XXV. SHOULD PATIENTS WITH PERSISTENT SYMPTOMS FOLLOWING STANDARD TREATMENT OF LYME DISEASE RECEIVE ADDITIONAL ANTIBIOTICS?

Recommendation:

1. For patients who have persistent or recurring nonspecific symptoms such as fatigue, pain, or cognitive impairment following recommended treatment for Lyme disease, but who lack objective evidence of reinfection or treatment failure, we recommend against additional antibiotic therapy *(strong recommendation, moderate-quality evidence).* **Comment**: Evidence of persistent infection or treatment failure would include objective signs of disease activity, such as arthritis, meningitis, or neuropathy.

Summary of The Evidence. Several clinical trials have investigated antibiotic re-treatment of patients with disabling symptoms that had persisted for months after standard treatment for documented Lyme disease.

In the largest trial 78 seropositive and 51 seronegative subjects with well-documented, previously treated Lyme disease but persistent musculoskeletal pain, neurocognitive symptoms, or dysesthesias, often associated with fatigue, were randomized to receive 30 days of IV ceftriaxone followed by 60 days of oral doxycycline; these treatments were compared to IV placebo followed by oral placebo [377, 378]. At 30, 60, and 180 days there was no difference between the treatment and placebo arms as assessed by symptom severity and neurocognitive measures. In a second trial 54 subjects were randomized to 28 days of IV ceftriaxone versus IV placebo, assessing a variety of outcome measures including fatigue, pain, and cognitive function [379]. At 6-month follow up there was an improved fatigue score compared with baseline in the treatment arm, though no improvement in the other domains tested; the fatigue scores and their interpretability are limited by methodological and statistical considerations [380]. A third trial evaluated a longer duration of therapy, comparing the outcome of IV ceftriaxone (23 subjects) to IV placebo (14 subjects), given for 10 weeks [381]. A cognitive index score at week 24 did not differ between treatment and placebo groups. A secondary outcome measure improved at week 12 and was sustained to week 24 for pain and physical functioning, but not fatigue, the opposite of the findings in the second study. In the second and third of these studies, fatigue improved over baseline among placebo-treated patients (9.1% and 14.5%, respectively). Finally, in a more recent trial 281 patients (89% of whom had previously received antibiotic treatment for the diagnosis of Lyme disease) were randomized to receive 14 days of IV ceftriaxone, followed by 12 weeks of either doxycycline, clarithromycin plus hydroxychloroquine, or placebo [382]. At the final observation point, 52 weeks following initiation of therapy, health-related quality of life scores did not differ significantly among the 3 groups.

In all studies, subjects improved—but the improvement was also experienced by placebo-treated subjects. Numerous adverse events were reported in all studies, including complications attributed to both antibiotics and to IV catheters. One serious antibiotic allergic reaction occurred in each of 2 studies. Additional adverse events in two of the studies (totaling <100 subjects) included 6 IV catheter complications and 1 instance of ceftriaxone-associated gallbladder pseudolithiasis requiring cholecystectomy. Diarrhea occurred in 43% of patients receiving ceftriaxone in 1 study. Despite these examples of harm from prolonged antibiotics, many patients continue to receive prolonged IV antibiotic therapy for symptoms following initial Lyme disease treatment—a practice that has been associated with documented deaths [383, 384].

Thus, the evidence does not support the hypothesis that persistent symptoms should be interpreted as clinical infection, or that antibiotic retreatment is safe and effective. Studies conducted in animal models have raised hypotheses of microbiologic persistence. However, these studies are methodologically highly heterogeneous and have limited generalizability to natural human infection [380]. Moreover, animal models cannot reproduce the human experiences of fatigue and pain, and it is unlikely that any animal study can give reliable insight into the biology of humans experiencing such symptoms following treatment of Lyme disease.

Rationale for Recommendation. This recommendation places a high value on avoiding harm due to unnecessary antibiotic exposure or to unnecessary IV access devices. The risks of these interventions were not matched by convincing evidence that antibiotics improved patients' symptom experiences or quality of life compared to placebo.

Chronic Lyme Disease

Early work in the field sometimes referred to patients with infection of more than 6 months duration—particularly North American patients with Lyme arthritis or European patients with acrodermatitis chronica atrophicans—as having chronic infection. This term has been largely supplanted by "late manifestations" as these syndromes often appear after a long period of apparent clinical latency. The term "chronic Lyme disease" as currently used lacks an accepted definition for either clinical use or scientific study. In practice, the term has been applied to a highly heterogeneous patient population, including patients with prolonged and unexplained symptoms who lack objective features of Lyme disease, many of whom prove to have alternative medical diagnoses. In 1 systematic study, more than half of patients previously given this diagnosis actually had other specific disorders including rheumatoid arthritis or osteoarthritis, amyotrophic lateral sclerosis, myasthenia gravis, or depression [385]. Regardless of their underlying diagnosis, many patients who receive the diagnoses of chronic Lyme disease are ill, highly symptomatic, and may be quite disabled by their underlying illnesses and symptoms. When evaluating such patients, clinicians should conduct a thorough and individualized history,