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Original article

# Comparison of phenoxymethylpenicillin, amoxicillin, and doxycycline for erythema migrans in general practice. A randomized controlled trial with a 1-year follow-up

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ABSTRACT

*Objectives:* To compare the three most commonly used antibiotics for erythema migrans (EM) in Norwegian primary care.
*Methods:* A randomized, parallel, controlled trial was carried out. Treatments were open to the patients, but blinded for the GPs and investigators. Patients eligible for inclusion were aged ≥18 years and clinically diagnosed with EM. Block randomization was processed in blocks of six. Patients were assigned to receive one of three antibiotic treatments for 14 days: phenoxymethylpenicillin (PCV), amoxicillin, or doxycycline. The primary outcome was the duration of EM in days in the three treatment groups. Patients kept a diary for the 14 days of treatment, in which they registered concomitant symptoms and side effects. The patients consulted their GP after 14 days of treatment and had a 1-year follow-up to monitor any development of disseminated Lyme borreliosis (LB). EMs with a duration of more than 14 days were followed until resolution. ClinicalTrials.gov NCT01368341 and EU Clinical Trials Register 2010-023747-15.
*Results:* One hundred and eighty eight patients (PCV: $n = 56$, amoxicillin: $n = 64$, doxycycline: $n = 68$) were included by 44 Norwegian general practitioners (GPs) from June 2011 to November 2013. Follow-up was completed by December 2014. The median duration of EM was altogether 14 days (range 3–293). For the PCV group median duration was 14 days (range 5–91), for amoxicillin 13 days (range 4–179) and for doxycycline 14 days (range 3–293). The duration of EM did not differ significantly between the three antibiotic groups (p 0.277). None of the patients developed disseminated LB within the 1-year follow-up.
*Conclusions:* We did not find 14 days of PCV, doxycycline, and amoxicillin treatments to differ in effectiveness or safety in the treatment of clinically diagnosed EM in primary care. **K.E. Eliassen, Clin Microbiol Infect 2018;24:1290**


## Introduction

Solitary erythema migrans (EM) is the most common manifestation of Lyme borreliosis (LB) [1]. EM is caused by *Borrelia burgdorferi* bacteria transmitted through tick bites, and is a clinical diagnosis based on the course and the appearance of a skin lesion together with a patient history of a tick bite or time spent outdoors in tick-infested areas [1]. An untreated EM will usually resolve itself, but may lead to a disseminated and severe stage of LB in 10–60% of cases [2,3]. Antibiotics are essential to avoid disseminated LB [4].

In Norway, *B. afzelii* accounts for more than 60% of *Borrelia* found in ticks [5]. The distribution of species causing EM is unknown. Although all species of the *B. burgdorferi* genocomplex can cause all manifestations of LB, *B. afzelii* is more likely to cause EM than is *B. burgdorferi sensu stricto*. The latter is the predominant species in North America.

Norwegian guidelines for antibiotic use recommend phenoxymethylpenicillin (penicillin V, PCV) as the drug of choice for EM, with amoxicillin or doxycycline as alternatives [6]. Norwegian GPs prescribe PCV in about 60% and doxycycline in 25% of EM cases [7]. Amoxicillin is used in about 3% of cases, mainly in children [7]. It

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has been debated whether more broad-spectrum antibiotics, with better penetration through the blood–brain barrier and intracellularly, should be recommended for local manifestations of LB, and whether the use of PCV as a first-choice drug may increase the risk for disseminated LB [8,9].

Previous RCTs comparing different antibiotic treatments for EM have been conducted in secondary care and may not be applicable to general practice [10,11]. Antibiotics with a broader spectrum than penicillin, such as doxycycline or ceftriaxone, were usually used in these settings. Such antibiotics may increase the risk of antimicrobial resistance. We compared the effects of PCV, doxycycline and amoxicillin for the duration of EM. We also assessed whether any patients developed a later-stage LB within a 1-year follow-up from the time of treatment.

## Methods

### *Design and study setting*

A single-blinded multicentre trial was carried out with three parallel treatment groups conducted in Norwegian general practices. The study was a non-commercial phase IV drug trial. The study protocol is available at http://www.med.uio.no/helsam/english/research/projects/tick-borne/index.html.

