Comment on IDSA Guidelines

The Deutsche Borreliose Gesellschaft e.V. (German Society of Lyme-Borreliosis) has objections to the IDSA Guidelines 2006. The objections relate to the late lyme disease (LD), chronic lyme borreliosis and the so-called post lyme syndrome.

- LD is always associated with a generalized dissemination throughout the entire organism, in other words with the involvement of the CNS, too. The antibiotic treatment should therefore be carried out with antibiotics that penetrate the CNS, irrespective of the various manifestations of the illness (arthritis, neuroborreliosis, neuropathy, ACA, carditis, encephalopathy). The antibiotics recommended by the IDSA, namely doxycycline, amoxicillin and cefuroxime, do not penetrate the CNS, unlike minocycline and gemifloxacine; the i.v. applicated cephalosporines of third generation obviously induce high concentration in CSF because high dosage is applicable referred to the minimal inhibitory concentration (MIC).
- Seronegativity is a frequent occurrence with LD and does not rule out a chronic persistent lyme borreliosis (1-18).
- Contrary to the opinion of the IDSA, the following antibiotics and methods of treatment have proven to be advantageous: carbapenems, ketolides and gemifloxacin (19), pulsed-dosing (20).
- The differential diagnosis MS / LNB based on serological investigations in CSF and serum is not possible in 25% of the cases (9-11, 21).
- Peripheral neuropathy is not rare but occurs in over 20% of the cases with LD (22-25).
- So-called two-tier testing is not suitable for a serological diagnosis of LB. This is particularly true of the late phase too for the following reasons:
    - The sensitivity of the screening tests is 50%-90%
    - The test methods available on the market are not standardized with respect to their analytical value

  - The sensitivity of the western blot is around 10% higher than that of the screening test
  - This different sensitivity thus means that there is a risk that the screening test will be negative whereas the western blot shows positive
  - Neither the screening test nor the western blot guarantee the proof of a borreliosis infection, i.e. there is a problem of seronegativity (based on the screening test and western blot) even though the illness persists and has been confirmed by identification of pathogenic agent.

- Objections to the proposed definition of post-lyme-disease-syndrome of IDSA:
  - Antibiotic treatment according to standard (guidelines IDSA) do not guarantee an elimination of the LB
  - If subjective complaints do not lead to a significant disturbance of the quality of life, the assumption of an illness (PLS) is not necessary

- The disease situation described by Steere et al (26) as minor signs and symptoms and by Bujak (27) as a post-lyme syndrome represented serious discomforts for the affected patients that were comparable with decompensated cardiac insufficiency, degenerative joint diseases, pronounced diabetes mellitus or a condition after a myocardial infarction according to the accounts of Klempner et al (2).

- The following facts suggest the existence of a chronic lyme borreliosis due to vital Borrelia:
  - Persistent symptoms of an LB with identification despite intensive antibiotic treatment (28-46)
  - Members of the Deutsche Borreliose Gesellschaft have documented 150 such cases (ISBN 978-3-640-19378-3, submitted to Future Drugs, Expert Review of antiinfective therapy)
  - Borrelia could still be identified in the skin even after multiple antibiotic treatment with ceftriaxone, doxycycline and cefotaxime (47-49)

  - There is an extensive body of literature on the existence of a chronic lyme borreliosis (45, 50-55)
  - The pathogen could be cultured in every stage of LB (28-44), even after intensive antibiotic treatment (20, 41, 56-60)
  - The resistance of Bb to numerous antibiotics has been proven (61)
  - Numerous publications deal with chronic LB and the problems of its antibiotic treatment (20, 48-49, 62-66)
  - The antibiotic treatment of EM displays a therapeutic failure rate of 10% (15, 41, 45, 47, 67-74)
  - There is a high therapeutic failure rate for the antibiotic treatment of lyme borreliosios in its late phase (52, 54-56, 65, 75-77)

- The so called adequate antibiotic therapy (according to IDSA guidelines) is subject to reservations:
  - Because of possible resistance of Bb to different antibiotics (included those recommended by IDSA guidelines) change to another antibiotic may be indicated (cf. 61)
  - (Erythromycine is not suitable for treatment of LB (26, 83-85))
  - Duration of treatment depends on organic manifestations, degree and course of disease (therapeutic effect) (cf. 2, 20, 25-26, 41, 45-47, 49, 51, 53-54, 56, 60-66, 71-73, 75, 86-94)

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Treatment recommendation for Lyme disease
(According to recent discussion with Deutsche Borreliose Gesellschaft)

Antibiotics which are effective against Borrelia burgdorferi (Bb) belong to different groups. However, only few substances of each group are effective against Bb, the only effective chinolone is gemifloxacin (cf. table 1).

