

Recommendations for diagnosis and treatment of Lyme borreliosis: guidelines and consensus papers from specialist societies and expert groups in Europe and North America

Sue O'Connell, Health Protection Agency Lyme Borreliosis Unit, HPA Microbiology Laboratory, Southampton University Hospitals Trust, Southampton SO16 6YD

Introduction

The European Union Concerted Action on Lyme Borreliosis (EUCALB) initiative, funded initially by the EU, continues to promote research and evidence-based clinical practice through European multi-disciplinary collaboration and a highly-regarded and frequently updated website. Its clinical case definitions for Lyme borreliosis were published in 1997 and an updated version is to be published shortly. EUCALB's current work programme includes a review of currently recommended treatments in Europe and the evidence on which they are based.

Since the publication of the Infectious Diseases Society of North America's updated guidelines for Lyme borreliosis in 2006 there has been considerable public dispute in the USA and elsewhere regarding choice of antibiotic agents and duration of antibiotic treatment for Lyme borreliosis, particularly for patients who have persistent symptoms following standard treatment. Some patient support groups and a minority of physicians have been very active in promoting prolonged or multiple repeated courses of antibiotics for patients with persistent symptoms in North America and in Europe.

There has also been criticism about the use of the IDSA guidelines for patients in Europe, prompting the evaluation of European guidelines and recommendations and a comparison with American recommendations.

Methods

EUCALB participants collated diagnostic and treatment guidelines prepared independently by specialist societies and expert groups in various European countries and in North America. National and/or specialist society guidelines and recommendations of experts from the Czech Republic, Denmark, Finland, France, Germany, the Netherlands, Norway, Poland, Slovenia, Sweden and Switzerland have been evaluated and compared with regard to clinical and laboratory diagnostic and treatment recommendations (including antibiotic agents, dosages and durations) for erythema migrans, neuroborreliosis and Lyme arthritis. They have also been compared to those of the IDSA and the American Academy of Neurology.

The first-line treatment recommendations of the various European and North American guidelines are presented in tabular form to permit easy comparison.

Findings

The majority of guidelines and reviews listed here give explicit details about the quality of evidence and strength of recommendations. They list references of published randomised controlled treatment trials and numerous other peer-reviewed papers on diagnosis and management of Lyme borreliosis in the international literature.

All guidelines give recommendations for clinical diagnosis and for the application of laboratory tests. There is overall agreement regarding the clinical features of Lyme borreliosis and on the requirement for supporting laboratory evidence of a clinical diagnosis of later-stage infection. Two-stage serological testing, with immunoblot as a second-stage test, is currently recommended in most guidelines and reviews in order to minimise false-positive serological results. No guideline or review recommends serological testing in support of a diagnosis of erythema migrans.

Overall there are great similarities of antibiotic choice between the various treatment guidelines and reviews, with some minor differences in dosing and duration.

The most commonly recommended first-line treatments for different stages of Lyme borreliosis in non-pregnant, non-breastfeeding adults in Europe are:

Erythema migrans:

or
Doxycycline 100mg bd (10-21 days)
or
Amoxicillin 500mg tid (14-21 days)

Early neuroborreliosis:

or
Ceftriaxone 2g daily (14 days)
or
Doxycycline 100mg-200mg bd (14-21 days)

Late neuroborreliosis:

Ceftriaxone 2g daily (14-28 days)

Lyme arthritis:

or
Doxycycline 100mg bd (28 days)
or
Amoxicillin 500mg tid (28 days)

These recommendations, independently developed by a wide range of European experts, are similar to those of the IDSA.

