Challenge to the Recommendation Restricting Specific Therapeutic Options in the Treatment of Lyme Disease

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This challenge is to recommendation #5, page 1105 of the 2006 IDSA guidelines, regarding the treatment of early Lyme disease. The recommendation states:

> *"Because of a lack of biologic plausibility, lack of efficacy, absence of supporting data, or the potential for harm to the patient, the following are not recommended for treatment of patients with any manifestation of Lyme disease: first generation cephalosporins, fluoroquinolones, carbapenems, vancomycin, metronidazole, tinidazole, amantadine, ketolides, isoniazid, trimethoprim-sulfamethoxazole, fluconazole, benzathine penicillin G, combinations of antimicrobials, pulsed-dosing (i.e., dosing on some days but not others), long-term antibiotic therapy, anti-Bartonella therapies, hyperbaric oxygen, ozone, fever therapy, intravenous immunoglobulin, cholestyramine, intravenous hydrogen peroxide, specific nutritional supplements, and others (see table 4) (EIII)."*

There are several unusual aspects to this recommendation which make it difficult to defend. To begin with, the recommendation cannot be supported as structured. It contains 26 dissimilar agents, therapeutic approaches and vaguely identified treatments such as "specific nutritional supplements" yet offers no reason as to why they were clustered together into a single group. Additionally, it does not offer a specific reason as to why each of the named entities should not be used; instead, it lists 4 potential reasons, leaving it to the reader to conclude which reason(s) apply to which item(s). Such ambiguity has no place in a recommendation limiting treatment options; the panel is obliged to state the specific reason for recommending against each item on the list.[1] Finally, the prohibition against the use of first generation cephalosporins had been discussed in recommendation 3, page 1104; it is unnecessary to repeat this in recommendation 5.

The panel's strong recommendation against the use of the items on the list is based on level III evidence. Presumably this evidence is, for the most part, panel opinion because the panel cites very few references regarding the agents in question and there is little discussion in the "Evidence to support treatment recommendations" section pertaining to recommendation 5. These 2 sentences are the only ones from that section which apply: *"B. burgdorferi is resistant to certain fluoroquinolones, rifampin, and first-generation cephalosporins [39, 40, 125, 127, 133]."* and *"In contrast to the second-generation cephalosporin cefuroxime and to certain third-generation cephalosporins (e.g., ceftriaxone), first-generation cephalosporins, such as cephalexin, are inactive in vitro against B. burgdorferi and are ineffective clinically [125, 133]."* In fact, the references detail the evidence against first generation cephalosporins and rifampin (which is not on the "not recommended" list); the limited activities of ciprofloxacin and ofloxacin were noted. Using expert opinion to justify a recommendation requires some safeguards, as noted in this statement from an IDSA guideline development article: *"The basis on which expert opinion was formed should be specified."*[2] Making a strong recommendation on weak evidence is discouraged by the American Academy of Pediatrics.[3] Section 5.6 of the US Preventative Services Task Force Procedure Manual details the principles used by the Task Force when formulating its evidence-based recommendations. Included in their principles is this: *"Recommendations are not based largely on opinion, such as expert opinion or subjective perceptions based on clinical experience."*[1]

The panel's lack of evidence in support of recommendation 5 is sufficient grounds for rejecting the recommendation. Yet their failure to cite references should not be interpreted to mean that the scientific literature is silent with regards to the effectiveness of the listed agents to kill *B. burgdorferi*. Several of the "not recommended" antibiotics have been evaluated for use in Lyme disease and the data suggests that these agents do or may have a place in the treatment of *B.burgdorferi* infections. There is no indication as to why the panel omitted this evidence. Each of these potentially useful antibiotics will be discussed separately.