Table 1
Groups of antibiotics suitable for treatment of LB

Betalactames
Tetracyclines
Macrolides
Chinolones
Nitroimidazoles

Antibiotics effective against Bb are displayed in table 2, regarding the intracellular efficiency, effectiveness in the central nervous system (CNS), half-time of plasma concentration and efficiency on cystic forms (round bodies) and biofilms.

Table 2
Effective antibiotics in Lyme Borreliosis

Antibiotic	**Intracellularly effective**	**Effective in CNS**	**Effective against cysts (round bodies)**	**Effective against biofilm**	**Half-time of concentration in plasma**
Betalactames					
Ceftriaxone	-	(+)*	-	-	8 h
Cefotaxim	-	(+)*	-	-	1 h
Cefuroxim-Axetil	-	-	-	-	1 h
(Benzyl-Penicillin)					
(G-Penicillin)	-	+	-	-	40 min
(Benzyl-Penicillin)					
(Benzanthin)	-	+	-	-	3 d
(Phenoxymethyl-Penicillin)	-	-	-	-	30 min
Amoxicillin	-	-	-	-	1 h
Imipenem	-	(+) (5%)	-	-	1 h
Mezlocillin	-	(+)*	-	-	1 h
Ertapenem	-	(+)*	-	-	1 h
Meronem	-	(+)*	-	-	1 h
Piperacillin	-	(+)*	-	-	45 min

Tetracyclines					
Doxycyclin	+	(+) (14%)	-	-	15 h
Minocyclin	+	(+) (40%)	-	-	15 h
Macrolides					
Clarithromycin	+	-(2-5%)	-	-	4 h
Acithromycin	+	+****	-	-	68 h (half-time in tissue)
Chinolones					
Gemifloxacin	+	+(20%)	-	-	>12 h
Tinidazol	**+**	**+**	**+**	**+**	**10 h**
Metronidazol	+	+	+	+	7 h

Half-time of concentration in plasma, effectiveness in the CNS, intracellular effectiveness and effectiveness on cysts (round bodies), concentration in the cerebrospinal fluid (CSF)/blood concentration in percent.
*** Betalactames reach only low concentration in the CSF but cerebral tissue concentration is sufficient because of the wide therapeutic range), significantly exceeding the minimal inhibitory concentration (MIC). (cf. 164)**
**** Tinidazol and metronidazol are effective against biofilms (tinidazol more than metronidazol, Kaur N et al, 2010 (unpublished)(70))**
***** Acithromycin: high enrichment in the CNS, but not found in cerebrospinal fluid**

Monotherapy, i.e. the treatment of LB with only one antibiotic is listed in table 3. However, new scientific findings show that monotherapy can only be used in the early stage of LB, that means in case of Erythema migrans or with a general medical condition compatible with early LB (in absence of EM). Antibiotic monotherapy success rate reaches 90%, treatment failure would be about 10%. If not effective, a change of the antibiotic is needed not later than 2 weeks after beginning the treatment with the first antibiotic. In stage III (late Lyme Disease, chronic Lyme Disease), antibiotic monotherapy shows a treatment failure in half of the cases. That failure is due to the fact that no antibiotic exists, which has all the capabilities needed for a successful treatment. Scientific research pleads for the necessity of a synchronically combined antibiotic treatment. The above mentioned antibiotics are elements of such combination, as shown in table 6-8.

