ORIGINAL ARTICLE

Efficacy and safety of pharmacological treatments for acute Lyme neuroborreliosis – a systematic review

R. Dersch[a,b], M. H. Freitag[c], S. Schmidt[a,d], H. Sommer[a,e], S. Rauer[b] and J. J. Meerpohl[a]

[a]*German Cochrane Centre, Medical Center – University of Freiburg, Freiburg;* [b]*Department of Neurology, Medical Center – University of Freiburg, Freiburg;* [c]*Division of General Practice, Department of Health Services Research, Carl von Ossietzky University Oldenburg, Oldenburg;* [d]*UroEvidence@Deutsche Gesellschaft für Urologie, Berlin; and* [e]*Institute of Medical Biometry and Statistics, Medical Center – University of Freiburg, Freiburg, Germany*

Keywords:
decision making, drug treatment, Lyme disease, Lyme neuroborreliosis, meta-analysis, non-randomized studies, randomized controlled trials, systematic review

Received 19 February 2015
Accepted 6 April 2015

European Journal of Neurology 2015, **0:** 1–11

doi:10.1111/ene.12744

Background and purpose: Our aim was to evaluate the available evidence for pharmacological treatment of acute Lyme neuroborreliosis as a basis for evidence-based clinical recommendations in a systematic review.

Methods: A systematic literature search of Medline, EMBASE, the Cochrane Library and three trial registries was performed. Randomized controlled trials (RCTs) and non-randomized studies (NRS) were evaluated. Risk of bias was assessed using the Cochrane risk of bias tools. The primary outcome was 'residual neurological symptoms' whilst the secondary outcomes were disability, quality of life, pain, fatigue, depression, cognition, sleep, adverse events and cerebrospinal fluid pleocytosis. The quality of the evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Results: After screening 5779 records, eight RCTs and eight NRS were included. Risk of bias was generally high. No statistically significant difference was found between doxycycline and beta-lactam antibiotics in a meta-analysis regarding residual neurological symptoms at 4–12 months [risk ratio (RR) 1.27, 95% confidence interval (CI) 0.98–1.63, $P = 0.07$] or adverse events (RR 0.82, 95% CI 0.54–1.25, $P = 0.35$). Significantly fewer neurological symptoms for cefotaxime compared with penicillin were found (RR 1.81, 95% CI 1.10–2.97, $P = 0.02$). Adverse events were significantly fewer for penicillin (RR 0.56, 95% CI 0.38–0.84, $P = 0.005$).

Conclusions: Evidence regarding pharmacological treatment of acute Lyme neuroborreliosis is scarce and therefore insufficient to recommend preference of beta-lactam antibiotics over doxycycline or vice versa. However, due to considerable imprecision, relevant differences between treatments cannot be excluded. No evidence suggesting benefits of extended antibiotic treatments could be identified. Further well-designed trials are needed. Individual treatment decisions should address patients' preferences and individual conditions like prior allergic reactions.

Introduction

Lyme neuroborreliosis is a tick-borne infectious disease caused by the spirochete bacterium *Borrelia burgdorferi*. Diagnosis of Lyme neuroborreliosis is based on clinical presentation, serological testing, and analysis of cerebrospinal fluid (CSF) [1]. Tiered case definitions exist regarding the likelihood of diagnosis on the basis of diagnostic results [2,3]. Controversy exists in the field of therapy, whereby choice, route of administration and length of treatment are the subject of intense debate. This is further illustrated by

Correspondence: R. Dersch, Department of Neurology, Medical Center – University of Freiburg, Breisacher Str. 64, D-79104 Freiburg, Germany (tel.: +49 (0) 761-270-51500; fax: +49 (0)761-270-53380; e-mail: Rick.Dersch@uniklinik-freiburg.de).

EUROPEAN JOURNAL OF NEUROLOGY

contradicting recommendations in different guidelines, some of which are aggressively advocated by patient support groups [4]. For instance, whilst the guidelines of the Infectious Diseases Society of America (IDSA) and the European Federation of Neurological Societies (EFNS) and the practice parameters of the American Academy of Neurology (AAN) recommend antibiotic treatment with a duration of 14–28 days [1,5,6], those of the International Lyme and Associated Diseases Society (ILADS) stipulate that, often, months of antibiotic therapy are required [7]. IDSA, EFNS and AAN guidelines recommend antibiotics such as cephalosporins, penicillin or doxycycline, whereas ILADS also recommends treatment with other substances like carbapenems and metronidazole or antimalarial drugs such as hydroxychloroquine [7]. These contradicting recommendations lead to considerable ambiguity and doubt in patients and healthcare providers alike when facing treatment decisions for neuroborreliosis. Therefore, it seems necessary to review and rigorously evaluate in an up-to-date systematic review the available evidence for drug treatment of acute neuroborreliosis as a sound basis for evidence-based clinical recommendations. To adequately consider the wealth of research that has been conducted and to overcome the limitations of availability of only a few randomized controlled trials (RCTs), this review also considered non-randomized studies (NRS) for the treatment of acute Lyme neuroborreliosis. For certain aspects, NRS may also be more suitable than RCTs, for example for the detection of rare adverse events [8].

