Lyme Disease
What's in a Name???

GOOD - authentic, honest, just, kind, pleasant, skillful, valid

NEIGHBOR - friend, near

ALLIANCE - affiliation, association, marriage, relationship

CORPORATION - company, business establishment

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COMMENTARIES

206 When Is a Somatic Disorder Psychiatric?  
Joseph H. Friedman, MD

207 The Awkward Birth Pangs of Bolero  
Stanley M. Aronson, MD

CONTRIBUTIONS

SPECIAL ISSUE: Lyme Disease
Guest Editors: Jerome Larkin, MD, and Jennifer Mitty, MD, MPH

208 Introduction: Lyme Disease  
Jerome Larkin, MD, and Jennifer Mitty, MD, MPH

209 Ticks and Tick-Related Illness  
Jerome Larkin, MD

212 Lyme Disease In Children and Pregnant Women  
Jerome Larkin, MD

213 Musculoskeletal Manifestations of Lyme Disease  
Imad Bitar, MD, and Amanda Diamond, MD

216 Neurological Complications of Lyme Disease  
Syed Rizvi, MD, and Amanda Diamond, MD

219 Updates and Controversy In the Treatment of Lyme Disease  
Jennifer Mitty, MD, MPH, and David Margolius

COLUMNS

224 Geriatrics for the Practicing Physician – Dementia Screening: Should We Screen Asymptomatic Older Adults?  
Ana Tiuya Fulton, MD

226 The Creative Clinician – Rituximab In Treating Refractory Thrombotic Thrombocytopenic Purpura: Three Case Reports  
Samir Dalia, MD, Brendan McNulty, MD, and Gerald A. Colvin, DO

229 Health By Numbers – Estimating the Incidence of New Onset Lyme Disease in Rhode Island  
John P. Fulton, PhD

232 Public Health Briefing – The RI Board of Medical Licensure and Discipline, 2007 Year Summary  
Robert Grauman, MD, Mary E. Salerno, MA, Linda Julian, Lauren Dixon, and Bruce McIntyre, JD

235 Physician’s Lexicon – The Eight Little Wrist Bones  
Stanley M. Aronson, MD

235 Vital Statistics

236 July Heritage
This issue is devoted to Lyme disease, an important illness in our state, which boasts, on Prudence Island, the highest seropositive region in the world. It is a disease with interesting clinical phenomena, similar to, but less devastating than its spirochete cousin, syphilis. Like syphilis, it may cause a chronic illness, quite different than the acute illness. Unlike syphilis, which may have been the final common answer for sporadic dementias and behavioral disorders, Lyme is being used to explain a large number of fairly nebulous symptoms that occur in the general American population. It may be the only illness in which an official medical group has been sued by a state government (Connecticut) for issuing evidence-based guidelines that contradict non-scientific beliefs embraced by a politically influential voting block. Medicine by democracy, as it were.

There are two fascinating aspects to this issue. One is the problem that clinical physicians (in contrast to test-based physicians like radiologists, interventionists and pathologists) face everyday, of discriminating the “psychogenic” from the organic, a topic I never tire of. The other is political.

There is no doubt that political beliefs influence medicine. It is hard to imagine that cultural change rather than scientific evidence alone altered the psychiatric classification of homosexuality. How did “neurasthenia” develop into chronic fatigue syndrome? Why is Chronic Fatigue Syndrome not in DSM IV, but classified by the Centers for Disease Control and Prevention? Why is fibromyalgia or Irritable Bowel Syndrome not in DSM? Where does multiple chemical sensitivity syndrome belong? When is a physiologically inexplicable syndrome a somatoform disorder, or a conversion disorder rather than a specific organ system disorder?