Table 3
Antibiotic Monotherapy of LB

Stage	**Antibiotic**	**Dosage**	**Duration**

Early Stage (localized)	Doxycyclin Acithromycin Amoxicillin Cefuroxime Clarithromycin	400 mg/d 250 mg/d 3000 mg/d 500 mg/d 500 mg/d	Depending on the course of disease, at least 4 weeks, in case of treatment failure change of antibiotic after 2 weeks
Early Stage (disseminated)	Ceftriaxone Cefotaxim Mezlocillin Imipenem Ertapenem Meronem Piperacillin Penicillin-G Minocyclin* Doxycyclin* Acithromycin Clarithromycin Gemifloxacin	2 g 2-3 x 4 g 2 x 4 g 2 x 1 g 1 g 2 x 1 g 2 x 4 g 24 Mio./d 200 mg/d 400 mg/d 500 mg/d 2 x 500 mg/d 320 mg	Depending on course of disease, in case of treatment failure change of the antibiotic after 6 to 8 weeks, complete duration of antibiotic treatment 3 months or longer
Chronic LB (Stage III)	Like disseminated early stage		3 months or longer
	Benzyl-Penicillin-Benzathin Tinidazol Metronidazol	1.2 Mega 2x per we 250 mg 400 mg	In a combined long-term antibiosis
	Imipenem Meropenem Mezlocillin Ertapenem Piperacillin	2 x 1 g 2 x 1 g 2 x 4 g 1 g 2 x 4 g	
	Gemifloxacin Vancomycin	320 mg 2 x 500 mg	6 weeks or longer (no sufficient data)

Remarks: control of blood count, ALAT, lipase creatinin.
Treatment with Ceftriaxone requires sonography of the gall bladder every two weeks in order to exclude sludge. When macrolides are used ECG is needed every two weeks. In all cases of antibiotic treatment of LB Herxheimer reaction may evolve, severe reactions are treated by one dosage of corticoides parenterally. In most cases interruption of antibiotic therapy for some days is sufficient before antibiotic treatment can be restarted with lower dosages in the first days.

Antibiotic treatment in the different stages of LB is shown in table 4.

Table 4
Stage-related antibiotic treatment of LB
(monotherapy)

Stage I
(early stage, EM)

Antibiotic	**Daily dosage**
Doxycyclin	400 mg
Acithromycin	250 mg
Amoxicillin	3 g
Cefuroxim	500 mg
Clarithromycin	1 g

Duration of treatment in general 4 weeks, change of antibiotic when ineffective after 2 weeks

Stage II
(acute LB und acute neuroborreliosis)

Antibiotic	**Daily dosage**
Ceftriaxone	2 g
Cefotaxim	2 x 4 g
Penicillin	24 Mio.
Ertapenem	1 gm
Piperacillin	2 x 4 g
Mezlocillin	2 x 4 g

Duration of treatment 4 weeks, afterwards treatment as recommended for stage III

Remark: Since monotherapy of LB in stage III has a failure rate of about 50%, a synchronically combined antibiosis is indicated. (cf. table 6-8)

Stage III
(Late disease, chronic LB)

Antibiotic	**Daily dosage**
Ceftriaxone	2 g
Cefotaxim	2 x 4 g
Benzyl-Penicillin-Benzathin	1.2 Mega, 2x per week 1 gm
Ertapenem	2 x 1 g
Imipenem	2 x 1 g
Meropenem	2 x 1 g
Piperacillin	2 x 4 g
Mezlocillin	2 x 4 g
Minocylin	200-300 mg
Acithromycin	250 mg
Clarithromycin	1 gm
Gemifloxacin	320 mg
Tinidazol	250 mg

Metronidazol 400 mg

Duration of treatment in general 3 months or longer

The mechanisms of antibiotic effectiveness of different antibiotics are demonstrated in table 5. They are the basis for the synchronically combined antibiosis.

Table 5
Antibiotic treatment of LB
Mechanisms of antibiotic effectiveness of different antibiotics

High tissue concentration	**Intracellularly effective**	**Effective in CNS**	**Effective against cysts (round bodies)**	**Effective against biofilm**
Betalactames (Ceftriaxone Cefotaxim Carbapeneme Piperacillin Mezlocillin)	Minocyclin Acithromycin Clarithromycin Gemifloxacin	Betalactames Minocyclin Acithromycin Gemifloxacin	Tinidazol Metronidazol	Tinidazol Metronidazol (POA)* (Otoba)**

Phytotherapeutica:
*POA= pentacyclic oxindol-alcaloid (Uncaria tomentosa)
**Otoba (Otoba parvifolia)

Antibiotics suitable for synchronically combined long-term antibiosis are displayed in table 6.