Methods

Search strategy and eligibility criteria

All randomized and non-randomized studies evaluating pharmacological treatment of adult patients with clinically diagnosed acute Lyme neuroborreliosis were screened for eligibility. The results of studies reporting no comparison group for an intervention were considered for descriptive reporting. Studies without a control group were not used to calculate pooled estimates and were not subject to a separate risk of bias assessment. Studies with a population of less than five patients were excluded. Lyme neuroborreliosis diagnoses were based on the clinical case definitions of Kaiser, Halperin *et al.* and Mygland *et al.* [2,3,9]. The diagnostic criteria for the case definitions were described in detail in our published review protocol (systematic review registration CRD42014008839) [10]. Studies on patients with 'post-Lyme disease', defined as previously treated people with persistent symptoms in the absence of evidence for ongoing infection, were excluded. All pharmacological treatments, including combinations of treatments, were considered. Single agents as well as groups of antibiotics were compared with each other. Three databases were searched, Medline (via Ovid, from 1950 to the present), EMBASE (via Scopus, from 1980 to the present) and the Cochrane Central Register of Controlled Trials, for eligible studies. The reference lists of the included studies were reviewed for further eligible studies. The search strategies are shown in Appendix S1. No language restrictions were used. Additionally, three trial registers (www.controlled-trials.com, www.clinicaltrials.gov, www.who.int/trialsearch/) were searched to identify additional published, unpublished or ongoing studies.

The primary outcome was residual neurological symptoms after treatment, defined as any neurological signs or symptoms reported by the original authors. If several time points were reported in a primary study, data from the last reported time point were considered. If the data permitted, the results were presented for short-term follow-up (4–12 months) and long-term follow-up (12 or more months following treatment). Initially it was planned to assess the outcome of neurological symptoms as a continuous outcome. However, the majority of included studies reported the outcome as dichotomous data, so the results are presented accordingly. If the neurological symptoms were reported as continuous or categorical variables, the data were appropriately dichotomized according to the measurement scales and categories used. Secondary outcomes were adverse events, overall disability, patient-reported outcomes (quality of life, pain, fatigue, depression, cognition and sleep) and CSF pleocytosis. Adverse events were considered as defined and reported by the original authors. Adverse events were reported as serious adverse events that required hospitalization, were life-threatening, fatal, or when reported as serious adverse events by the original authors.

Data extraction and analysis

First, one reviewer (RD) evaluated titles and abstracts to determine the eligibility of the studies. Secondly, each full text was independently evaluated by two reviewers (RD, SS or MF) for eligibility. Disagreements were resolved by discussion with a third reviewer (JM). Two review authors independently extracted data from the full texts of included studies using a specifically developed extraction form. The data were entered into Review Manager (RevMan 5.3; for details see our review protocol) [10]. The assessment of risk of bias in the RCTs was performed

independently by two reviewers according to the Cochrane risk of bias tool [11]. In the event of disagreement, consensus was achieved through discussion with all the review authors. It was initially planned to assess risk of bias in the NRS with both the ACROBAT-NRSI tool (which was not yet released at the protocol stage) and the Newcastle–Ottawa scale (NOS) [12,13]. During the review process, the ACROBAT-NRSI was officially released, so it was decided to omit the NOS assessment to avoid duplicity. According to the recommendations for the ACROBAT-NRSI, studies which were assessed as having a 'critical' risk of bias were not included in any data synthesis. Their results were reported descriptively.

Risk for publication bias was reduced in our systematic review by ensuring a comprehensive search for eligible studies, including three trial registries. Only a small number of studies were available for the different comparisons, so funnel plots were not used.

The pooling of the data and the meta-analysis of the studies were only considered amongst studies with a similar design and limited heterogeneity. Heterogeneity amongst studies was investigated using the χ^2 and I^2 tests. The estimation of treatment effects was based on a fixed effect model according to the Mantel–Haenszel method. Subgroup analyses were planned to consider drug dosage, geographical origin of studies, length of treatment and case definition. Sensitivity analyses were planned to assess the effect of risk of bias in the included studies. Whenever possible, the data were analysed on an intention-to-treat basis. If the data were only available in a graphical format, a thorough estimation of the numerical values was conducted.

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach was used to assess the quality of the evidence for each outcome [14].

Results

The search identified 5779 bibliographic records after the removal of duplicates, of which 5660 were excluded and 119 full-text articles were retrieved for detailed examination. Sixteen publications met our inclusion criteria (Fig. 1) [15–29]; 17 single-arm studies were considered for descriptive analysis (Appendix S2 and Table S1). Eighty-six articles were excluded (reasons are listed in Fig. 1). The search in the trial registries revealed no eligible unpublished studies; information on one ongoing study on the treatment of Lyme neuroborreliosis is shown in Table S2 [30].

Details on participants and interventions are summarized in Table 1. Similar interventions were combined to compare the effects of different classes of antibiotic agents. The length of treatment was between 14 and 21 days in all but one RCT [16]. The NRS showed considerable differences regarding length of treatment, from 10 to 30 days, with some studies not specifying the length of treatment at all.

Neurological symptoms after treatment were measured with a clinical score in one RCT [15]; all other studies measured neurological symptoms on the basis of clinical examination or self-reports by patients. Adverse events were reported in five RCTs and two NRS [15–17,19,21,23,24]. Disability and sleep were not reported in any study. Patient-reported outcomes were reported in one RCT [15]. Two studies reported data on pain [22,31], but not for our predefined time points. CSF pleocytosis was reported in two RCTs [15,17]. Seventeen single-arm studies meeting our inclusion criteria were found. The length and choice of treatment were heterogeneous, as was the proportion of patients with neurological symptoms after treatment. No case series reported durations of treatment longer than 30 days (Appendix S2 and Table S1). No eligible studies comparing extended antibiotic treatments of 14–21 days could be identified.

Due to poor reporting, detailed data could only be extracted from a few studies. Consequently, there was serious risk of bias issues with most studies. The RCTs suffered from poor reporting on allocation concealment, random sequence generation, and blinding (Fig. S1), and selective reporting could not be ruled out in any of the studies. Risk of bias and poor reporting were even more problematic in the NRS (Fig. S2). Sampling bias, baseline confounding, and lack of blinding of outcome assessment were major issues in all the studies. Interventions were often insufficiently described, and patients were omitted without stating appropriate reasons. All but one NRS had a 'critical' overall risk of bias [23].