Many disorders have moved from the psychological column to the organic column in the last few decades. Undoubtedly many more will. Restless legs syndrome was described about 30 years ago but didn’t “catch on” until recently, getting a big boost from drug companies that market drugs that treat the disorder. Most doctors, who didn’t suffer from RLS, considered it a non-entity. After all, everyone gets restless sometime. But when polysomnography became popular, it turned out that 60% of people who reported RLS had a peculiar kicking movement during sleep, obviously something that was organic and not emotionally based. This year two genes have been found to explain RLS, and more are likely to be found.

Writer’s cramp had been considered a psychiatric syndrome until recently. It is very clear how one might divine an unconscious urge to twist one’s hand, when it occurred only when writing, but not doing anything else, an explanation that makes a lot more intuitive sense than an organic physiological one. There is no more evidence today that these are organic than there was before, but we’ve developed a greater reliance on psychiatric experience to exclude a psychodynamic formulation rather than found an objective measure of organicity. This is an unusual form of nosology. We often do tests to exclude certain diagnoses, and, like Sherlock Holmes, conclude that when all the various possibilities one can think of have been eliminated, what is left must be the truth. Yet one can never be “sure” in excluding psychiatric etiologies.

Another organic disorder that provided fuel for psychoanalysis is cataplexy. The sudden loss of body tone, causing people with narcolepsy to fall to the ground when experiencing a sudden emotion. I will never forget, in the early days of sleep medicine, hearing a lecture from a sleep doctor pioneer, who described a teenage boy who would deliberately provoke his father to the point of getting him to jump out of his chair to confront him, the father then falling helplessly to the ground because of cataplexy.

In the 1800s the term “neurosis” described neurological syndromes that had no known pathological basis. Charcot, the great French neurologist, who renamed “Paralysis agitans” Parkinson’s disease (PD), classified that disease as a neurosis. The term was then hijacked by Freud and colleagues, although it should be pointed out that Freud studied with Charcot. Affixing the term neurosis did not imply that a pathology wouldn’t be found, just that it wasn’t known. Interestingly however, some psychoanalysts in the mid-20th century published papers blaming childhood conflicts for the tremors, and rigid personalities for muscle rigidity, in PD, misunderstanding, perhaps, the difference between Charcot’s neurosis and Freud’s.

In this issue the authors grapple with the battle between the infectious disease experts who base recommendations on evidence-based medicine, and self-proclaimed Lyme experts who base opinions on their common experience, without addressing the pathophysiology of “post treatment Lyme disease”. Post treatment Lyme disease is an entity, perhaps based on an organic etiology, probably, like neurasthenia, a disorder that is so diffuse that it includes a large overlap between the organic and the psychological, making it a daunting challenge to figure out. The fact is that long term antibiotic treatment hasn’t worked and causes complications. Yet a lay organization has sued an organization of bone fida experts to claim that double blind placebo controlled trials have been inadequate, not because of study design but because their results fly in the face of the organization’s common experience.

If blood letting didn’t work, why would we use it, asked our predecessors two hundred years ago, or steroids a mere 20 years ago? I think there is a rationale
for a democratic process for disease classification, limiting voting to experts, but surely not for disease treatment.

— JOSEPH H. FRIEDMAN, MD

Disclosure of Financial Interests
Joseph Friedman, MD, Consultant: Acarta Pharmacy, Ovation, Transoral; Grant Research Support: Cephalon, Teva, Novartis, Boehringer-Ingelheim, Sepracor, Glaxo; Speakers’ Bureau: AstraZeneca, Teva, Novartis, Boehringer-Ingelheim, GlaxoAcadia, Sepracor, Glaxo Smith Kline

The Awkward Birth Pangs of Bolero

Creative genius in the arts, as portrayed in our current mythology, is allegedly born in travail, matures in unyielding poverty and ultimately enriches the world despite rampant tuberculosis. Survival is typically brief – Keats is given only 26 years, Mozart 35 years and Schubert a mere 31 years. And disease is always there, an insistent impediment to be overcome in some unhealed attic.

