7. Jha TK, Olliaro P, Thakur CPN, et al. Randomised controlled trial of aminosidine (paromomycin) v. sodium stibogluconate for treating visceral leishmaniasis in North Bihar, India. BMJ **1998**; 361:1200–5.
8. Herwaldt BL, Berman JD. Recommendations for treating leishmaniasis with sodium stibogluconate (Pentostam) and review of pertinent clinical studies. Am J Trop Med Hyg **1992**; 46:296–306.
9. Sundar S, Goyal AK, More DK, Singh MK, Murray HW. Treatment of antimony-unresponsive Indian visceral leishmaniasis with ultra-short courses of amphotericin-B-lipid complex. Ann Trop Med Parasitology **1998**; 92:755–64.
10. Kenney RT, Gam AA, Ray M, Pai K, Sundar S. Resistance to treatment in kala-azar: speciation of isolates from northeast India [abstract]. Clin Infect Dis **1999**; 29:965.
11. Meyerhoff A. US Food and Drug Adminstration approval of AmBisome (liposomal amphotericin B) for treatment of visceral leishmaniasis. Clin Infect Dis **1999**; 28:42–8.
12. Sundar S, Sundar S, Gupta LB, et al. Oral treatment of visceral leishmaniasis with miltefosine. Ann Trop Med Parasitol **1999**; 93:589–97.
13. Wali JP, Aggarwal P, Nandy A, et al. Efficacy of sodium antimony gluconate and ketoconazole in the treatment of kala-azar: a comparative study. J Commun Dis **1997**; 29:73–83.
14. Herwaldt BL. Leishmaniasis. Lancet **1999**; 354:1191–9.
15. Lira R, Sundar S, Makharia A, et al. Evidence that the high incidence of treatment failure in Indian kala-azar is due to the emergence of antimony-resistant strains of *Leishmania donovani.* J Infect Dis **1999**; 180:564–7.
16. Alvar J, Canavate C, Gutierrez-Solar B, et al. *Leishmania* and human immunodeficiency virus coinfection: the first 10 years. Clin Microbiol Rev **1997**; 10:298–319.
17. Olliaro P, Jha TK. Clarification of comments on trial of aminosidine in visceral leishmaniasis [letter]. BMJ **1998**; 317:1250.
18. Osman OF, Oskam L, Zijlstra EE, El-Hassan AM, El-Naeim DA, Kager PA. Use of the polymerase chain reaction to assess the success of visceral leishmaniasis treatment. Trans Roy Soc Trop Med Hyg **1998**; 92:397–400.
19. Murray HW, Pepin J, Nutman TB, Hoffman SL, Mahmoud ADA. Recent advances in tropical medicine. BMJ **2000**; 320:490–4.

Death from Inappropriate Therapy for Lyme Disease

A 30-year-old woman died as a result of a large *Candida parapsilosis* septic thrombus located on the tip of a Groshong catheter. The catheter had been in place for 28 months for administration of a 27 month course of intravenous cefotaxime for an unsubstantiated diagnosis of chronic Lyme disease.

A 30-year-old woman was admitted to the Mayo Clinic (Rochester, MN) in May 1999 following a grand mal seizure. She reported a several-week history of anorexia that was accompanied by a 23-kg weight loss over an 8-month period; 4 days before admission, she noticed twitching of her upper extremities. She appeared ill and had a blood pressure of 124/82 mm Hg, a pulse rate of 85, a temperature of 37°C, and a respiratory rate of 20. The patient was confused and unable to provide a coherent history. She was icteric and had diffuse myoclonus. Cardiac auscultation revealed a prominent pulmonic second sound. A Groshong catheter was in place. Hepatosplenomegaly was noted.

Her family provided a pertinent medical history. She had had a history of bilateral knee pain since childhood. She resided in Iowa; however, she had lived in Westchester County, New York, until the age of 16 years and in northern California for a short period thereafter. In 1994, she underwent cholecystectomy and since that time she had had chronic abdominal pain, whole body pain, an episode of Bell's palsy, occasional headaches, and periods of what were described as "mental fogginess" and "transient numbness." She also reportedly had a periodic rash that was thought to be a possible "Lyme rash." In 1996, she was evaluated by an infectious diseases physician in New York who specializes in chronic Lyme disease and was diagnosed with chronic Lyme disease. This diagnosis was made despite 6 EIAs negative for *Borrelia burgdorferi,* 7 Western blot assays negative or indeterminate for *B. burgdorferi,* and 4 PCR assays of blood, 5 PCR assays of urine, and 1 PCR assay of CSF, all negative for *B. burgdorferi.* MRI of the brain, as well as CSF examination, had been unremarkable in 1996. One PCR assay of blood for the *ospA* gene (Boston Biomedica Inc., New Britain, CT) was reportedly positive in January 1997.