Three RCTs with a total of 229 patients reported data on treatment with beta-lactam antibiotics (ceftriaxone [15] and penicillin [17,20]) compared with doxycycline. Regarding the primary outcome of residual neurological symptoms at 4–12 months after treatment initiation, the data from these RCTs suggest that patients treated with beta-lactam antibiotics had more residual symptoms compared to patients treated with doxycycline; however, this was not statistically significant [Fig. 2; risk ratio (RR) 1.27, 95% confidence interval (CI) 0.98–1.63, $P = 0.07$].

Data from two prospective cohort studies [23,24] with a total of 122 patients and four retrospective cohort studies [25,27–29] with a total of 48 patients showed no statistically significant difference between the two treatments regarding the outcome residual

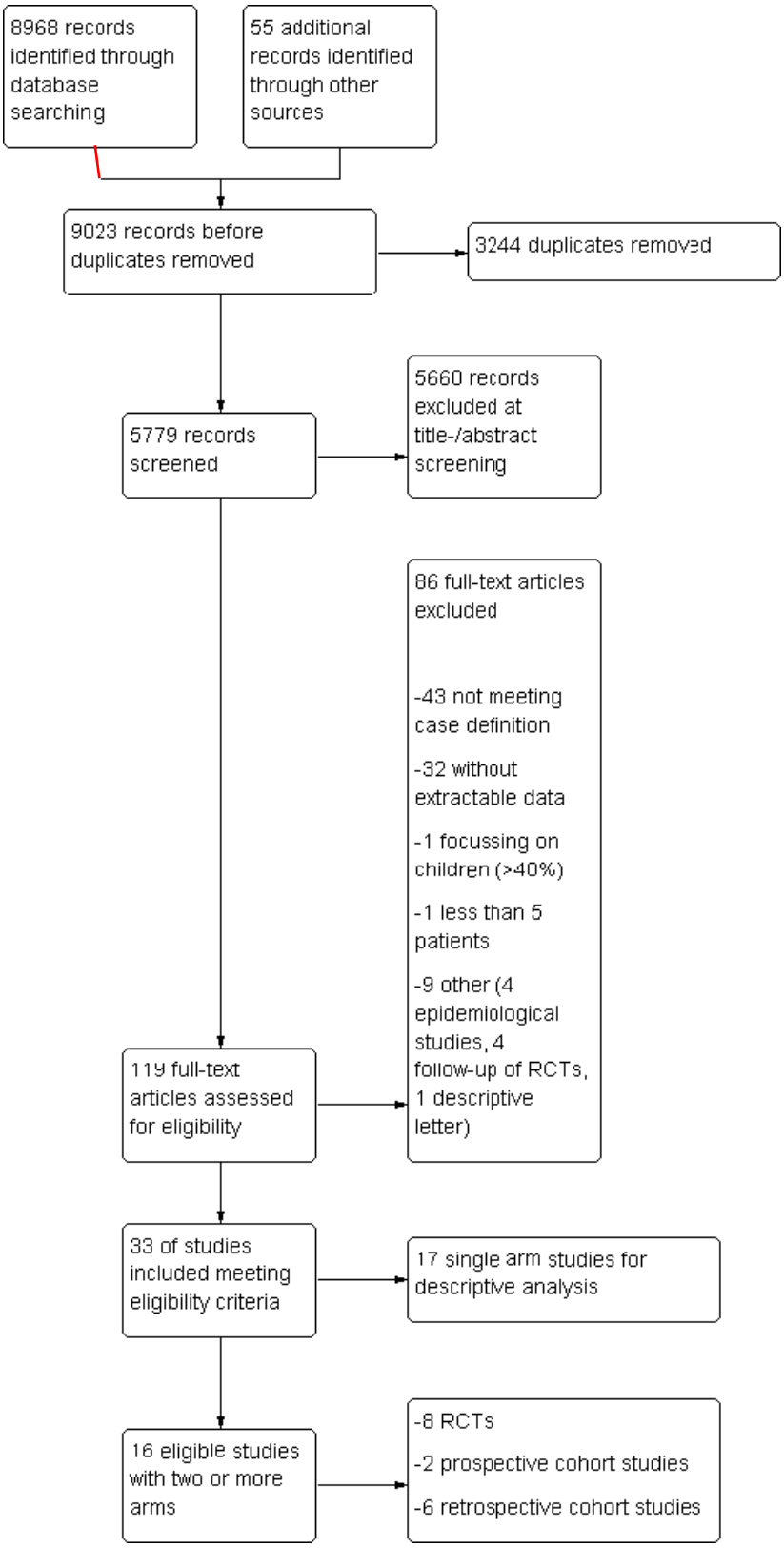

Figure 1 Study flow diagram.