When assembling the biography of many an artist, the word, despite, seems to be an essential element of this bohemian scenario. [For example, we read: “The artist managed to write three slim books of immortal poetry despite his lung disease.”] It therefore becomes an act of sheer perversity, outright blasphemy, to suggest that some great work of art might never have been created were it not for the accompanying burden of some disease. Yet, as the creative forces underlying art are evaluated, three possibilities emerge. The disease and the concerto are causally unrelated; or the virtuoso writes an immortal concerto despite the weight of his illness; or this same virtuoso writes an immortal concerto because of the weight of his illness, with the inescapable implication that this concerto might never have been born were it not for the malign illness. The third possibility, however, seems implausible. Yet the life of Joseph-Maurice Ravel, one of France’s greatest musical geniuses, might say otherwise.

Ravel, of Swiss-Basque heritage, was born in the French village of Ciboure near Biarritz, on March 7, 1875. The family moved to Paris when Ravel was seven. He began piano lessons then and within a few years was enrolled in Conservatoire de Paris. His cohort of students described him as slight and delicate of build, remote in behavior, a perfectionist in his musical efforts, suspicious of others, a fractious personality easily given to argument and perhaps slightly paranoid toward his colleagues and teachers. He was not known to enter into any intimate relationships with either men or women; and rumors of a labile sexuality followed him throughout his life.

The legendary impresario, Sergei Diaghilev, was impressed with Ravel’s musical genius; and in 1920 the two collaborated in staging Ravel’s “Daphnis et Chloe,” danced by the immortal Valsav Nijinsky. By 1925 Ravel and Diaghilev were no longer on speaking terms; perhaps slightly paranoid toward his colleagues and teachers. He was not known to enter into any intimate relationships with either men or women; and rumors of a labile sexuality followed him throughout his life.

Ravel was invited to the United States in 1928 where his concerts were uniformly successful. He met George Gershwin in one of his California performances and the two shared their musical thoughts on jazz, altered tonality and Afro-Caribbean folk music. For the remainder of Ravel’s life, less than a decade, he felt that only America understood and appreciated his music.

In a motor accident in 1932, Ravel sustained a mild head injury. His behavior from this point on visibly deteriorated although many colleagues dated his neurological deficits back to 1928. Colleagues noted then subtle changes in Ravel’s behavior and personality. He exhibited a gradual loss of empathy, showing an increasing indifference to the illnesses and travails of others. His remarks became increasingly inappropriate, tactless, annoyingly repetitive, even embarrassing, with evidence of a loss of inhibitions. Even his eating became both repetitive and indiscriminately excessive.

In the next year Ravel withdrew from the public eye, became apathetic, increasingly incommunicative and only belatedly, losing his sense of memory, orientation and capacity to compose – or even understand – music. A diagnosis of frontotemporal dementia [Pick’s disease] was offered. In 1937 an ill-considered neurosurgical intervention was attempted, but Ravel died without regaining consciousness.

Frontotemporal dementia is not as common as Alzheimer’s disease. It differs not only in frequency but in its manifestations of behavioral and judgmental deterioration long before there is loss of orientation or memory. The mean duration of frontotemporal dementia tends to be somewhat longer and the disease tends to be hereditary in about 40% of cases. Patients frequently exhibit repetitive, compulsive behavior associated with outbursts of chagrin and decay of social graces, a loss of cognitive skills in planning and organizing – yet with relative preservation of memory.

Ravel’s works have been characterized by musicologists as graceful, intricately nuanced, impressionistic, subtle, highly inventive, discriminating, ingeniously contrived and delicate. But then there is Bolero, admittedly Ravel’s most famous, most financially successful venture [and the title for at least two motion pictures, the first, starring George Raft and Carole Lombard in 1934, and the second, starring Bo Derek in 1984.]