### *Participants*

#### *GPs*

Eighty GPs were enrolled, and 44 of them contributed one or more patients; 69 of the 80 GPs (86.3%) had attended a 2-day course on tick-borne diseases before the trial.

#### *Patients*

All patients with EM and aged ≥18 years were eligible for inclusion. The case definition for EM was that described by Stanek et al. as a rash expanding from the site of a tick bite [12]. Exclusion criteria were pregnancy, inability to give consent, use of immunosuppressive medication, use of antibiotics 14 days before inclusion, and daily use of medication with potential serious interaction with, or allergy to, any of the three study medications.

### *Intervention*

All three groups of patients received active treatment for EM for 14 days: (a) PCV, 650 mg, two tablets three times daily, or (b) amoxicillin 500 mg, one capsule three times daily, or (c) doxycycline, 100 mg, one tablet twice daily.

### *Baseline and follow-up assessment*

#### *Baseline*

Patients were included and evaluated by their GP. A blood sample was obtained from each patient and tested for *Borrelia* antibodies. IgG was chosen, as IgM has low sensitivity and specificity [13]. A voluntary punch biopsy of the EM rash was obtained at the time of diagnosis and was subjected to PCR analysis for *Borrelia* DNA. The GPs completed a questionnaire about the diagnostics of the EM for each patient.

#### *Two-week follow-up*

Patients completed a symptom diary for the first 14 days and were evaluated by their GP again after the 14 days of treatment. At this follow-up, the GP went through the diary with each patient, asked for concomitant symptoms, and screened for any signs of disseminated LB. If the rash had resolved in <14 days, the duration was confirmed by the GP. If the rash had not resolved, the researchers followed the patients weekly until the rash had gone. Patients with other symptoms that could possibly come from disseminated LB or with an EM duration of >3 months were sent back to their GP for evaluation and, if necessary, referred to secondary care.

#### *One-year follow-up*

The 1-year follow-up was based on a self-reported questionnaire, by which patients assessed whether they experienced symptoms that could possibly be caused by disseminated LB. Patients who replied affirmative or were uncertain, were contacted by telephone to assess symptoms further and evaluate the need for a new GP consultation.

### *Laboratory tests*

For *Borrelia* IgG, a commercial kit, Enzygnost Borrelia® Lyme link VlsE/IgG was used. The punch biopsies were examined for *Borrelia* DNA using two different real-time PCR methods [14,15].

### *Randomization and masking*

Block randomization was processed in blocks of six, wherein each block of six contained two of each of the three treatments in randomized order. The distribution for three patients at a time to the GPs did not necessarily contain one of each. Randomization lists were encrypted, sent directly from the statistician to the pharmacy, and not revealed until the last patient had completed follow-up.

Each patient was given a neutral carton of medication to be opened after the first consultation. Patients therefore knew the identity of the medication they were given, while their GP and the researchers did not.

### *Outcomes*

All outcomes were predefined and remained unchanged throughout the study.

The primary outcome was the duration of the EM lesion, in days, in each group. The duration was also analysed in the subgroups of patients with positive *Borrelia* DNA in the punch biopsies.

Secondary outcomes were reports of concomitant symptoms, side effects, compliance with the medication given, and disseminated LB.

In the patient diaries, patients were asked to register any of 17 listed concomitant symptoms and four side effects every day. GPs screened for signs of disseminated LB at the 2-week follow-up.

### *Sample size*

The distribution of species of *Borrelia* in Norway resembles the distribution in Sweden [5,16]. Based on data from a Swedish EM study [17], a median duration for EM of 8 days from the start of treatment, with a range of 1–35 days, was anticipated. A difference in duration of 2 days was considered clinically significant. On a log scale, with an assumed standardized difference of 0.69 based on the given spread above, a significance level of 0.05 and a power of 90%, we needed 46 patients in each group.

### *Statistics*

The baseline characteristics are presented as frequencies or means. The primary outcome is shown in a Kaplan–Meier plot and tested using the log-rank test. The resolution rate by day 28 was calculated from the survival table of EM duration. Analyses for the

subgroups of PCR-positives were performed in the same way. For the secondary outcomes, the means were compared using ANOVA, and categorical data were analyzed using $\chi$-square tests. Multiple pair-wise comparisons were carried out if the $\chi$-square test rejected the null hypothesis of equality of the proportions. The method is also called post-hoc $\chi$-square test of proportions. For all tests, 0.05 was used as the significance level. Analyses were performed using IBM SPSS Statistics for Windows (v. 22; IBM Corp., Armonk, NY, USA) and Stata/SE 14.1 (StataCorp LP, College Station, TX, USA).