Table 1 Characteristics of included studies

Study, first author	Sample size	Case definition	Intervention	Length of treatment	Setting	Country
RCTs						
Ljostad 2008 [15]	118	Definite (n = 71) Possible (n = 31)	Ceftriaxone 2 g/day (n = 59) Doxycycline 200 mg/day (n = 59)	14 days	Tertiary care centre	Norway
Oksi 1998 [16]	60	Possible	Cefixime 200 mg + probenecid 500 mg (n = 30) Amoxicillin 500 mg + probenecid 500 mg (n = 30)	100 days	Tertiary care centre	Finland
Karlsson 1994 [17]	54	Probable	Penicillin G 12 g/day (n = 23) Doxycycline 200 mg/day (n = 31)	14 days	Tertiary care centre	Sweden
Pfister 1991 [18]	33	Probable	Ceftriaxone 2 g/day (n = 17) Cefotaxime 8 g/day (n = 16)	10 days	Tertiary care centre	Germany
Hassler 1990 [19]	135	Possible	Penicillin G 20 MioU/day (n = 44) Cefotaxime 6 g/day (n = 49)	10 days	Tertiary care centre	Germany
Kohlhepp 1989 [20]	75	Possible	Penicillin G 20 MioU/day (n = 36) Doxycyclin 100 mg/day (200 mg at 1 day) (n = 39)	10 days	Tertiary care centre	Germany
Pfister 1989 [21]	21	Possible	Cefotaxime 6 g/day (n = 11) Penicillin G 20 MioU/day (n = 10)	10 days	Tertiary care centre	Germany
Pfister 1988 [22]	21	Possible	Penicillin/ doxycycline + methylprednisolone 60 mg/day Penicillin/doxycycline + placebo	7 days	Tertiary care centre	Germany
Prospective cohort studies						
Borg 2005 [23]	65	Probable	Ceftriaxone 2 g/day (n = 29) Doxycycline 400 mg/day (n = 36)	10–14 days	Two tertiary care centres	Sweden and Slovenia
Berglund 2002 [24]	70	Probable	Penicillin G (n = 18), doxycycline (n = 39), combinations (n = 13) Dose not standardized	Not stated	Teritary care centre	Sweden
Retrospective cohort studies						
Elamin 2010 [25]	15	Possible	Doxycycline (n = 4), cefotaxime/ ceftriaxone (n = 7), amoxicillin (n = 2), unknown (n = 2) Dose not stated	Not stated	Tertiary care centre	Ireland
Krüger 1990 [26]	123	Possible	Penicillin G 20 MioU/day (n = 46), doxycycline 100 mg (200 mg at 1 day, n = 20), no treatment (n = 57)	10–13 days	Tertiary care centre	Germany
Viader 1989 [27]	12	Possible	Penicillin (n = 7), penicillin + ampicillin (n = 2), penicillin + doxycycline (n = 1), doxycycline (n = 1), methylprednisolone (n = 1) Dose not stated	10–30 days	Tertiary care centre	France
Bateman 1988 [28]	8	Probable	Penicillin (n = 1), tetracycline (n = 1), combination (n = 5), no treatment (n = 1) Dose not stated	Not stated	Tertiary care centre	UK
Hirsch 1987 [29]	34	Possible	Penicillin G 20 MioU/day (n = 8), tetracycline oral (n = 17), symptomatic treatment (n = 9)	Tetracycline 15 days Penicillin 10 days	Tertiary care centre	France
Kristoferitsch 1987 [31]	43	Possible	Penicillin G 20 MioU/day (n = 19), no treatment (n = 24)	10 days	Tertiary care centre	Austria

neurological symptoms (not shown). A quantitative synthesis was not justified due to the overall critical risk of bias in all but one of these studies [23]. Regarding the primary outcome of residual neurological symptoms at 12 or more months after treatment, no significant difference could be found between

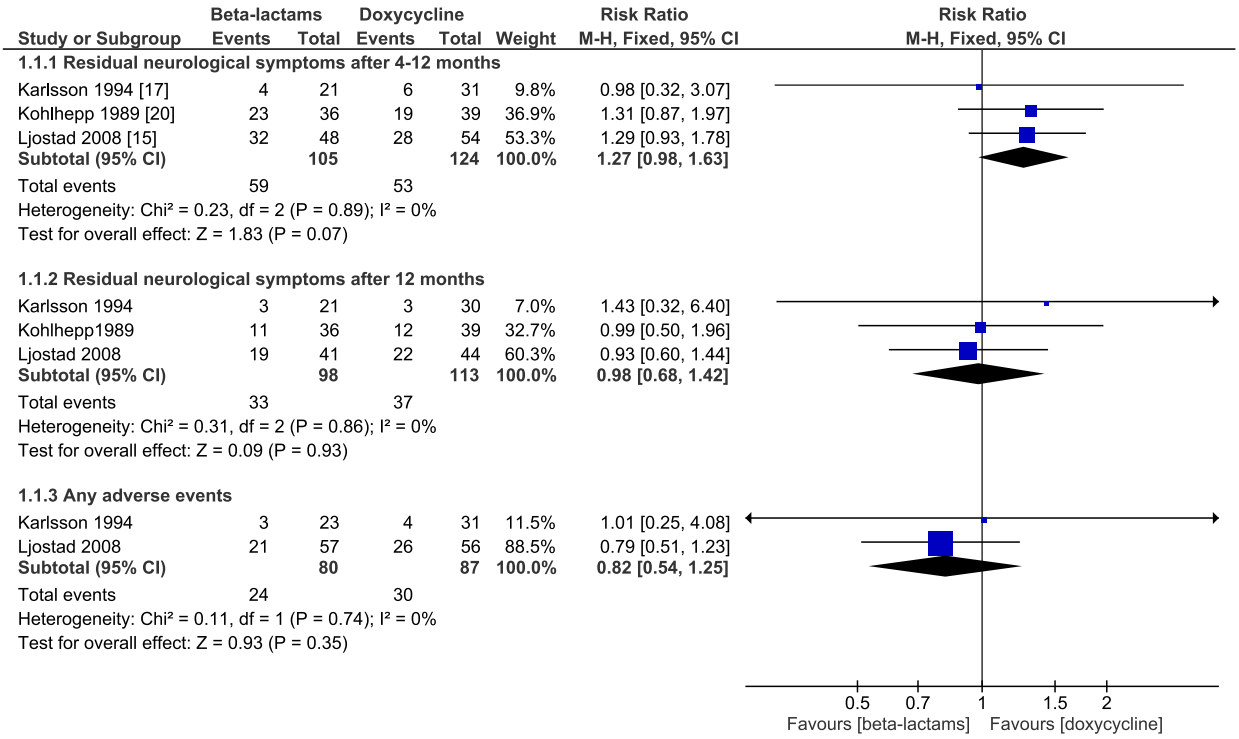

Figure 2 Comparison of beta-lactams versus doxycycline for 'residual neurological symptoms' and adverse events. Forest plot for the comparison beta-lactams versus doxycycline for the outcomes 'residual neurological symptoms' at 4 or more months and 12 months after treatment and adverse events.