European and American Lyme Borreliosis Diagnostic / Treatment Guidelines							
1st line treatment recommendations for non-pregnant, non-breastfeeding adults – See individual guidelines for further details							
Diagnostic / Treatment Guideline	Diagnostic criteria specified?	Erythema migrans	Early disseminated (non-nervous system)	Neuroborreliosis	Lyme arthritis	Refs cited ⁽¹⁾	Comment
Czech Republic Vancousova D, Herczegova J. Lyme borreliosis treatment. <i>Dermatol Ther</i> 2008;21:101-9.	Yes	Doxycycline 100mg bd or Amoxicillin 1g tid (14-21 days)	Ceftriaxone 2g daily or Penicillin G 5MU qid (14-21 days) or Doxycycline 100-200mg bd (14-28 days)	Ceftriaxone 2g daily or Penicillin G 5MU qid (14-21 days) or Doxycycline 100-200mg bd (14-28 days)	Doxycycline 100mg bd or Penicillin G 5MU tid (21-28 days) or Ceftriaxone 2g daily (14-21 days)	40	NRVPM ⁽²⁾
Denmark Dansk Selskab for Klinisk Mikrobiologi, Dansk Selskab for Infektionsmedicin og Dansk Neurologisk Selskab 2006. 35pp. Dessau R, Bangsbo JM, Ejlertsen TP et al. <i>Ugeskr Læger</i> 2006;166(26):5-7 (summary)	Yes	Penicillin V 1.5MU tid or Doxycycline 200mg stat then 100mg daily or Cefuroxime axetil 500mg bd (10 days)	Doxycycline 100mg bd or Penicillin V 1.5MU tid (10 days)	Penicillin G 5MU qid (10 days) or Doxycycline 200mg bd on day 1, then 100mg bd (14 days) or Ceftriaxone 2g daily or Cefotaxime 2g tid (10 days; 14 days for late NB)	Penicillin V 1.5MU tid or Doxycycline 100mg bd (21 days)	175	NRVPM ⁽²⁾
Finland Oksa J, Seppala JJ, Hytonen J. <i>Lymen borreliosisin diagnostiikka ja hoito</i> . <i>Duodecim</i> 2008;134:1633-91.	Yes	Amoxicillin 500mg-1g tid or Doxycycline 100mg bd (14 days)	Ceftriaxone 2g daily (14-21 days)	Ceftriaxone 2g daily (14-21 days) or Doxycycline 100mg bd (1-3 months)	Ceftriaxone 2g daily (14-21 days) or Amoxicillin 500mg tid or Doxycycline 100mg bd (1-2 months)	13	NRVPM ⁽²⁾
France Societe de Pathologie Infectieuse de Langue Francaise. Lyme borreliosis: diagnostic, therapeutic and preventive approaches. <i>Med Mal Infect</i> 2007;37(S3):9153-74.	Yes	Doxycycline 100mg bd or Amoxicillin 1g tid (14-21 days)	Doxycycline 100mg bd or Amoxicillin 1g tid (21-28 days)	Ceftriaxone 2g daily or Penicillin G 18-24MU daily or Doxycycline 200mg daily (facial palsy) (21-28 days)	Doxycycline 200mg daily or Amoxicillin 1g tid (21-28 days) or Ceftriaxone 2g daily (14-21 days)	160	NRVPM ⁽²⁾
Germany Leitlinien der Deutschen Gesellschaft für Neurologie 2008 http://leitlinien.net ; AWMF Leitlinien-Register Nr 030/071	Yes	Not applicable	Not applicable	Doxycycline 100mg bd or tid or Ceftriaxone 2g daily or Cefotaxime 2g tid or Penicillin G 18-24 MU daily (14 days; acute NB) (14-21 days late NB; iv first-line in late NB)	Not applicable	60	NRVPM ⁽²⁾
Germany Leitlinien der Deutschen Dermatologischen Gesellschaft 2009 http://leitlinien.net ; AWMF Leitlinien-Register Nr 013/044	Yes	Doxycycline 100mg bd or Amoxicillin 500mg-1g tid or Cefuroxime 500mg bd (14-21 days) or Azithromycin 250mg bd (5-10 days)	Doxycycline 100mg bd or Amoxicillin 500mg-1g tid (21-30 days)	Not applicable	Not applicable	64	NRVPM ⁽²⁾
Netherlands CBO Richtlijn Lyme Borreliose 2004 ISBN: 90-7606-89-0 Speelman P, de Jongh BM, Wolfs TF, Wittenberg J. <i>CBO, Med Tijdschr Geneesk</i> 2004;148(59-63) (summary)	Yes	Doxycycline 100mg bd (10 days) or Amoxicillin 500mg tid (14 days)	Doxycycline 100mg bd (21 days) or Ceftriaxone 2g daily (14 days)	Ceftriaxone 2g daily or Penicillin G 3-3 MIU 4 hourly (14 days; 30 days for late NB) or Doxycycline 200mg bd (21 days; 30 days for late NB)	Doxycycline 100mg bd (30 days) or Amoxicillin 500mg tid (30 days) or Ceftriaxone 2g daily (14 days)	38 ⁽³⁾	NRVPM ⁽²⁾
Norway Ljøstad U, Mygland A. Lyme-borreliose hos voksne. <i>Tidsskr Nor Lægeforen</i> 2008; 128:1172-9. Norsk legemiddelhandbøkk for helsepersonell (www.legemiddelhandboka.no)	Yes	Doxycycline 200mg daily or Amoxicillin 500mg tid (14 days)	Doxycycline 200mg daily (14 days)	Ceftriaxone 2g daily or Cefotaxime 2g tid or Penicillin G 5MU qid or Doxycycline 200mg daily (14-28 days)	Doxycycline 200mg daily (20-30 days)	50 ⁽⁴⁾	
