[157]	Excluded due to an incorrect intervention
Sjowall 2011[156]	Excluded due to an incorrect study design
Skogman 2003[159]	Excluded due to an incorrect intervention
Skogman 2008[158]	Excluded due to an incorrect study design
Skoldenberg 1988[160]	Excluded due to an incorrect study design
Smith 2002[161]	Excluded due to an incorrect study design
Solomon 1998[162]	Excluded due to an incorrect intervention
Spathling 1992[163]	Article not in English
Stanek 1999[164]	Excluded due to an incorrect study design
Steere 1980[168]	Excluded due to an incorrect study design
Steere 1983[169]	Excluded due to an incorrect study design
Steere 1987[165]	Excluded due to an incorrect study design
Steurer 2016[170]	Article not in English
Stricker 2011[171]	Excluded due to an incorrect study design
Stricker 2010[172]	Excluded due to an incorrect study design
Strle 1996[173]	Excluded due to an incorrect outcome
Strle 1996[174]	Excluded due to an incorrect outcome
Strle 1992[175]	Excluded due to an incorrect study design
Strle 1993[176]	Excluded due to an incorrect outcome
Stupica 2015[178]	Excluded due to an incorrect comparison
Stupica 2011[177]	Excluded due to an incorrect comparison
Suarez-Magdalena 2017[179]	Not available
Thompson 2012[180]	Excluded due to an incorrect study design
Thorstrand 2002[181]	Excluded due to an incorrect study design
Thyresson 1949[182]	Excluded due to an incorrect study design
Torbahn 2016[183]	Excluded due to an incorrect study design
Tory 2010[184]	Excluded due to an incorrect comparison
Tseng 2017[185]	Excluded due to an incorrect outcome
Valesova 1996[186]	Excluded due to an incorrect comparison
Vazquez 2003[188]	Excluded due to an incorrect study design
Vazquez-Lopez 2016[187]	Excluded due to an incorrect study design
Wahlberg 1994[189]	Excluded due to an incorrect intervention
Weber 1988[191]	Excluded due to an incorrect study design
Weber 1987[190]	Excluded due to an incorrect population

Reference	Reason for exclusion
Weissenbacher 2005[192]	Excluded due to an incorrect intervention
White 2013[193]	Excluded due to an incorrect study design
Zochling 1996[194]	Excluded due to an incorrect study design

I.2 Excluded health economic studies

Table 20: Studies excluded from the health economic review

Reference	Reason for exclusion
None	None