treatment with beta-lactam antibiotics and doxycycline in the RCTs (Fig. 2; RR 0.98, 95% CI 0.68–1.42, $P = 0.93$) [15,17,20].

The difference in patients reporting adverse events between doxycycline and beta-lactam antibiotics was not statistically significant in two RCTs with a total of 167 patients (Fig. 2; RR 0.82, 95% CI 0.54–1.25, $P = 0.35$) [16,18]. Two prospective cohort studies consisting of a total of 122 patients reported indecisive results (not shown) [23,24]. The adverse events reported were diarrhoea, nausea, constipation, rash, vertigo and thrombophlebitis. Reports of serious adverse events in the RCTs were too scarce to allow a valid comparison. The serious adverse events reported were cholecystitis, stomatitis, allergic reactions and duodenal ulcers. The NRS did not provide information on serious adverse events.

Secondary outcomes – quality of life, fatigue, cognition and depression – were reported in patients from one study in three separate follow-up reports [15,32–34]. Only data on quality of life and fatigue were reported on the basis of treatment groups. The original authors reported no statistically significant differences in quality of life or fatigue between treatment with doxycycline or ceftriaxone at 30 months after treatment (Fig. S3). Two RCTs reported data on CSF pleocytosis for treatment with doxycycline or beta-lactam antibiotics, albeit in different ways, so the data could not be combined in a meta-analysis [15,17]. None of the studies reported significant differences between the two treatments in terms of CSF pleocytosis.

Two RCTs compared cefotaxime and penicillin treatments [19,21]. The combined estimates from a total of 114 patients showed that treatment with cefotaxime results in statistically significantly fewer residual neurological symptoms compared to penicillin after 4–12 months (Fig. 3; RR 1.81, 95% CI 1.10–2.97, $P = 0.02$). No data were available for the time point of 12 months after treatment. Adverse events were reported in one RCT with 138 patients for this comparison [19]. The difference between patients with adverse events for penicillin and cefotaxime was statistically significant, favouring the penicillin group (Fig. 3; RR 0.54, 95% CI 0.35–0.83, $P = 0.005$). The adverse events reported were mild diarrhoea and Herxheimer-like reactions. Serious adverse events were reported in one RCT [19], albeit with low event rates (4/138 patients overall). The serious adverse events reported were colitis, shock and allergic reactions.

Two retrospective cohort studies consisting of a total of 18 patients reported data on neurological symptoms

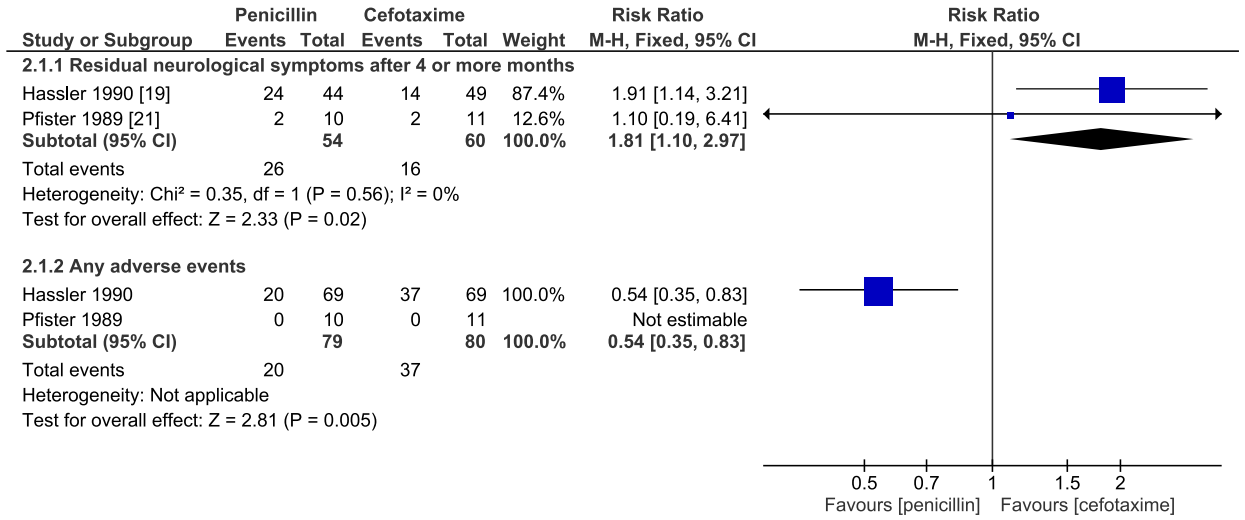

Figure 3 Comparison of penicillin versus cefotaxime for 'residual neurological symptoms' and adverse events. Forest plot for the comparison penicillin versus cefotaxime for the outcomes 'residual neurological symptoms' at 4 months after treatment and patients with adverse events.

after treatment with combinations of antibiotics versus single drug applications [27,28]. As they had an overall critical risk of bias and were heterogeneous, no quantitative synthesis was performed (Fig. S4).