As mentioned above, there is no single antibiotic for an effective treatment. Therefore it is necessary to combine antibiotics synchronically for a sufficient period of time. The principle of a synchronically combined antibiosis is visualized by frequently used treatment schedules (table 7). Some other combinations and alternatives are depicted in table 8.

Table 6:
Synchronically combined antibiosis in LB stage III (overview)

Antibiotic	**Dosage**	**Duration**
Betalactames		
Ceftriaxone	2 g daily	3 months
Cefotaxim	2 x 4 g daily	(depending on course
Imipenem	2 x 1 g	of disease and

Meropenem	2 x 1 g	treatment success,
Mezlocillin	2 x 4 g	duration of treatment
Ertapenem	1 g	approximately 1 month
Piperacillin	2 x 4 g	beyond resolvement of symptoms)
Tetracycline		
Minocyclin	200 mg daily	
Doxycyclin	400 mg daily	
Macrolides		
Acithromycin	500 mg daily	
Clarithromycin	2 x 500 mg daily	
Chinolones		
Gemifloxacin	320 mg daily	
Tinidazol	250 mg	
Metronidazol	400 mg	

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Remark: Principally a third-generation cephalosporine should be used. If cephalosporines are ineffective, alternatives are imipenem, meropenem, mezlocillin or piperacillin. Tinidazol and metronidazol are effective on cysts (round bodies) and biofilms, tinidazol is more effective than metronidazol. The combined antibiosis therefore should include tinidazol (if not available metronidazol). Synchronically combined antibiotic treatment in general includes three antibiotics: third- generation-cephalosporine, minocyclin, tinidazol or metronidazol. Minocyclin and gemifloxacin are the only antibiotics, which penetrate into the CNS and which are effective intracellularly. Acithromycin reaches high concentrations in the cerebral tissue, but is not found in cerebrospinal fluid, i.e. Acithromycin is equivalent to Minocyclin. If cephalosporines and Minocyclin are not tolerated, gemifloxacin may be an alternative (effective in CNS and intracellularly).

Tables 7 and 8 contain examples for a synchronically combined antibiosis.

Table 7
Synchronically combined antibiosis of LB stage III
(frequently used treatment protocols)

<u>Example A</u>	
Ceftriaxone	**effective in CNS** **high concentration in tissue**
+ Minocyclin	**effective in CNS** **intracellularly effective**
+ Tinidazol	**effective on cysts and biofilms**
<u>Example B</u>	
Acithromycin	**effective in CNS** **intracellularly effective**
+ Minocyclin	**effective in CNS**

	intracellularly effective
+ Tinidazol	**effective against cysts (round bodies) and biofilms**

Example C

Acithromycin	**effective in CNS**
	intracellularly effective
+ Tinidazol	**effective against cysts (round bodies) and biofilms**
+ POA + Otoba (and/or Serrapeptidase)	**effective against biofilms**

Table 8
Synchronically combined antibiosis of LB stage III (examples, overview)

Ceftriaxone 2 g
Minocyclin 150-300 mg
Tinidazol 250 mg

Ceftriaxone 2 g
Minocyclin 150-300 mg
Tinidazol 250 mg

Ceftriaxone 2 g
Acithromycin 250 mg
Tinidazol 250 mg

Gemifloxacin 320 mg
Acithromycin 250 mg
Tinidazol 250 mg

Acithromycin 250 mg
Tinidazol 250 mg

Minocyclin 150-300 mg
Tinidazol 250 mg

Acithromycin 250 mg
Minocyclin 150-300 mg
Tinidazol 250 mg

Alternatives to Acithromycin 250 mg

- Clarithromycin 1 g

Alternatives to Ceftriaxone 2 g

- Cefotaxime 2x4 g
- Ertapenem 1 g
- Imipenem 2x1 g
- Mezlocillin 2x4 g
- Piperacillin / Tazobactam 2x4 g
- Benzyl-Penicillin-Benzathin 1.2 Mio IE 2 times per week

Phytotherapeutica may also be used against Borrelia burgdorferi. POA (pentacyclic oxindol-alcaloid) and Otoba (otoba parvifolia, active substance: farnesyl-homogentisin-acid) have proven effective against mobile spirochetes, cystic forms (round bodies) and biofilms (81). Effectiveness of Serrapeptidase was found in in-vitro experiments with different bacteria (82, 83, 84).

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