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Comparative effectiveness and toxicity of oral antibiotics for early Lyme disease associated with erythema migrans: a systematic review and network meta-analysis

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Background: Lyme disease (LD) is caused by transmission of *Borrelia burgdorferi* bacteria through a tick bite. Approximately two thirds of patients with early LD develop erythema migrans (EM), an annular erythematous skin lesion that expands around the tick bite site. If left untreated, the bacteria can disseminate to major organ systems, causing disease manifestations such as meningitis or arthritis. Though many antibiotics are available to treat early LD, it is difficult to pinpoint the best treatment due to a limited number of RCTs comparing different antibiotics head-to-head. Therefore, we conducted a network meta-analysis to compare effectiveness and toxicity of various oral antibiotics in achieving acute treatment response and preventing disease dissemination in patients with LD associated with EM.

Material/methods: We searched MEDLINE, EMBASE, Web of Science, Google Scholar, and the Cochrane Database from inception to March 2016. We included all RCTs that involved patients with early LD presenting with EM and compared two or more oral antibiotics. We categorized antibiotic treatments by therapeutic class: cephalosporins, macrolides, penicillins, and tetracyclines. Our outcomes were acute treatment response (defined as the resolution of EM and LD symptoms at the end of treatment and within 1 month post-treatment), dissemination of LD (defined as the presence of objective findings of LD at ≥6 months), and proportion of patients reporting ≥1 treatment-related adverse event (TAE). We performed network meta-analysis using a Bayesian random effects model with non-informative priors.

Results: We identified 16 studies comprising 1,659 patients aged 0.5 to 83 years. The proportion of males ranged from 44% to 62%. Cephalosporins were comparable with macrolides, penicillins, and tetracyclines in achieving acute response (**Table**). Macrolides were significantly less effective in achieving acute response compared with penicillins (Odds Ratio: 2.72 [95% Credible Interval:1.14, 6.65]), but were not significantly different from tetracyclines. Penicillins showed a significant benefit over tetracyclines (0.28 [0.09,0.94]). The majority of patients recovered completely within 6 months. None of the treatments were significantly different with regard to the number of patients reporting dissemination of LD. Patients taking penicillins were less likely to experience a TAE than patients receiving any other therapeutic class. Fewer patients experienced TAEs from penicillins compared with cephalosporins (0.23 [0.06,0.66]). Patients taking tetracyclines were more likely to report TAEs, and the effect was significant in comparison with penicillin patients (6.54 [2.31,24.15]) and macrolides (4.00 [1.19,14.75]).

Conclusions: Our results showed that penicillins demonstrated a significant benefit over macrolides and tetracyclines with regard to acute treatment response and a more favorable safety profile than cephalosporins and tetracyclines in patients with early LD associated EM. We found that different therapeutic classes of oral antibiotics were similarly effective in preventing disease dissemination. These results could prove valuable to clinicians selecting appropriate first-line treatments for early LD patients.

Table. Effect estimates for Achievement of Acute Treatment Response by 1 month and Dissemination of Lyme Disease by ≥6 months by therapeutic class *

		Achievement of Acute Treatment Response Odds ratio (95%CrI)			
		Cephalosporin	Macrolide	Penicillin	Tetracycline
Dissemination of Lyme Disease Odds ratio (95%CrI)	Cephalosporin		1.27 (0.26, 5.03)	3.42 (0.64, 14.63)	0.95 (0.33, 2.60)
	Macrolide	0.10 (0.00, 4.26)		**2.72 (1.14, 6.65)**	0.75 (0.29, 2.19)
	Penicillin	0.20 (0.00, 7.56)	2.07 (0.39, 14.83)		**0.28 (0.09, 0.94)**
	Tetracycline	0.17 (0.00, 6.18)	1.64 (0.27, 12.45)	0.83 (0.09, 6.53)	

*For Achievement of Acute Treatment Response, an odds ratio greater than 1 favors the therapeutic class in column heading. For Dissemination of Lyme Disease, an odds ratio less than 1 favors the therapeutic class in row heading.