### *Ethics and approvals*

The trial was conducted in accordance with the WMA Helsinki Declaration for patient safety [18] and the WHO Good Clinical Practice guidelines [19], and has been clinically monitored accordingly. All patients signed an informed consent form. The regional ethics committee (REK Sør-Ost, University of Oslo) has approved the trial (application no. 2010/2994, 9 May 2011), as has The Norwegian Medicines Agency, EudraCT (number 2010-023747-15, 3 May 2011).

## Results

Patients were included from June 2011 to November 2013. Follow-up was completed by December 2014. Forty-four of the 80 GPs contributed 188 patients in total; each GP included between one and 11 patients (Fig. 1).

Fifty-nine of 187 patients (31.4%) had experienced another tick-borne disease before the current EM; 50 of these were earlier EMs, while seven patients reported an earlier disseminated LB. Two patients did not specify their earlier disease. No patients reported any tick-borne diseases other than LB (Table 1).

One-hundred-forty-nine of 188 patients (79.3%) consented to the voluntary punch biopsy; 104 of these biopsies (69.8%) were positive for *Borrelia* DNA, and three were inconclusive. Half of the patients (94/188) had positive IgG antibodies at the time of inclusion (Table 1).

The median duration of EM was 14 days (range 3–293) for all patients, 13 days (range 4–179) for the amoxicillin group, and 14 days for the PCV group (range 5–91) and the doxycycline group (range 3–293). The duration of EM did not differ significantly between the three antibiotic groups (log-rank test, p 0.277) (Fig 2a).

For the total EM cohort, 141 of 188 cases of EM (75%) were resolved by day 28, with no significant differences between the treatment groups; 109 of the 188 cases of EM (58%) lasted $\leq$14 days.

A subgroup analysis of the *Borrelia* PCR-positive patients ($n = 104$) gave a similar result—median duration of 14 days (range 3–179), with no significant difference between the treatment groups (log-rank test, p 0.604). Resolution was observed by 28 days in 78 of the 104 patients (75%) (Fig. 2b).

At least one side effect was reported by 46% of the patients (86/186). The rate of side effects did not differ significantly between the treatment groups (Table 2). Nausea 17.2% (32/186) and diarrhoea 15.1% (28/185) were the most common in the total cohort. There was a trend towards less diarrhoea in the doxycycline group (7.5% (5/67) versus mean 15.1%), and less nausea in the amoxicillin group (9.4% (6/64) versus mean 17.2%). Skin rash appeared only in the amoxicillin group (in 3.1% (2/64)).

Patients reported a mean of two out of 17 concomitant symptoms during the 14 days of treatment; 116 of 187 patients (62%) reported at least one concomitant symptom, while 30 of 187 patients (16%) reported five or more symptoms. The most common symptoms were tiredness 31.2% (58/186), headache 30.1% (56/186) and nausea 19.9% (37/186) (Table 3).

The frequency of concomitant symptoms differed significantly between groups for only two symptoms; a higher percentage of patients reported palpitations in the doxycycline group (9%, 6/67) than in the amoxicillin group (0%, 0/64), and a higher percentage reported chills in the doxycycline group (11.9%, 8/67) than in the