She was initially treated with oral doxycycline, and then, for an 8-month period (1995–1996), she was treated with iv ceftriaxone; this treatment was followed by courses of oral clarithromycin and minocycline as well as parenteral penicillin G benzathine. A Groshong catheter was placed in January 1997, and a prolonged course of therapy with iv cefotaxime (up to 4 g every 8 h) was started. Intravenous doxycycline (300 mg every 12 h) was added to this therapeutic regimen in 1998. The patient reported only partial relief of her chronic symptoms during administration of this antibiotic regimen. Therapy with iv antibiotics was discontinued 1 month before evaluation at our institution, when a family physician noted abnormal results of liver function tests and thrombocytopenia. Another infectious diseases physician was consulted; this physician thought that the patient did not have chronic Lyme disease.

The patient was also being treated for chronic diffuse body pain, with several pain medications, including sustained release morphine sulfate (300 mg t.i.d.) and immediate release morphine sulfate (~45 mg/d), according to the recommendations of a fourth physician in Illinois.

At our institution, laboratory tests revealed the following abnormal results: hemoglobin level, 6.3 g/dL; WBC count, 2.2×10^9 cells/L; platelet count, 16×10^9 cells/L; rare schistocytes and helmet cells on a peripheral blood smear; prothrombin time, 19.9 s; alkaline phosphatase level, 435 U/L; aspartate

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aminotransferase level, 131 U/L; bilirubin level, 5.2 mg/dL; and creatinine level, 6.5 mg/dL. In our laboratory, EIA was reactive for *B. burgdorferi,* but a Western blot assay showed only 1 66-kDa band. CSF examination was unremarkable, and PCR assay of CSF was negative for *B. burgdorferi.*

One day after admission, the patient reportedly became confused, and she fell, pulled and fractured her Groshong catheter, and became unresponsive. Electromechanical dissociation was diagnosed, and she died despite aggressive attempts at resuscitation. After her death, cultures of blood obtained at the time of admission yielded *Candida parapsilosis.*

Postmortem examination revealed acute fatal obstruction of the tricuspid valve orifice by a large infected thrombus located on the fractured tip of her Groshong catheter (figure 1). Grocott-Gomori methenamine–silver nitrate staining of microscopic sections of the thrombus revealed extensive *Candida* organisms (figure 2). Other significant findings at autopsy included an old *Candida*-infected pulmonary thromboembolus with total occlusion of the left main artery at the hilum as well as scattered old peripheral emboli bilaterally. Marked splenomegaly with reactive follicular hyperplasia and congestion were noted. At autopsy, there was no myositis, neuritis, meningitis, vasculitis, or myocarditis suggestive of chronic Lyme disease.

The premature death of our patient resulted from a complication of her chronic indwelling central venous catheter, which was used for prolonged iv administration of antimicrobial therapy for a disease that was not fully documented. Lyme disease is curable with antibiotic treatment, and, although resolution of true neurological complications of Lyme disease may be slow after appropriate therapy, there is no evidence that our patient ever had Lyme disease. Her chronic symptoms were nonspecific, and results of her laboratory tests were nondiagnostic and did not fit the criteria for Lyme disease [1]. Furthermore, chronic antibiotic therapy, such as that described here, is never indicated

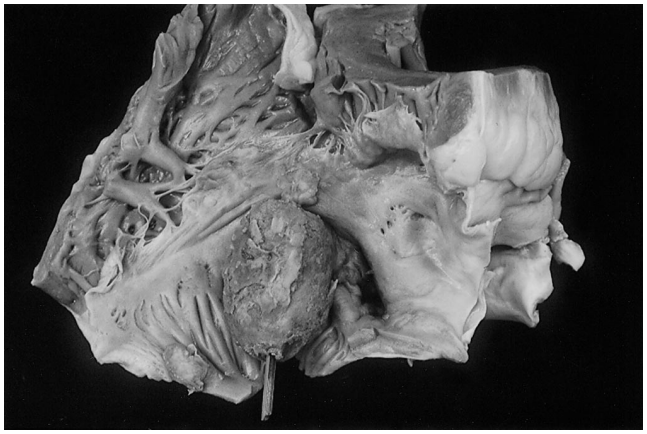

Figure 1. Opened right atrium from a patient who died because of inappropriate therapy for Lyme disease. The photo shows a large infected thrombus on the fractured tip of the patient's Groshong catheter.