References

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Benzathine penicillin G

Benzathine penicillin G has been shown to be an effective and safe treatment for some patients with Lyme disease. A 1992 paper provides case reports on two patients with Lyme arthritis resistant to prior antibiotic treatment. Both were successfully treated with long-term benzathine penicillin G.[1] A small double-blind, placebo-controlled study also found benzathine penicillin G efficacious, as compared to placebo, in the treatment of Lyme arthritis.[2] The safety of benzathine penicillin G was assessed in a study of patients with a history of rheumatic fever. After 32,430 injections over 2736 patient years of observation, 57 of the 1790 patients (3.2%) had an allergic reaction. 4 patients had anaphylaxis, an incidence of 0.2% (1.2/10,000 injections), all were over 12 years of age; 1 patient died, yielding a fatality incidence of 0.05% (0.31/10,000 injections).[3] The safety of long-term use of benzathine penicillin G is also noted by the FDA.[4]

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Fluoroquinolones

In recent years researchers have investigated the ability of newer antibiotics to kill *B.burgdorferi*. While fluoroquinolones are more likely to be used for the treatment of Bartonella infections, (a discussion beyond the scope of the 2006 guidelines) than *B. burgdorferi*, *in vitro* studies have demonstrated that fluoroquinolones also have enhanced activity against *B.burgdorferi*.[1,2]

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Carbapenems

Carbapenems, like other cell-wall agents, may be effective agents for the eradication of *B.burgdorferi*. Several investigators have studied these antibiotics *in vitro* and demonstrated the enhanced activity many of these agents have against *B.burgdorferi*.[1-4]

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Vancomycin

In vitro studies investigated the susceptibility of *B.burgdorferi* strain B31 to vancomycin.[1,2] Although vancomycin's mechanism of action against the bacterial cell wall is different from the beta-lactams, electron microscopic evaluation of strain B31 after exposure to vancomycin demonstrated cellular disruption identical to that seen with penicillin exposure. This evidence suggests that vancomycin would be an effective antibiotic against strain B31 and, possibly, all *B.burgdorferi* strains.[1] However, another *in vitro* study found vancomycin to have a MIC 90 of 0.83mg/l and *in vivo* mouse studies demonstrated that low-dose vancomycin did not eradicate infection in immunodeficient animals.[2,3]

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Ketolides

Ketolides have been studied *in vitro* and found to be effective against *B.burgdorferi*.[1-4] In one such study, testing of 17 isolates of Bb s.l. demonstrated that both cethromycin and telithromycin were effective against the bacteria. Their relative MIC (90)s were 0.0019 micro g/ml) and 0.0078

micro g/ml. Both agents demonstrated enhanced effectiveness in electron microscopic analysis and time-kill studies.[1]

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Fluconazole

In a small observational study, 11 patients with neuro-borreliosis, who were unsuccessfully treated with previous antibiotic therapy, received 200 mg of fluconazole daily for 25 days. At the conclusion of active treatment, eight patients were asymptomatic and continued to be relapse-free during the one year follow-up period.[1]

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Metronidazole, tinidazole

The pleomorphic nature of many bacteria, including spirochete species, is well established.[1-3] For more than 20 years, researchers have been observing and investigating the pleomorphic qualities of *Borrelia burgdorferi*.[4-25] The bacteria may exist as a mobile spirochete or a cell-wall deficient, cyst form.[7,9-25] *B. burgdorferi* also forms membrane-derived granules containing intact spirochetal DNA.[5,6,22,23]

Borrelia burgdorferi's morphologic shift from mobile spirochete to cyst form occurs as an active response to unfavorable changes in the bacteria's environment.[7,11,14,17,18] Two studies found that cyst formation occurred via a physical-chemical rearrangement of the outer membrane.[17,18] This process requires protein synthesis; cysts are not merely a breakdown product of the motile form.[14] Exposing *B. burgdorferi* to agents interfering with protein synthesis led to a low level of cyst formation.[9,14] Cyst forms of *B. burgdorferi* contain non-motile spirochetes.[10,14,18] Transformation from cyst to motile spirochete has been demonstrated *in vitro* and *vivo*.[7,11,14,17,18] Cysts have been identified in human CSF, skin and brains; the patient sources for these specimens all had confirmed Lyme disease.[8,11,22-24] Cysts may be extracellular or intracellular.[22-25]