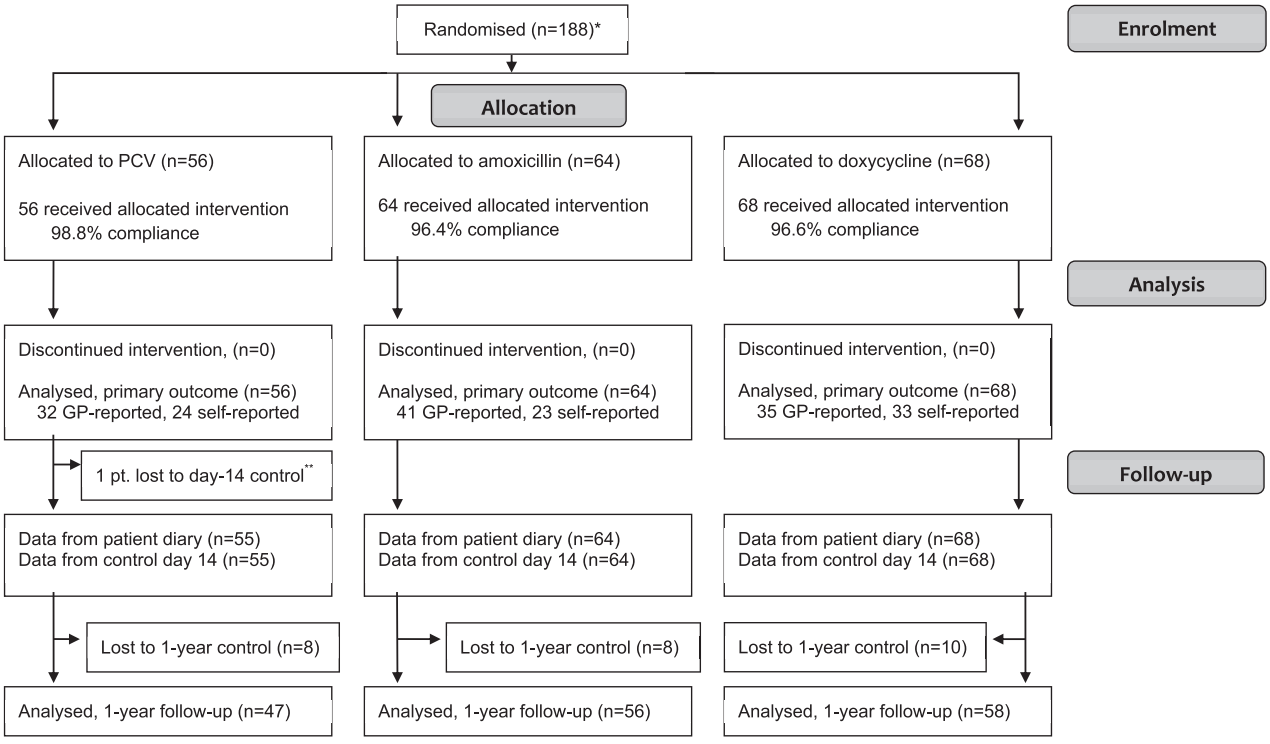


**Fig. 1. Flow diagram for a randomized controlled trial comparing three antibiotic regimens for erythema migrans (EM).** GP, general practitioner; pt, patient(s), *A screening log was not used. Number of eligible patients is unknown. **Data about the durations of EM were obtained by telephone, giving data for the primary outcome for all 188 patients.

**Table 1**
Baseline data for the three intervention groups of erythema migrans (EM) patients

| | PCV | | Amoxicillin | | Doxycycline | | Total | Mean |
|---|---|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % | *n*[a] | % |
| **Number of patients** | 56 | 29.8 | 64 | 34.0 | 68 | 36.2 | 188 | 100 |
| Women | 32 | 57.1 | 39 | 60.9 | 42 | 61.8 | 113 | 60.0 |
| Age, mean (range) | 56.7 | 18–76 | 55.0 | 21–80 | 55.4 | 20–85 | 55.7 | 18-85 |
| Uncertainty of diagnosis, annotated by the GP | 1 | 1.8 | 2 | 3.2 | 2 | 2.9 | 5/187 | 2.7 |
| **Microbiology** | | | | | | | | |
| Positive *Borrelia* PCR in punch biopsy[b] | 30/40 | 75.0 | 32/46 | 69.6 | 42/60 | 72.0 | 104/149 | 69.8 |
| Positive *Borrelia* IgG antibody test at time of diagnosis | 27/56 | 48.2 | 32/64 | 50.0 | 35/68 | 51.5 | 94/188 | 50.0 |
| **Status** | | | | | | | | |
| Any tick-borne disease, earlier | 20/56 | 35.7 | 19/63 | 29.7 | 20/68 | 29.9 | 59/187 | 31.4 |
| Neurological symptoms, earlier | 4/56 | 7.1 | 0/62 | 0.0 | 2/68 | 2.9 | 6/186 | 3.2 |
| Neurological symptoms, current[c] | 1/56 | 1.8 | 2/62 | 3.2 | 2/68 | 2.9 | 5/186 | 2.7 |
| Any chronic disease, current | 16/56 | 28.6 | 12/64 | 18.8 | 16/68 | 23.5 | 44/188 | 23.4 |

PCV, phenoxymethylpenicillin.
[a] The *n* values differ because of missing data.
[b] In the total cohort, 149 of 188 patients volunteered to have a punch biopsy taken; three of the 149 punch biopsies were inconclusive.
[c] None of the neurological symptoms was considered to be associated with the current EM.