Poland Fisak R, Franciszcz S. Diagnosis and treatment of Lyme borreliosis: recommendations of the Polish Society of Epidemiology and Infectious Diseases. <i>Przegl Epidemiol</i> 2008;62:193-199.	Yes	Doxycycline 100mg bd or Amoxicillin 500mg tid or Cefuroxime axetil 500mg bd (14-21 days)	Doxycycline 100mg bd or Amoxicillin 500mg tid or Cefuroxime axetil 500mg bd (14-28 days)	Ceftriaxone 2g daily or Penicillin G 3-4 MIU four-hourly (14-28 days)	Doxycycline 100mg bd or Amoxicillin 500mg tid or Ceftriaxone 2g daily or Penicillin G 3-4MIU four-hourly (14-28 days)	Not stated	NRVPM ⁽²⁾
Slovenia Stek F. <i>Wien Klin Wochenschr</i> 1999;111:911-915.	Yes	Doxycycline 100mg bd or Amoxicillin 500mg tid or Cefuroxime 500mg bd (14 days; range 10-30) or Azithromycin 1g on day 1; 500mg daily for 4 days.	Doxycycline or Amoxicillin or Cefuroxime (14 days; range 10-21)	Ceftriaxone 2g daily or Penicillin G 20 MIU daily (14 days; range 10-30) or Doxycycline 200mg bd (28 days; range 14-30)	Doxycycline 100mg-200mg bd or Amoxicillin 0.5-1g tid or Ceftriaxone 2g daily or Penicillin G 20MIU daily (14 days; range 10-30)	30	NRVPM ⁽²⁾
Sweden Läkemedelsbehandling av borreliainfektion - ny rekommendation. Information från Läkemedelsverket 4/2009 12-17	Yes	Penicillin V 1g tid or Doxycycline 100mg bd (10 days)	Doxycycline 100mg bd (10 days)	Doxycycline 200mg daily (14 days) or 200mg bd (10 days) or Ceftriaxone 2g daily (14 days)	Doxycycline 200mg daily or Ceftriaxone 2g daily (14 days)	Not stated	NRVPM ⁽²⁾
Switzerland Evison J, Aebi C, Francioli P et al. Borreliose de Lyme. Diagnostic et traitement de la borreliose de Lyme chez l'adulte et l'enfant: recommandations de la Societe Suisse d'Infectiologie. <i>Rev Med Suisse</i> 2006; 2, 19-40.	Yes	Doxycycline 100mg bd (10 days) or Amoxicillin 500mg tid (14-21 days)	Doxycycline 100mg bd or Amoxicillin 500mg tid (14-21 days)	Ceftriaxone 2g daily or Penicillin G 3-4MIU x 6/day (28 days)	Doxycycline 100mg bd or Amoxicillin 500mg tid (30-60 days)	135	NRVPM ⁽²⁾
European Federation of Neurological Societies Mygland A, Ljøstad U, Fingerle V et al. European Federation of Neurological Societies guidelines on the diagnosis and management of European Lyme neuroborreliosis <i>Eur J Neurol</i> (in press).	Yes	Not applicable	Not applicable	Early NB without encephalitis: doxycycline 200mg daily or Ceftriaxone 2g daily (14 days) Early encephalitis or myelitis: Ceftriaxone 2g daily (14 days) Late encephalomyelitis: Ceftriaxone 2g daily (21 days) ACA and peripheral neuropathy: Doxycycline 200mg daily or Ceftriaxone 2g daily (21 days)	Not applicable	124	NRVPM ⁽²⁾
EUCALB website European Union Concerted Action on Lyme Borreliosis	Yes	Doxycycline 200mg daily or 100mg bd or Amoxicillin 500mg tid or 1g bd or Penicillin V 1g tid (14 days; range 10-21)	Doxycycline 200mg daily or 100mg bd or Amoxicillin 500mg tid or 1g bd or Penicillin V 1g tid (21 days; range 14-30)	Ceftriaxone 2g daily or Cefotaxime 2g tid or Penicillin G 3g tid (14 days; range 10-30) or Doxycycline 100-200 mg bd (21 days; range 14-30)	Doxycycline 100mg bd or Amoxicillin 500mg-1g tid or Ceftriaxone 2g daily (21 days; range 14-30 days)	Not stated	NRVPM ⁽²⁾
USA Wormser GP, Dattwyler DJ, Shapiro ED et al. The clinical assessment, treatment and prevention of Lyme disease, human granulocytotropic anaplasmosis and babesiosis. <i>Clinical Practice Guidelines by the Infectious Diseases Society of America. Clin Infect Dis</i> 2006; 43, 1089-1134.	Yes	Doxycycline 100mg bd or Amoxicillin 500mg tid (14 days; range 14-21)	Doxycycline 100mg bd or Amoxicillin 500mg tid (14 days; range 14-21)	Ceftriaxone 2g daily or Cefotaxime 2g tid or Penicillin G 3-4 MIU x 6/day (14 days; range 10-28) or Doxycycline 100-200mg bd (21 days; range 14-21)	Doxycycline 100mg bd or Amoxicillin 500mg tid (28 days)	405 ⁽⁵⁾	NRVPM ⁽²⁾
USA Halperin JJ, Shapiro ED, Loggion E et al. Practice Parameter: Treatment of nervous system Lyme disease (an evidence-based review) <i>Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology</i> 2007;69:1-102.	Yes	Not applicable	Not applicable	Ceftriaxone 2g daily or Cefotaxime 2g tid or Penicillin G 3-4 MIU x 6/day or Doxycycline 100-200 mg bd (14 days; range 10-28)	Not applicable	66	NRVPM ⁽²⁾