Cyst forms have a lower metabolic rate than the motile spirochete;[18] cyst formation in response to nutrient deprivation is an adaptive response which may increase *B. burgdorferi* survival.[14] Survival may also be enhanced via immune system evasion. Cyst forms present different antigens to hosts than the spirochetal forms, as evidenced by Western blot testing.[14] Such differences may allow cysts to avoid the humoral response, leading to improved survival of this form. Latent periods, lasting months to years, are not unusual in patients infected with *B. burgdorferi*;[26,27] these periods are reminiscent of the natural course of untreated syphilis. The presence of *in vivo* cysts, able to transform to motile forms under more favorable conditions, is one plausible explanation for this phenomenon. Burgdorfer commented specifically on this possibility: *"It is tempting to speculate, however, that the survival mechanism of spirochetes is responsible for the diverse pathology of these organisms as well as for their ability to survive as cystic forms thereby producing prolonged, chronic and periodically recurrent disease."*[28]

Having established that the cyst form holds certain survival advantages over the motile form, that it exists *in vivo* and is able to transform to the motile form *in vivo*, it would appear clinically prudent to investigate the cyst form's role in treatment failures and relapses. The effects of various antibiotics in relation to cyst forms of *B. burgdorferi* have been investigated. Kersten et al. found that exposing mobile spirochetes to penicillin G or ceftriaxone favored the production of cysts while exposure to doxycycline led to low levels of cyst formation.[7] These are logical outcomes given our knowledge of *B. burgdorferi's* pleomorphic abilities. *B. burgdorferi's* survival in the presence of cell-wall agents would be enhanced by the transformation to the cystic form, which is less affected by these agents. Because transformation to the cyst form requires protein synthesis, a metabolic process inhibited by doxycycline, it is understandable that few cysts would form in the presence of this antibiotic. It is reasonable to hypothesize that other antibiotics which impair protein synthesis would yield similar results. Brorson demonstrated that telithromycin was effective against the motile spirochete but not the cyst form.[20] In addition to the telithromycin study, the effectiveness of other antibiotics against the cyst form of *B. burgdorferi* has been investigated. While cell-wall agents, tetracyclines and a macrolide have proven ineffective against the cyst form, Brorson demonstrated that metronidazole, tinidazole and hydroxychloroquine successfully destroy this form.[13,16,19] CSF concentrations of metronidazole are similar to that of plasma,[29] an important consideration in patients with CNS involvement. Further studies on the cyst form, its role in disease and its response to antibiotics are needed.

Based on *B. burgdorferi's* pleomorphic nature, the potential for alternative morphologic forms to provide mechanisms for both survival and ongoing infection and the results from studies investigating the effects of various antibiotics on the cystic form of B.burgdorferi, the panel's recommendation against the use of metronidazole and tinidazole is not supported and it should be rejected.

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Safety

All medications carry the potential for causing both benefit and harm. The probability of minor and major side effects to oral antibiotics is 0.04 and 0.0001, respectively; the probability of minor and major side effects to IV antibiotics is 0.03 and 0.001, respectively.[1] Safety evaluations were performed for benzathine penicillin G, vancomycin fluconazole, metronidazole and tinidazole prior to their approval by the FDA.[2] The same can be said for the specific agents in the fluoroquinolones, carbapenems and ketolide classes which are currently available for use.[1] The long-term safety of benzathine penicillin G has been demonstrated.[3]

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Anti-Bartonella therapies

Recommendation 5 includes "anti-Bartonella therapies" in the list of treatments not recommended for use in patients with Lyme disease. While a full discussion of tick-borne Bartonella infections is beyond the scope of this challenge and the scope of the 2006 guidelines, a few comments are warranted. The recommendation against anti-Bartonella therapies is an interesting inclusion, in that it suggests physicians withhold treatment of known pathogens. Presumably the panel justifies this advice based on the single sentence in the guidelines devoted to the discussion of Bartonella: *"Bartonella DNA has been found in some Ixodes species, but there is no convincing evidence that Bartonella infections can be transmitted to humans by a tick bite [260]."* Reference 260 is an editorial written by panel members Halperin and Wormser in 2001.[1]