Three retrospective cohort studies consisting of a total of 173 participants reported data on treatment with antibiotics versus no treatment [26,29,31]. A quantitative synthesis was not justified due to the overall critical risk of bias in all three studies. One of these studies made suggestions on the benefit of treatment whilst the other two did not. None of these studies reported a statistically significant difference (Fig. S5).

None of our pre-planned subgroup and sensitivity analyses considering dose, geographical origin, length of treatment, likelihood of diagnosis or risk of bias was possible for any comparison due to the paucity of data.

The quality of evidence was rated according to the GRADE approach (Tables 2, 3, and S3, S4). Risk of bias in the NRS as well as in the RCTs, as assessed with the corresponding risk of bias tools, was generally high, considerably lowering the overall confidence in the presented results. The reasons for downrating the quality of evidence were mainly risk of bias and the imprecision of the results in the RCTs and risk of bias, indirectness and imprecision in the NRS.

Conclusions

To gather all relevant studies, a comprehensive literature search in three databases and trial registers was performed. Statistical investigation of publication bias and small study effects was not possible due to the limited number of available studies. The level of applicability may have been hampered as only a few studies yielding relevant data could be found, so the results come from small study populations. Due to the small number of studies included in the meta-analyses and the considerable risk of bias, only limited conclusions can be drawn from them. Different strains of *Borrelia burgdorferi* show different patterns of geographical distribution. As all the eligible studies were conducted in Europe, the results from this review may be less applicable to regions with different distributions of these strains, as in the case of North America. The spectrum of disease included mainly cranial neuropathies, polyradiculoneuritis or meningitis. Patients with potentially more severe affections, such as cerebral vasculitis, were seldom reported. Whether these patients would benefit from alternative treatments (e.g. a combination of antibiotics with steroids or platelet aggregation inhibitors) remains unclear.

In a systematic review of eight studies, Halperin *et al*. [6] reported no statistically significant difference between doxycycline and beta-lactam antibiotics on the clinical response outcome. These results are in line with our findings on the comparison between doxycycline and beta-lactam antibiotics on neurological symptoms. The authors did not perform a risk of bias assessment, included studies focusing on children, and pooled data from studies of different designs. Several studies considered in our review were not included by these authors. An ongoing Cochrane review on neurological complications of Lyme disease focuses on RCTs only and has stricter inclusion criteria. It is

Table 2 GRADE evidence table for the comparison beta-lactams versus doxycycline for the treatment of acute Lyme neuroborreliosis

Quality assessment							No. of patients (%)		Effect	
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Beta-lactams	Doxycycline	Relative risk (95% CI)	Quality
Residual neurological symptoms (follow-up 4–12 months)										
3	Randomized trials	Serious[a]	Not serious	Not serious	Serious[b]	None	59/105 (56.2)	53/124 (42.7)	RR 1.27 (0.98–1.63)	⊕⊕◯◯ LOW
Residual neurological symptoms (follow-up 12 or more months)										
3	Randomized trials	Serious[a]	Not serious	Not serious	Serious[c]	None	33/98 (33.7)	37/113 (32.7)	RR 0.98 (0.68–1.42)	⊕⊕◯◯ LOW
Adverse events										
3	Randomized trials	Serious[a]	Not serious	Not serious	Serious[c]	None	24/80 (30.0)	30/87 (34.5)	RR 0.82 (0.54–1.25)	⊕⊕◯◯ LOW

[a]Two unblinded trials, concerns about allocation concealment and selective reporting; [b]Small sample size, optimal information size not met, relevant benefit for doxycycline cannot be excluded; [c]Optimal information size not met, relevant benefit for either beta-lactams or doxycycline cannot be excluded.

Table 3 GRADE evidence table for the comparison penicillin versus cefotaxime for the treatment of acute Lyme neuroborreliosis

Quality assessment							No. of patients (%)		Effect	
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Penicillin	Cefotaxime	Relative risk (95% CI)	Quality
Neurological symptoms (follow-up 4 or more months)										
2	Randomized trials	Serious[a]	Not serious	Not serious	Serious[b]	None	26/54 (48.1)	16/60 (26.7)	RR 1.81 (1.1–2.97)	⊕⊕◯◯ LOW
Adverse events										
2	Randomized trials	Serious[a]	None[c]	Not serious	Serious[b]	None	20/79 (25.3)	37/80 (46.3)	RR 0.54 (0.35–0.83)	⊕⊕◯◯ LOW

[a]No blinding, concerns about allocation concealment and selective reporting; [b]Small sample size, optimal information size not met; [c]One study reports no adverse events for both interventions, so provided estimates derive from only one study. Inconsistency cannot be excluded.

possible that its scope may be narrower than that of our review [35].

Implications for practice

The literature on pharmacological treatments of acute Lyme neuroborreliosis is scarce and of limited quality. As such, drawing conclusions for clinical practice from the available body of evidence is difficult. Three heterogeneous studies with considerable risk of bias compared antibiotic treatment to no treatment and showed imprecise and contradictory results. However, considering reports of severe disabilities following untreated neuroborreliosis, it seemes unethical to omit treatment [36].

The available evidence is insufficient to support recommendations preferring beta-lactam antibiotics over doxycycline or vice versa. However, due to the small sample sizes of the eligible studies and the resulting imprecision, relevant differences between treatments regarding both harms and benefits cannot be excluded. Whilst treatment with cefotaxime leads to a lower rate of residual neurological symptoms compared to penicillin, a greater number of patients report adverse events from cefotaxime. The reported adverse events were generally mild and may only partially influence treatment choice. Due to the low event rates for serious adverse events, it was not possible to perform an informative comparison.

