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. applied 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:
  
  o The sensitivity of the screening tests is 50%-90%

  o 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)


  - 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:

  o Because of possible resistance of Bb to different antibiotics (included those recommended by IDSA guidelines) change to another antibiotic may be indicated (cf. 61)

  o (Erythromycin is not suitable for treatment of LB (26, 83-85))

  o 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)
References

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18. Nadelman RB et al, Isolation of Borrelia burgdorferi from the blood of seven patients with Lyme disease, American Journal of Medicine (1990), 88: 21-6


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Department of Neurology, Centre Hospitalier de Mont de Marsan, 40000 Mont de Marsan, France


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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

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

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dosage</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxycyclin</td>
<td>(+) (14%)</td>
<td>15 h</td>
</tr>
<tr>
<td>Minocyclin</td>
<td>(+) (40%)</td>
<td>15 h</td>
</tr>
</tbody>
</table>

**Macrolides**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dosage</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin</td>
<td>-(2-5%)</td>
<td>4 h</td>
</tr>
<tr>
<td>Acithromycin</td>
<td>+****</td>
<td>68 h</td>
</tr>
</tbody>
</table>

**Chinolones**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dosage</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemifloxacin</td>
<td>+(20%)</td>
<td>&gt;12 h</td>
</tr>
<tr>
<td>Tinidazol</td>
<td>+</td>
<td>10 h</td>
</tr>
<tr>
<td>Metronidazol</td>
<td>+</td>
<td>7 h</td>
</tr>
</tbody>
</table>

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**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Antibiotic</th>
<th>Dosage</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Early Stage (localized)  
Doxycyclin  400 mg/d  
Acithromycin  250 mg/d  
Amoxicillin  3000 mg/d  
Cefuroxime  500 mg/d  
Clarithromycin  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  2 g  
Cefotaxime  2-3 x 4 g  
Mezlocillin  2 x 4 g  
Imipenem  2 x 1 g  
Ertapenem  1 g  
Meronem  2 x 1 g  
Piperacillin  2 x 4 g  
Penicillin-G  24 Mio./d  
Minocycline  200 mg/d  
Doxycycline  400 mg/d  
Acithromycin  500 mg/d  
Clarithromycin  2 x 500 mg/d  
Gemifloxacin  320 mg  
Depending on course of disease, in case of treatment failure change of antibiotic after 6 to 8 weeks, complete treatment 3 months or longer.

Chronic LB (Stage III)  
Like disseminated early stage  
Benzyl-Penicillin- Benzathin  1.2 Mega 2 x per week  
Tinidazol  400 mg  
Metronidazole  1 g  
Imipenem  2 x 1 g  
Meropenem  2 x 1 g  
Mezlocillin  2 x 4 g  
Ertapenem  1 g  
Piperacillin  2 x 4 g  
Gemifloxacin  320 mg  
Vancomycin  2 x 500 mg  
3 months or longer  
In a combined long-term antibiosis  
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)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Daily dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxycyclin</td>
<td>400 mg</td>
</tr>
<tr>
<td>Acithromycin</td>
<td>250 mg</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>3 g</td>
</tr>
<tr>
<td>Cefuroxim</td>
<td>500 mg</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>1 g</td>
</tr>
</tbody>
</table>

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

**Stage II**
(acute LB und acute neuroborreliosis)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Daily dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxon</td>
<td>2 g</td>
</tr>
<tr>
<td>Cefotaxim</td>
<td>2 x 4 g</td>
</tr>
<tr>
<td>Penicillin</td>
<td>24 Mio.</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>1 gm</td>
</tr>
<tr>
<td>Piperacillin</td>
<td>2 x 4 g</td>
</tr>
<tr>
<td>Mezlocillin</td>
<td>2 x 4 g</td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Daily dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxon</td>
<td>2 g</td>
</tr>
<tr>
<td>Cefotaxim</td>
<td>2 x 4 g</td>
</tr>
<tr>
<td>Benzyl-Penicillin-Benzathin</td>
<td>1.2 Mega, 2x per week</td>
</tr>
<tr>
<td></td>
<td>1 gm</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>2 x 1 g</td>
</tr>
<tr>
<td>Imipenem</td>
<td>2 x 1 g</td>
</tr>
<tr>
<td>Meropenem</td>
<td>2 x 1 g</td>
</tr>
<tr>
<td>Piperacillin</td>
<td>2 x 4 g</td>
</tr>
<tr>
<td>Mezlocillin</td>
<td>2 x 4 g</td>
</tr>
<tr>
<td>Minocycin</td>
<td>200-300 mg</td>
</tr>
<tr>
<td>Acithromycin</td>
<td>250 mg</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>1 gm</td>
</tr>
<tr>
<td>Gemifloxacin</td>
<td>320 mg</td>
</tr>
<tr>
<td>Tinidazol</td>
<td>250 mg</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>High tissue concentration</th>
<th>Intracellularly effective</th>
<th>Effective in CNS</th>
<th>Effective against cysts (round bodies)</th>
<th>Effective against biofilm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betalactames (Ceftriaxone Cefotaxim Carbapenem Piperacillin Mezlocillin)</td>
<td>Minocyclin Acithromycin Clarithromycin Gemifloxacin</td>
<td>Betalactames Minocyclin Acithromycin Gemifloxacin</td>
<td>Tinidazol Metronidazol Metronidazol (POA)*</td>
<td>Tinidazol Metronidazol (Otoba)**</td>
</tr>
</tbody>
</table>

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:
Synchronously combined antibiosis in LB stage III (overview)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dosage</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betalactames</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>2 g daily</td>
<td>3 months</td>
</tr>
<tr>
<td>Cefotaxim</td>
<td>2 x 4 g daily</td>
<td>(depending on course of disease and)</td>
</tr>
<tr>
<td>Imipenem</td>
<td>2 x 1 g</td>
<td></td>
</tr>
</tbody>
</table>
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 resolution 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

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)

**Example A**
Ceftriaxone effective in CNS
+ Minocyclin high concentration in tissue effective in CNS
+ Tinidazol intracellularly effective effective on cysts and biofilms

**Example B**
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**
Synchronously combined antibiosis of LB stage III (examples, overview)

- Ceftriaxone 2 g
- 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).

References


46. Kleemann W et al. Prolonged antibiotic therapy in PCR confirmed persistent Lyme disease (in Vorbereitung)?