What the guidelines authors fail to mention is that the editorial was in response to an article by Eskow et al. which presented the case histories of 4 patients, suggesting they represented *"cases of concomitant central nervous system infection with B henselae and B burgdorferi"*.[2] Two patients in Poland were also thought to be dually infected with *B henselae* and *B burgdorferi,* as described by Podsiadly et al..[3] Billeter et al. reviewed clinical studies supporting the tick transmission of Bartonella species and concluded: *"Studies of this type strengthen evolving evidence suggesting Bartonella species are being transmitted by currently unidentified arthropod vectors, such as ticks."*[4] Thus it would appear that anti-Bartonella may be an appropriate treatment strategy in some patients with Lyme disease and on that basis the recommendation should be rejected.

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Combinations of antimicrobials

The use of antimicrobial combinations is not a new concept or an uncommonly applied one. Paging through The Sanford Guide quickly reveals the wide variety of infections treated with combinations of antibiotics – *H. pylori*, breast abscesses, diverticulitis, and PID are just a few examples.[1] In fact, the concept of combination therapy is so widely applied that most clinicians have forgotten that, though the medications are found in a single formulation, TMP/SMX

treatment represents combination antibiotic therapy. Combination therapy may lead to antibiotic synergy; Dever et al. demonstrated synergy against *B. burgdorferi* using a combination of penicillin and vancomycin.[2]

Given its frequent use in other infections, it is unclear why the panel specifically recommends against combination therapy in Lyme disease. The variety of morphologic forms, as discussed earlier in this challenge, demands combination therapy as, to date, no single agent appears able to eradicate both the mobile and cystic forms. Additionally, *B. burgdorferi* can exist as both an extracellular and intracellular pathogen. Multiple researchers have studied *B. burgdorferi* within *post mortem* and *ex vivo* specimens of human endothelial cells, fibroblasts, synovial cells, keritinocytes, lymphocytes, neurons and glial cells.[3-9] An intracellular existence allows *B. burgdorferi* to escape recognition and destruction by the immune system and to avoid the effects of certain classes of antibiotics. For example, residence inside fibroblasts has been shown to protect *B. burgdorferi* from the bactericidal effects of ceftriaxone.[4] In such instances, adding an antibiotic with intracellular capabilities may increase the potential to eradicate the infection. Lastly, it has been well documented that some patients harbor multiple tick-borne infections.[10-14] No studies have investigated how such situations should be addressed; namely, is there a preferred sequential order to treating the infections or should simultaneous therapy occur? While treatment strategies may overlap for early Lyme disease and HGA or HME, this is not necessarily the case for other tick-borne disease combinations. For example, simultaneous therapy for *B. burgdorferi* and *Babesia ssp* may result in a combined use of doxycycline, atovaquone and azithromycin. In dually infected patients, combinations of antibiotics are both justified and necessary.

Borrelia burgdorferi's pleomorphic nature, its capacity to exist in intracellular locations and its presence in patients infected with multiple tick-borne agents makes it a difficult pathogen to eradicate. Treatment success requires a carefully constructed antibiotic treatment regimen which may include the use of combination therapy. The recommendation against the use of antimicrobials combinations is not supported and should be rejected.

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Pulsed-dosing

The use of pulsed-dose therapy in Lyme disease has been discussed in the literature.[1-2] Preac-Mursic et al. suggested this approach may be useful in treating complicated early disease and late stage disease.[1] Hassler described two cases in which this therapy was successful.[2] In both instances, the patient had received several weeks of IV antibiotic therapy yet continued to have positive results for *B. burgdorferi* on skin biopsy specimens. Pulsed regimens, consisting of repeated cycles of high dose antibiotics for 1-2 days followed by several antibiotic-free days, resulted in symptom resolution and negative biopsies on follow-up; patients remained well during the 6 month post-treatment observation period.