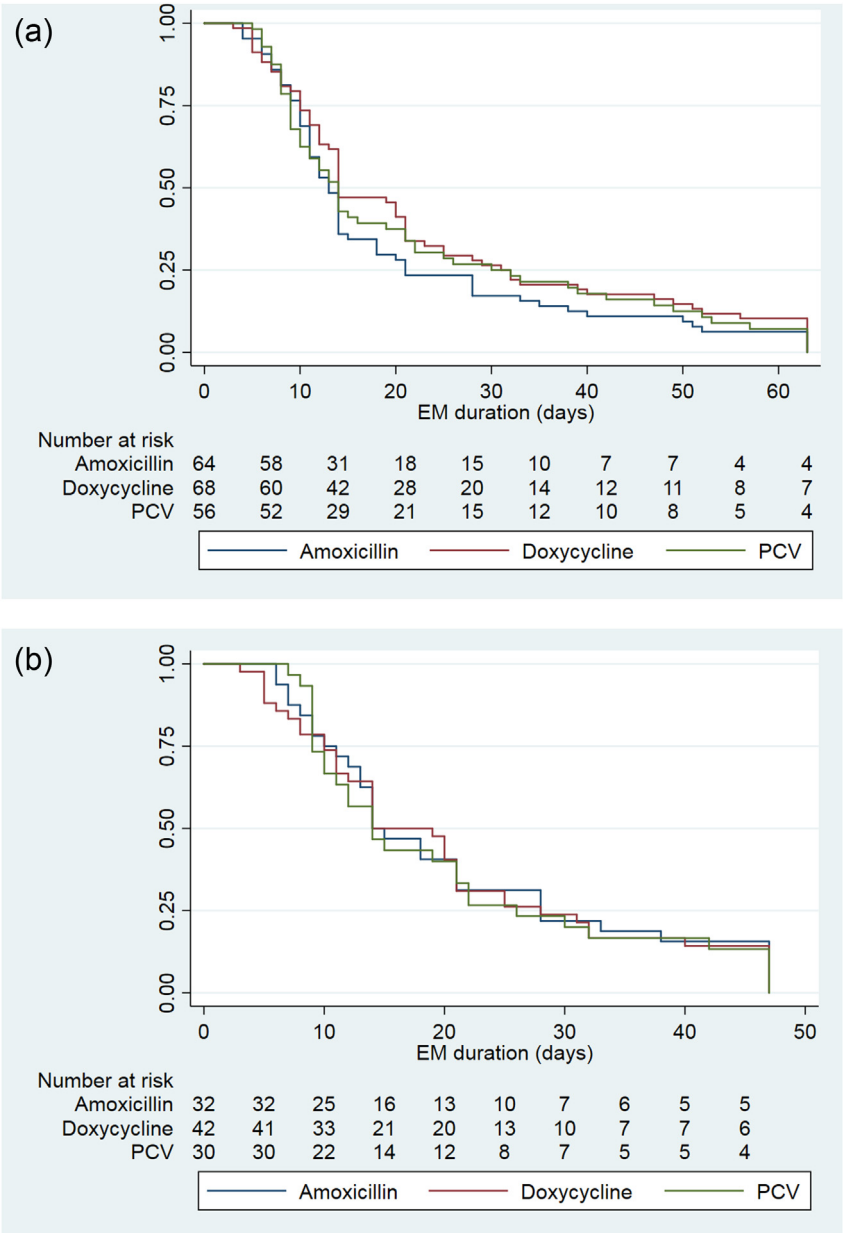


**Fig. 2.** (a) Erythema migrans (EM) duration in the three intervention groups, *all patients*. Complete figure with all patients ($n = 188$) is available in the Online supplement. (b) EM duration in the three intervention groups, *PCR-positive patients only*. Complete figure with all patients ($n = 104$) is available in the Online supplement. PCV, phenoxymethylpenicillin.