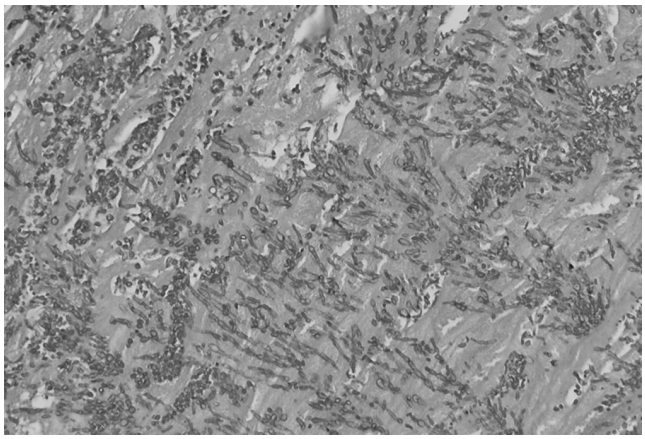

Figure 2. Stained section of a right atrial thrombus in a patient who died because of inappropriate therapy for Lyme disease. The photomicrograph shows extensive *Candida* species (Grocott-Gomori methenamine–silver nitrate stain; original magnification, × 360).

for Lyme disease, and such therapy has a significant risk of side effects. Even in cases of clear-cut Lyme disease, abnormal test results return to baseline with no measurable sequelae after appropriate treatment [2].

Lyme disease is primarily a clinical syndrome confirmed by microbiological tests [3, 4]. For our patient, the diagnosis of Lyme disease was made despite negative or indeterminate results of Western blot assays, perhaps because the presence of only 1 or 2 highly specific bands on a Western blot was considered a potential harbinger of further expansion over time [5]. We are of the opinion that acceptable diagnostic criteria for Lyme disease include the presence of multiple bands of specific molecular weight and that the serological analysis of the patient described here did not confirm a diagnosis of Lyme disease [3]. Notably, in our laboratory, a Western blot assay showed only 1 66-kDa band, thereby revealing no expansion over time. The 1 positive PCR assay is intriguing, but this finding may have been the result of DNA contamination.

It has been suggested that *B. burgdorferi* infection may trigger parainfectious pain or fatigue syndromes, which may persist indefinitely after eradication of the spirochete by antimicrobial therapy. In addition, fibromyalgia, chronic pain syndromes, and chronic fatigue syndrome may be incorrectly diagnosed as chronic Lyme disease [1, 6]. Patients with these disorders have disabling and generalized symptoms, including marked fatigue, severe headache, widespread musculoskeletal pain, multiple symmetrical tender points in characteristic locations, pain and stiffness in many joints, dysesthesias, paresthesias, difficulty with concentration, memory loss, and sleep disturbances; their symptoms are not relieved with antimicrobial therapy [1, 6–8].

Of 788 patients referred to the New England Medical Center (Boston) with a presumptive diagnosis of chronic Lyme disease, 23% had active Lyme disease, 20% had previous Lyme disease and another current illness (most commonly chronic fatigue

syndrome or fibromyalgia), and 57% did not have Lyme disease (patients in this last group most commonly had fatigue or pain syndromes) [1]. In another study [7], of 209 patients referred to the Yale University Lyme Clinic (New Haven, CT) with a presumptive diagnosis of Lyme disease, 21% had active Lyme disease, 19% had previous but not active Lyme disease, and 60% had no evidence of current or previous Lyme disease. Patients with no evidence of Lyme disease had a median of 4 serological tests for Lyme disease, 7 office visits, and 42 days of antibiotic treatment for Lyme disease and were noted to have high levels of disability and distress.

Appropriate treatment of Lyme disease has been associated with complications (e.g., ceftriaxone-associated biliary complications, iv catheter–associated gram-positive and gram-negative bacterial bloodstream infections, and *Clostridium difficile*–associated diarrhea). Ceftriaxone-associated biliary complications have been described in patients receiving ceftriaxone therapy for unsubstantiated diagnoses of Lyme disease [9]. Inappropriate antimicrobial therapy for Lyme disease has also been associated with septic thrombophlebitis, neutropenia, serum sickness, and antibiotic-associated colitis [7]. Overall, empirical treatment with iv antibiotics of patients with nonspecific chronic fatigue or myalgia, based on positive serological results alone, has been determined to result in many more instances of antibiotic toxicity than cures of atypically symptomatic true Lyme disease [10].