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Long-term antibiotic therapy

Recommendation 5 advises against the use of "long-term" antibiotics but does not precisely define the term and table 4 is also vague on this point. While the panel's rationale for limiting treatment duration is unclear, there are several clear reasons for treatment to be extended. *Borrelia burgdorferi* invades protected sites and, as previously discussed in this challenge, has the ability to inhabit intracellular locations.[1-7] *B.burgdorferi* alters the immune response in multiple ways, favoring survival.[8-12] *B.burgdorferi* is able to avoid complement-mediated killing; one avoidance mechanism is via a surface protein which interacts with human factor H and FHL-1.[9,10] *B.burgdorferi* also avoids destruction by antibodies and alters the function of neutrophils and dendritic cells.[9,11,12] *B.burgdorferi's* ability to alter or avoid humoral, innate and cellular killing by the immune system results in patients being, for this particular pathogen, relatively immunocompromised. The survival strategies of *B.burgdorferi* are examples of *"characteristics of other infections that justify longer treatment courses"* as described by the panel on page 1118.

Long-term use of antibiotics may be one way to improve outcomes in certain subsets of patients. The treatment trials cited in the section on early Lyme disease noted risk factors which were related to treatment failure. Dysesthesias,[13] paresthesias,[14] multiple EM,[14,15] increased irritability,[13] persistent fatigue,[15] headache,[15] stiff neck[15] and increased severity of the initial illness[15] were associated with an increased risk of treatment failure. Luft noted in his comparison trial of amoxicillin and azithromycin that the former performed better in human trials while the latter performed better in vitro.[16] He speculated that duration of therapy may be crucial. In an unrelated mouse study, Zeidner found that single-dose sustained-release doxycycline yielded measurable levels for 19 days and significantly out-performed a single oral dose in preventing Lyme disease post-tick bite.[17] He, too, raised the theory that duration of therapy is important. Rather than offer shorter courses and wait for the expected failures, it would be reasonable to offer patients at high risk of failure alternative regimens utilizing a longer initial course of therapy.

Studies on the treatment of late neurologic Lyme disease demonstrate that treatment at this stage is difficult.[18,19] In a 1990 study by Logigian et al., 27 patients were treated with 2 gm of IV ceftriaxone for 2 weeks.[18] At 6 months post treatment, 63% were improved (not cured), 22 % had improved then relapsed and 15% were unchanged from baseline; these results suggest that 2 weeks of ceftriaxone therapy is inadequate. A follow-up study by the same author treated 18 patients who had Lyme encephalopathy with 2 gm of IV ceftriaxone for 30 days.[19] At their final evaluation, only 39% considered themselves "normal". One patient, who was improved at the 6 month follow-up visit, relapsed at 8 months and was retreated. Given these poor outcomes, patients and physicians may decide that longer treatment durations are worth pursuing.

While some may argue that the retreatment study by Klempner proved that longer durations of antibiotic treatment are not useful,[20] that conclusion is faulty. A full discussion of that trial is beyond the scope of this challenge however, a critique of the study design used in the Klempner trial is applicable to this discussion. The study excluded patients who had received 60 or more days of IV antibiotics but patients who received less than 60 days remained eligible; 33% of the patients in the study had received IV antibiotics for a mean of 30 days. If prior experience can predict future outcomes, such patients would be more likely to fail than those who were never treated with IV antibiotics. Their inclusion represents a selection bias favoring treatment failure (a curious design flaw for a treatment trial). Note that Logigian (1999) specifically excluded patients previously treated with 30 days of ceftriaxone from his trial and Dattwyler (2005) excluded patients who had previously been treated for late Lyme disease.[19,21] Additionally, Klempner was a re-treatment trial and would not necessarily inform discussions on the use of long-term treatment as initial therapy.