**Table 2**
Side effects of treatment as recorded in erythema migrans (EM) patients' diaries for days 1–14

| Side effects | PCV | | Amoxicillin | | Doxycycline | | p | Total | |
|---|---|---|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % | | *n*[a] | % |
| Diarrhoea | 10/55 | 18.2 | 13/63 | 20.6 | 5/67 | 7.5 | 0.082 | 28/185 | 15.1 |
| Nausea | 10/55 | 18.2 | 6/64 | 9.4 | 16/67 | 23.9 | 0.092 | 32/186 | 17.2 |
| Skin rash | 0/55 | 0.0 | 2/64 | 3.1 | 0/67 | 0.0 | 0.203 | 2/186 | 1.1 |
| Other | 4/55 | 7.3 | 12/64 | 18.8 | 8/67 | 11.9 | 0.182 | 24/186 | 12.9 |
| Any side effect | 24/55 | 43.6 | 33/64 | 51.6 | 29/67 | 43.3 | 0.759 | 86/188 | 45.7 |
| Response rate | | 98.2 | | 99.6 | | 98.5 | | | 98.8 |

PCV, phenoxymethylpenicillin
[a] The *n* values differ because of missing data.

PCV group (1.9%, 1/54). In addition, there was a trend towards less neck stiffness and nausea in the amoxicillin group (9.4% (6/64) versus mean 15.1% and 12.5% (8/64) versus mean 19.9%, respectively) (Table 3).

The GP-reported frequency of concomitant symptoms resembled that from the patients' diaries: a mean of 1.9 symptoms. At the day 14 control, the GPs screened the patients for signs of disseminated LB (Table 4). None of the patients had disseminated infection.

If there were any signs of potentially disseminated LB during the telephone interview, the patients visited their GP again. Thus, eight patients were controlled in addition to the planned follow-ups: one in the PCV group, three in the amoxicillin group, and four in the doxycycline group. None of these patients were suspected of having disseminated LB after the GP follow-up examination. One patient (duration 293 days) was referred to a dermatologist, who via a new punch biopsy diagnosed eczema.

At the 1-year follow-up, no patients reported disseminated disease. Two patients reported new solitary EMs; both were in the doxycycline group.

## Discussion

### *Strengths and limitations of the study*

The strengths of this study are the primary care setting, the use of a clinical diagnosis as an inclusion criterion, and the use of PCR analysis to confirm clinically diagnosed *Borrelia* infection. One could ask whether a control by the GP at the 1-year follow-up would have been a more certain way of excluding disseminated LB than the questionnaire.

### *General discussion*

The duration of EM was equal in the three treatment groups. The groups did not differ significantly in compliance or side effects of antibiotic treatment, but there were some clinical differences between the treatments. None of the patients developed disseminated LB during the 1-year follow-up.

Untreated EM can reactivate or progress to disseminated disease. However, there are few well-conducted studies of the natural course of infection with any of the *Borrelia* species [4]. In the first description of EM by Afzelius in 1909, the EM disappeared after several weeks or a few months [20]. The median duration of 14 days in our study is shorter than expected for untreated EM, which suggests that each of the three antibiotics was effective in the treatment of EM. Other studies have differentiated between minor and major manifestations of LB, as described by Steere and coworkers in 1983 [21]. Several RCTs have compared different antibiotic regimens for EM [10,11]. These studies were performed in secondary-care settings and have reported a shorter duration of EMs, more concomitant symptoms, fewer side effects, and more frequent development of major manifestations of LB than in our trial. Some of them included only subgroups of EM patients, such as