1. Refs cited: Number of references cited in the guideline.
2. NRVPM⁽²⁾ = No recommendation for very prolonged or multiple courses of treatment
3. Netherlands references are for the treatment section only. (38)
4. Norwegian references are for the summary only.
5. IDSA references are for the complete guideline, including diagnosis, treatment and prevention of Lyme borreliosis, anaplasmosis and babesiosis (405)

Comments

There are only minor differences in antibiotic treatment recommendations, with two Scandinavian countries favouring the use of high dose penicillin V over amoxicillin as first-choice B-lactam agent for erythema migrans, and slightly shorter treatment courses.

Doxycycline is widely recommended for in the treatment of all stages of Lyme borreliosis.

Ceftriaxone is the antibiotic most widely recommended for parenteral use.

The most recently prepared guidelines have stronger recommendations for the use of doxycycline in neuroborreliosis without encephalitic or myelitic features, following publication in 2008 of a Norwegian double-blind randomised controlled trial which showed non-inferiority of oral doxycycline 200mg daily versus intravenous ceftriaxone 2g daily for 14 days. (Ljøstad U et al. *Lancet Neurology* 2008;7:690-95)

No evidence-based European or North American guideline recommends prolonged or multiple courses of antibiotics for persistent symptoms following previously treated Lyme disease.

Acknowledgements

I am most grateful to Drs Ram Dessau, Volker Fingerle, John Halperin, Joppe Hovius, Janusz Janiec, Benoit Jaulhac, Satu Kurkela, Marjorie Monnickendam, Dag Nyman, Katharina Ornstein, Tone Skarpaas, Robert Smith, Gary Wormser, Mrs Anne Southwell, Miss Nicki Daughtrey and Mr Derek Nudd for their support in the development of this work. I thank Ms Loraine Chant and colleagues at SUHT Learning Media for skilled help and patience in poster preparation.