The use of long-term antibiotic therapy is a reasonable approach to consider for patients with early Lyme disease at high risk for treatment failure, for patients with late Lyme disease and for those who have failed shorter courses of antibiotics for any stage of illness. Long-term oral antibiotics are safely and successfully used in other medical conditions, such as acne and rheumatoid arthritis.[22,23] The decision to use long-term antibiotics is best left to patients and their treating physicians because they can best weigh the risks and benefits of this therapeutic option. The recommendation against long-term antibiotic therapy is unsupported and should be rejected.

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Restricting the exploration of potential therapies

This challenge opened with criticism regarding the structure and ambiguity of recommendation 5, its use of panel opinion as a substitute for scientific evidence and concerns that this weak evidence was subsequently used to formulate a strong recommendation against a wide range of treatments. The net effect of prohibiting the use of atypical administration regimens, specific antibiotics or entire classes of antibiotics is a reduction in therapeutic options and innovation.

Why would the panel choose this course when our understanding of Lyme disease is far from complete? Our microbiologic knowledge continues to grow via the discovery of new species within the *Borrelia burgdorferi* sensu lato group (including one in the US),[1,2] the identification of additional Babesia species and the evolving evidence supporting the view that Bartonella infections can be transmitted by ticks.[3-6] Appreciation of the effects strain variability has on disease manifestations, testing and treatment has only recently emerged.[7-9] Immunologic evidence continues to mount regarding *B. burgdorferi's* ability to modulate the host immune response to infection, thereby allowing it to evade the immune system which enhances its survival.[10-14] Co-infecting pathogens are receiving greater research attention but trials investigating treatment strategies for co-infected patients have yet to be initiated. Deficiencies in testing are apparent for both diagnostic and therapeutic assessment purposes, hindering objective measures of treatment response in an illness marked by a paucity of readily apparent exam findings and a propensity towards long periods of disease latency.[15,16] Treatment trials have been flawed, sometimes fatally,[17-19] and outcomes have been poor, particularly in late disease,[20-22] yet no human trial is currently underway; efforts to tease out subgroups which may benefit from new strategies for initial treatment have been nonexistent. And, amidst this scientific uncertainty, the number of new Lyme disease cases continues to rise.[23]

To limit options and innovation at this juncture is imprudent. On page 1096, the panel asserts*: "In the treatment of Lyme disease, as in all infectious diseases, basic medical and scientific principles must be considered. In selecting an antibiotic, there should be evidence of activity in vitro, evidence for penetration into the infected sites, and well-designed clinical studies to support the treatment regimen."* This approach, reasoned on paper, falls apart in practice. Studies of *in vitro* antibiotic activity conflict with the results of treatment trials;[24] agents with impressive MICs yield poor treatment outcomes and are surpassed by antibiotics which demonstrated only modest *in vitro* effectiveness.[25] There have been too few well-designed and executed trials, and the completed trials utilized a therapeutic spectrum which was too narrow.

The most basic medical and scientific principles have not been followed. We have leapt from a position of limited evidence to formulate recommendations which ignore observations from those closest to the problem - patients and their treating physicians. Randomized, controlled trials do not arise de novo. Rather, they begin with an observation or question. The initial question in

Lyme disease was: "What is causing this cluster of rash- associated arthritis?"; the current question is: "Why do some patients remain ill despite treatment?" Laboratory research is investigating this question from many perspectives but lags behind the needs of today's patients. This is not the time to tie clinicians' hands as recommendation 5 would do. Insights gained from the judicious off-label use of FDA-approved antibiotics may lead to successful clinical trials and improved outcomes. Consider this statement from the FDA regarding off-label use of medications: *"After a drug is put on the market, health professionals continuously experiment with new uses. We think that is appropriate and don't want to restrict that kind of use of drugs."* The FDA recognizes the value of physician innovation; it would be wise for the panel to do the same.

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For all of the reasons discussed in this challenge, Recommendation 5, page 1105 should be rejected.