**Table 3**
Concomitant symptoms in erythema migrans (EM) patients as recorded in patients' diaries for days 1–14

| Concomitant symptoms | PCV | | Amoxicillin | | Doxycycline | | p | Total | |
|---|---|---|---|---|---|---|---|---|---|
| | % | *n* | % | *n* | % | n | | % | *n*[a] |
| Tiredness | 32.7 | 18/55 | 29.7 | 19/64 | 31.3 | 21/67 | 0.960 | 31.2 | 58/186 |
| Headache | 29.1 | 16/55 | 29.7 | 19/64 | 32.8 | 22/67 | 0.885 | 30.1 | 56/186 |
| Joint pain | 9.1 | 5/55 | 17.2 | 11/64 | 23.9 | 16/67 | 0.098 | 17.2 | 32/186 |
| Neck stiffness | 12.7 | 7/55 | 9.4 | 6/64 | 22.4 | 15/67 | 0.100 | 15.1 | 28/186 |
| Fever | 3.7 | 2/54 | 4.7 | 3/64 | 4.5 | 3/67 | 1.00 | 4.3 | 8/185 |
| Palpitations[b] | 5.5 | 3/55 | 0.0 | 0/64 | 9.0 | 6/67 | **0.038** | 4.8 | 9/186 |
| Myalgia | 10.9 | 6/55 | 18.8 | 12/64 | 17.9 | 12/67 | 0.473 | 16.1 | 30/186 |
| Sore throat | 14.5 | 8/55 | 6.3 | 4/64 | 10.4 | 7/67 | 0.334 | 10.2 | 19/186 |
| Tender skin | 3.6 | 2/55 | 6.3 | 4/63 | 9.0 | 6/67 | 0.527 | 6.5 | 12/185 |
| Dizziness | 10.9 | 6/55 | 10.9 | 7/64 | 10.4 | 7/67 | 1.00 | 10.8 | 20/186 |
| Nausea | 23.6 | 13/55 | 12.5 | 8/64 | 23.9 | 16/67 | 0.187 | 19.9 | 37/186 |
| Chest pain | 3.7 | 2/54 | 4.7 | 3/64 | 4.5 | 3/67 | 1.00 | 4.3 | 8/185 |
| Diarrhoea | 14.5 | 8/55 | 21.9 | 14/64 | 10.4 | 7/67 | 0.198 | 15.6 | 29/186 |
| Chills[c] | 1.9 | 1/54 | 3.1 | 2/64 | 11.9 | 8/67 | **0.037** | 5.9 | 11/185 |
| Hot flushes | 0.0 | 0/55 | 3.1 | 2/64 | 4.5 | 3/67 | 0.379 | 2.7 | 5/186 |
| Coughing | 9.1 | 5/55 | 9.4 | 6/64 | 7.5 | 5/67 | 0.948 | 8.6 | 16/186 |
| Multiple EMs | 0.0 | 0/55 | 0.0 | 0/64 | 0.0 | 0/67 | — | 0.0 | 0/186 |
| Mean number of symptoms | | 1.9 | | 1.9 | | 2.3 | 0.441 | | 2.0 |
| Response rate | 97.9 | | 99.9 | | 98.5 | | | 98.8 | |

PCV, phenoxymethylpenicillin.
[a] The *n* values differ because of missing data.
[b] Significant difference between amoxicillin and doxycycline groups.
[c] Significant difference between PCV and doxycycline groups (p 0.042).

**Table 4**
Concomitant symptoms recorded in the GP questionnaires at the 2-week follow-up

| | PCV | | Amoxicillin | | Doxycycline | | p | Total | |
|---|---|---|---|---|---|---|---|---|---|
| | % | *n* | % | *n* | % | *n* | | % | *n*[a] |
| Neurological symptoms, day 14 | 0.0 | 0/55 | 1.6 | 1/63 | 5.9 | 4/68 | 0.163 | 2.7 | 5/186 |
| Arthritis, day 14[b] | 0.0 | 0/55 | 0.0 | 0/63 | 1.5 | 1/68 | 1.00 | 5.4 | 1/186 |
| Multiple EMs, day 14[c] | 1.8 | 1/55 | 0.0 | 0/63 | 0.0 | 0/68 | 0.296 | 5.4 | 1/186 |
| Other symptoms, day 14 | 1.8 | 1/55 | 1.6 | 1/63 | 7.4 | 5/68 | 0.230 | 3.8 | 7/186 |
| Abruption of intervention | 0.0 | 0/55 | 0.0 | 0/64 | 0.0 | 0/68 | — | 0.0 | 0/186 |
| Mean number of concomitant symptoms | | 1.7 | | 1.7 | | 2.3 | 0.321 | | 1.9 |
| Median number of concomitant symptoms | | 1.0 | | 1.0 | | 1.0 | 0.181 | | 1.0 |
| Response rate | 98.2 | | 99.0 | | 100.0 | | | 98.9 | |