The relevance of these findings, statistically significant or not, remains unclear. Confidence intervals were wide, even for statistically significant differences, whereas the non-significance of other differences could be due to rather low sample sizes.

Regarding the comparison between single drugs versus drug combinations, small event rates were reported in primary studies and therefore the CIs of the estimates were too wide to draw accurate conclusions.

It was not possible to identify studies on doses of doxycycline of >200 mg/day, so no recommendations could be made regarding the use of higher doses. Only one study reported a length of treatment of >30 days. No evidence was found of further extended antibiotic courses as studies (not even single-arm studies) addressing this question could not be identified. Studies suggesting benefits of extended antibiotic treatments compared to treatments of <30 days could not be identified. Moreover, studies evaluating hydroxychloroquine, carbapenem antibiotics or metronidazole could not be identified. Individual treatment decisions should address patients' preferences as to the route of administration, the risk of adverse events and other individual conditions, such as prior allergic reactions.

Implications for research

Due to considerable imprecision in the calculated estimates, it is likely that the results of future RCTs on this topic may change the findings presented here. Currently, only one ongoing study compares ceftriaxone and doxycycline treatments in Lyme neuroborreliosis [30]. There is clearly a need for large high quality trials evaluating pharmacological treatments for acute Lyme neuroborreliosis. The included population should be adequately described according to consensually derived case definitions [37], and trials should be registered prior to the enrolment of the first patient and should use predefined outcomes. Of considerable interest are trials regarding different lengths of treatment. Another relevant question is whether disease manifestations of different levels of severity require different therapeutic approaches. Trials should also address whether doxycycline is of comparable efficacy to beta-lactam antibiotics in the treatment of more severe manifestations, such as meningitis or encephalomyelitis.

Acknowledgements

We thank Edith Motschall who was instrumental in helping us with the development of search strategies. The Department of Neurology of the Medical Center – University of Freiburg and the German Academy of Neurology granted support for this project.

Disclosure of conflicts of interest

SR reports receiving consulting and lecture fees, grant, and research support from Bayer Vital GmbH, Biogen Idec, Merck Serono, Novartis, Sanofi-Aventis, Baxter, RG and Teva. Furthermore, SR indicates that he is a founding executive board member of ravo Diagnostika GmbH. MF reports receiving grant support from the German Federal Ministry of Education and Research. All other authors state no competing interests.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Risk of bias summary for RCTs.
Figure S2. Risk of bias summary for NRS.
Figure S3. Forest plot for the outcomes 'fatigue' and 'quality of life' after treatment with ceftriaxone versus doxycycline.
Figure S4. Forest plot for the outcome 'residual neurological symptoms' 4 or more months after treatment for single drug versus combination of drugs.

Figure S5. Forest plot for the outcome 'residual neurological symptoms' 4 or more months after treatment for antibiotic treatment versus no treatment.
Table S1. Characteristics of single-arm studies.
Table S2. Characteristics of ongoing studies.
Table S3. GRADE evidence table for the comparison combinations of antibiotics versus single drugs for the treatment of Lyme neuroborreliosis.
Table S4. GRADE evidence table for the comparison antibiotic treatment versus no treatment for the treatment of Lyme neuroborreliosis.
Appendix S1. Search strategies for Medline, EMBASE and CENTRAL.
Appendix S2. References to single-arm studies.