The cost associated with prolonged parenteral therapy can be substantial [10]. The potential for emergence of antimicrobial-resistant bacteria exists with prolonged courses of antimicrobial therapy. Furthermore, the opportunity costs of administering prolonged courses of inappropriate parenteral antimicrobial therapy are enormous. In a study of 30 pediatric patients referred to the Lyme Disease Center at Robert Wood Johnson Medical School (New Brunswick, NJ) for evaluation of ongoing Lyme arthritis who were ultimately diagnosed with fibromyalgia, it was noted that many of the children had been subjected to unnecessary antibiotic therapy, many had missed prolonged periods of school (up to 9 months), and some required home tutoring [11].

Many patients with nonspecific complaints seek an explanation for their fatigue, pain, and mental fogginess [12]. Patients may be more willing to accept a diagnosis of chronic Lyme disease than an alternative diagnosis because Lyme disease is a "real," potentially curable disease [12]. For some patients, a diagnosis of Lyme disease may be an acceptable end to a search for an explanation of their symptoms; in such a setting, seronegativity may not be viewed as evidence against the diagnosis [12]. Incorrect physician diagnoses, as opposed to self-diagnoses, of chronic Lyme disease may contribute to depression and stress when symptoms do not abate despite protracted courses of antimicrobial therapy [7]. Survey data show that 38% of physicians would recommend >6 months of antibiotic therapy for chronic Lyme disease, and that the most frequently recommended antimicrobial agent for the treatment of chronic Lyme disease would be iv ceftriaxone [13]. The relative ease of administering prolonged courses of iv antimicrobial regimens in the current era has undoubtedly impacted this practice.

Our case report and review of the literature validate the position of the American College of Rheumatology and the Council of the Infectious Diseases Society of America [14], both of which try to discourage the use of antibiotics for a patient with a nonspecific clinical presentation who does not meet the criteria for the case definition standard accepted for Lyme disease. The use of prolonged high-dose iv antimicrobial therapy for our patient's chronic symptoms of mental fogginess, poor memory, chronic fatigue, and body numbness and pain was, in our opinion, unwarranted and ultimately led to her death.

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References

1. Steere AC, Taylor E, McHugh GL, Logigian EL. The overdiagnosis of Lyme disease. JAMA **1993**;269:1812–6.
2. Seltzer EG, Gerber MA, Cartter ML, Freudigman K, Shapiro ED. Long-term outcomes of persons with Lyme disease. JAMA **2000**;283:609–16.
3. Tugwell P, Dennis DT, Weinstein A, et al. Laboratory evaluation in the diagnosis of Lyme disease. Ann Intern Med **1997**;127:1109–23.
4. American College of Physicians. Guidelines for laboratory evaluation in the diagnosis of Lyme disease. Ann Intern Med **1997**;127:1106–8.
5. Liegner KB, Kochevar J. Guidelines for the clinical diagnosis of Lyme disease. Ann Intern Med **1998**;129:422–3.
6. Hsu VM, Patella SJ, Sigal LH. "Chronic Lyme disease" as the incorrect diagnosis in patients with fibromyalgia. Arthritis Rheum **1993**;36:1493–500.
7. Reid MC, Schoen RT, Evans J, Rosenberg JC, Horwitz RI. The consequences of overdiagnosis and overtreatment of Lyme disease: an observational study. Ann Intern Med **1998**;128:354–62.
8. Dinerman H, Steere AC. Lyme disease associated with fibromyalgia. Ann Intern Med **1992**;117:281–5.
9. Ettestad PJ, Campbell GL, Welbel SF, et al. Biliary complications in the treatment of unsubstantiated Lyme disease. J Infect Dis **1995**;171:356–61.
10. Lightfoot RW Jr, Luft BJ, Rahn DW, et al. Empiric parenteral antibiotic treatment of patients with fibromyalgia and fatigue and a positive serologic result for Lyme disease: a cost-effectiveness analysis. Ann Intern Med **1993**;119:503–9.
11. Sigal LH, Patella SJ. Lyme arthritis as the incorrect diagnosis in pediatric and adolescent fibromyalgia. Pediatrics **1992**;90:523–8.
12. Sigal LH. The Lyme disease controversy: social and financial costs of misdiagnosis and mismanagement. Arch Intern Med **1996**;156:1493–500.
13. Ziska MH, Donta ST, Demarest FC. Physician preferences in the diagnosis and treatment of Lyme disease in the United States. Infection **1996**;24:182–6.
14. American College of Rheumatology and the Council of the Infectious Diseases Society of America. Appropriateness of parenteral antibiotic treatment for patients with presumed Lyme disease. Ann Intern Med **1993**;119:518.