EM, erythema migrans; PCV, phenoxymethylpenicillin.
[a] The *n* values differ because of missing data.
[b] One patient who reported arthritis had a swollen metacarpophalangeal joint, which was unlikely to be Lyme arthritis.
[c] One patient who reported multiple EMs had five local reactions from five different tick bites.

children or those with culture-confirmed EM. The patients in our trial seemed to have longer duration and a lower symptom load than the patients in other studies. The most probable cause for this is the prevalence of different *Borrelia* species. None of the patients in our trial developed a more severe form of LB. This finding is similar to retrospective findings in Swedish general practice in 2003 [22]. Although the results do not suggest an increased risk of Lyme neuroborreliosis, with the number of patients in our trial (188) there is a potential risk of a type-II error. However, neuroborreliosis has a low incidence in Norway—about seven cases of disseminated LB per 100 000 inhabitants per year [23]—although two out of three EM patients are treated with PCV [7].

We found a wide range of duration of EM: 3–293 days. This raises the question of the validity of a clinical diagnosis. Here, almost 70% of the EMs tested were positive for *Borrelia* DNA. The EM with the shortest duration of 3 days was confirmed by PCR. However, the EM with the longest duration was PCR-negative, and later diagnosed as eczema. Because this trial was performed in general practice, it was essential to include all patients with clinically diagnosed EM to be consistent with the intention to treat.

LB infection may give symptoms concomitant with the EM, and the treatment can cause side effects. It can be difficult for both the patient and the GP to differentiate the side effects from concomitant symptoms. Joint pain, myalgia, and neck stiffness are common symptoms, but may more likely be caused by the infection itself than by the treatment. Non-specific symptoms such as tiredness and headache can also be attributed to diseases other than LB. These symptoms were evenly distributed in the groups.

In conclusion, we did not find 14 days of PCV, doxycycline, and amoxicillin treatments to differ in effectiveness or safety in the treatment of clinically diagnosed EM in primary care. The results consolidate the Nordic guidelines for EM treatment, and may also inspire the use of PCV for EM elsewhere.

Use of broad-spectrum antibiotics increases the risk of antimicrobial resistance, which is one of the great challenges in modern medicine [24]. Although the *Borrelia* bacterium itself is seldom involved in antimicrobial resistance [2], the use of antibiotics to treat LB may affect the development of antimicrobial resistance in other bacteria present in and around patients.

We suggest that PCV should be the drug of choice for solitary EM. The distribution of *Borrelia* species varies geographically, thus regional studies may be indicated as a basis for treatment recommendations.

## Transparency declaration

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years. ML is the editor of the Norwegian guidelines for antibiotic use in primary care. DB and KEE are members of the editorial board for the guidelines. DB, HR, and KEE are authors of the Lyme borreliosis chapter in the guidelines.

This is a non-commercial drug trial sponsored by the University of Oslo, Norway. The participating patients received a free follow-up by their GP. The study covered the normal patient fee to the GP for the follow-up consultation. Costs for the microbiology tests were covered by the sponsor and the co-operating laboratory. Funding for the study was granted by the Institute of Health and Society within the University of Oslo and the Norwegian Research Fund (15161) for General Practice. Additional funding was received from the Antibiotic Centre for Primary Care, the Norwegian surveillance programme (11_01) for antibiotic resistance in human pathogens, the National Centre of Rural Medicine, and the Eckbo Trust. None of the organizations that provided financial support was involved in the study design, data collection, analysis or interpretation of data, writing of the report, or in the decision to submit the article for publication.

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All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. KEE is the guarantor. The dataset is available from the corresponding author on reasonable request.

All authors cooperated in designing the trial and writing the protocol. ML was the principal investigator of the trial. KEE was the project manager. KEE drafted and revised the manuscript. KEE performed the statistical analyses with the assistance of statistician Ibrahimu Mdala, PhD, Institute of Health and Society within the University of Oslo. All authors have contributed in the writing of and have approved the final manuscript.

## Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.cmi.2018.02.028

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