References

1. Mygland A, Ljostad U, Fingerle V, *et al*. EFNS guidelines on the diagnosis and management of European Lyme neuroborreliosis. *Eur J Neurol* 2010; **17:** 8–16, e1–4.
2. Kaiser R. Neuroborreliosis. *J Neurol* 1998; **245:** 247–255.
3. Halperin JJ, Logigian EL, Finkel MF, Pearl RA. Practice parameters for the diagnosis of patients with nervous system Lyme borreliosis (Lyme disease). Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 1996; **46:** 619–627.
4. Auwaerter PG, Bakken JS, Dattwyler RJ, *et al*. Antiscience and ethical concerns associated with advocacy of Lyme disease. *Lancet Infect Dis* 2011; **11:** 713–719.
5. Wormser GP, Dattwyler RJ, Shapiro ED, *et al*. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2006; **43:** 1089–1134.
6. Halperin JJ, Shapiro ED, Logigian E, *et al*. Practice parameter: treatment of nervous system Lyme disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2007; **69:** 91–102.
7. Cameron D, Gaito A, Harris N, *et al*. Evidence-based guidelines for the management of Lyme disease. *Expert Rev Anti Infect Ther* 2004; **2**(1 Suppl.)**:** S1–S13.
8. Reeves B, Higgins J, Ramsay C, Shea B, Tugwellf P, Wellsg G. An introduction to methodological issues when including non-randomised studies in systematic reviews on the effects of interventions. *Res Synth Methods* 2013; **4:** 11.
9. Mygland A, Ljøstad U, Fingerle V, Rupprecht T, Schmutzhard E, Steiner I. EFNS guidelines on the diagnosis and management of European Lyme neuroborreliosis. *Eur J Neurol* 2010; **17:** 8–16.
10. Dersch R, Freitag MH, Schmidt S, *et al*. Efficacy and safety of pharmacological treatments for neuroborreliosis – protocol for a systematic review. *Syst Rev* 2014; **3:** 117.
11. Higgins J, Green S. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* [updated March 2011]. The Cochrane Collaboration, 2011. www.cochrane-handbook.org (accessed 31/05/2015).
12. Sterne J, Higgins J, Reeves B, on behalf of the development group for ACROBAT-NRSI. A Cochrane risk of bias assessment tool: for non-randomized studies of interventions (ACROBAT NRSI), version 1.0.0. 2014. http://www.riskofbias.info (accessed 19/12/2014).
13. Wells G, Shea B, O'Connell D, *et al*. The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2000. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed 23/1/2015).
14. Balshem H, Helfand M, Schunemann HJ, *et al*. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol* 2011; **64:** 401–406.
15. Ljostad U, Skogvoll E, Eikeland R, *et al*. Oral doxycycline versus intravenous ceftriaxone for European Lyme neuroborreliosis: a multicentre, non-inferiority, double-blind, randomised trial. *Lancet Neurol* 2008; **7:** 690–695.
16. Oksi J, Nikoskelainen J, Viljanen MK. Comparison of oral cefixime and intravenous ceftriaxone followed by oral amoxicillin in disseminated Lyme borreliosis. *Eur J Clin Microbiol Infect Dis* 1998; **17:** 715–719.
17. Karlsson M, Hammers-Berggren S, Lindquist L, Stiernstedt G, Svenungsson B. Comparison of intravenous penicillin G and oral doxycycline for treatment of Lyme neuroborreliosis. *Neurology* 1994; **44:** 1203–1207.
18. Pfister HW, Preac-Mursic V, Wilske B, Schielke E, Sorgel F, Einhaupl KM. Randomized comparison of ceftriaxone and cefotaxime in Lyme neuroborreliosis. *J Infect Dis* 1991; **163:** 311–318.
19. Hassler D, Zöller L, Haude M, Hufnagel HD, Heinrich F, Sonntag HG. Cefotaxime versus penicillin in the late stage of Lyme disease – prospective, randomized therapeutic study. *Infection* 1990; **18:** 16–20.
20. Kohlhepp W, Oschmann P, Mertens HG. Treatment of Lyme borreliosis. Randomized comparison of doxycycline and penicillin G. *J Neurol* 1989; **236:** 464–469.
21. Pfister HW, Preac-Mursic V, Wilske B, Einhaupl KM. Cefotaxime vs penicillin G for acute neurologic manifestations in Lyme borreliosis. A prospective randomized study. *Arch Neurol* 1989; **46:** 1190–1194.
22. Pfister HW, Einhäupl KM, Franz P, Garner C. Corticosteroids for radicular pain in Bannwarth's syndrome: a double-blind, randomized, placebo-controlled trial. *Ann N Y Acad Sci* 1988; **539:** 485–487.
23. Borg R, Dotevall L, Hagberg L, *et al*. Intravenous ceftriaxone compared with oral doxycycline for the treatment of Lyme neuroborreliosis. *Scand J Infect Dis* 2005; **37:** 449–454.
24. Berglund J, Stjernberg L, Ornstein K, Tykesson-Joelsson K, Walter H. 5-y follow-up study of patients with neuroborreliosis. *Scand J Infect Dis* 2002; **34:** 421–425.
25. Elamin M, Monaghan T, Mulllins G, *et al*. The clinical spectrum of Lyme neuroborreliosis. *Ir Med J* 2010; **103:** 46–49.
26. Kruger H, Kohlhepp W, Konig S. Follow-up of antibiotically treated and untreated neuroborreliosis. *Acta Neurol Scand* 1990; **82:** 59–67.
27. Viader F, Poncelet AM, Chapon F, *et al*. [Neurologic forms of Lyme disease. 12 cases]. *Rev Neurol (Paris)* 1989; **145:** 362–368.
28. Bateman DE, Lawton NF, White JE, Greenwood RJ, Wright DJ. The neurological complications of *Borrelia*

burgdorferi in the New Forest area of Hampshire. *J Neurol Neurosurg Psychiatry* 1988; **51:** 699–703.
29. Hirsch E, Sellal F, Christmann D, *et al*. [Meningoradiculitis after a tick bite. Study of 31 cases]. *Rev Neurol (Paris)* 1987; **143:** 182–188.
30. Libá-Vrabelová Z, Kayserová J, Komárek V. Časťy výskyt lymeské neuroboreliózy u dětí v České Republice [Frequent incidence of Lyme neuroborreliosis in children in the Czech Republic]. *Cesk Slov Neurol N* 2013; **76:** 63–69.
31. Kristoferitsch W, Baumhackl U, Sluga E, Stanek G, Zeiler K. High-dose penicillin therapy in meningopolyneuritis Garin–Bujadoux–Bannwarth. Clinical and cerebrospinal fluid data. *Zentralbl Bakteriol Mikrobiol Hyg A* 1987; **263:** 357–364.
32. Ljostad U, Mygland A. Remaining complaints 1 year after treatment for acute Lyme neuroborreliosis; frequency, pattern and risk factors. *Eur J Neurol* 2010; **17:** 118–123.
33. Eikeland R, Ljostad U, Mygland A, Herlofson K, Lohaugen GC. European neuroborreliosis: neuropsychological findings 30 months post-treatment. *Eur J Neurol* 2012; **19:** 480–487.
34. Eikeland R, Mygland A, Herlofson K, Ljostad U. European neuroborreliosis: quality of life 30 months after treatment. *Acta Neurol Scand* 2011; **124:** 349–354.
35. Cadavid D, Auwaerter P, Aucott J, Rumbaugh J. Treatment for the neurological complications of Lyme disease (Protocol). *Cochrane Database Syst Rev* 2008.
36. Bensch J, Olcen P, Hagberg L. Destructive chronic borrelia meningoencephalitis in a child untreated for 15 years. *Scand J Infect Dis* 1987; **19:** 697–700.
37. Stanek G, Fingerle V, Hunfeld KP, *et al*. Lyme borreliosis: clinical case definitions for diagnosis and management in Europe. *Clin Microbiol Infect* 2011; **17:** 69–79.