Bolero, one of Ravel’s last compositions, differs appreciably from his other works and does not seem to be the culmination of his genius. Instead of intricate orchestration, it is a somewhat primitive, iterative and erotic enterprise that emphasizes insistence and crude rhythmicity rather than subtle tonalities or musical development. And so, some neurologists have quietly speculated that this late orchestral effort, thought banal by many, is more a consequence of Ravel’s organic dementia than his innate musical genius. They express these tentative speculations in whispers, knowing that Bolero is one of the world’s most played, most popular pieces of music.

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Disclosure of Financial Interests
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Lyme disease is named for a small town on the southeast coast of Connecticut. In 1977, Steere et al described a clustering of 51 patients (39 children and 12 adults) in three contiguous towns with recurrent attacks of arthritis of the large joints. Approximately 25% of patients had developed a preceding erythematous annular rash. Arthritic attacks typically lasted one week. Although originally thought to be juvenile rheumatoid arthritis, diagnostic testing did not support this hypothesis; and seasonal and geographic clustering suggested transmission by an arthropod vector. Over the next few years effective antibiotic regimens were developed, and in 1982 Willy Burgdorfer cultured a spirochete (subsequently named Borrelia burgdorferi and demonstrated to be the cause of Lyme disease) from the mid-gut of ixodes (hard-bodied) ticks. Ixodes dammini (formerly scapularis) was eventually shown to be the vector for Lyme disease (borreliosis) as well as for babesiosis and erlichiosis (anaplasmosis). It is also now apparent that human disease attributable to B. burgdorferi has been described in the medical literature, particularly in Europe, since at least 1909 and likely as early as 1883. Since 1977, other aspects of the disease have also been described, in particular the involvement of the central nervous and cardiovascular systems in addition to the more typical skin and musculoskeletal manifestations of illness.

A unique aspect of Lyme disease and its history since 1977 is advocacy. The original investigation of the outbreak was in part spurred by two parents who contacted the Connecticut State Health Department and physicians at Yale University School of Medicine, questioning the seemingly too frequent incidence of JRA in their community. This has, in a sense, set the tone for the public medical and political debate over Lyme disease. As with many previously unrecognized illnesses, the period following its original description was characterized by an expanding body of knowledge regarding pathophysiology, diagnosis and treatment. However, concurrent with this progress came a growing tendency on the part of some clinicians and patients to attribute a wide variety of often subjective and nonspecific symptoms, persisting at times for decades, to Lyme disease. Unfortunately, the debate has reached a level such that clinicians are intimidated and threatened for withholding antibiotics despite the scientific validity of this position, and patients are therefore exposed to the toxicity of long courses of antimicrobial agents of no proven benefit. Misinformation abounds on the internet and even such lay publications as Yankee Magazine, usually confining itself to serious topics such as country inns and flower arrangements, have joined in the fray. It is a free for all.

The diagnosis of Lyme disease relies on three principal findings: epidemiologic exposure, appropriate clinical manifestations and serology. All residents of the mid-Atlantic states and coastal New England are at risk of infections regardless of occupation or habits. Typical symptoms include headache, myalgias, arthralgias and fatigue. Frank meningitis may be present as part of the acute illness. Physical findings include erythema migrans, arthritis and Bell’s Palsy. Other cranial nerves may be involved and transverse myelitis is a rare but reported manifestation. Serology may be negative initially and should not be used to rule out acute infection but may be helpful if positive or if seroconversion can be demonstrated with later testing. Most if not all illness, when diagnosed acutely and even for weeks to months after the initial manifestations, responds promptly to oral antibiotics. Central nervous system involvement, however, should be treated parenterally. Later manifestations of illness, in particular heart block, arthritis and neurologic symptoms may warrant judicious use of antibiotics but should be limited to patients with serologic evidence of infection and rarely if ever should be extended beyond a month of treatment. There is no scientific evidence that long term (months to years) of antimicrobial therapy is ever indicated.

In October, 2006 the Infectious Diseases Society of America published guidelines for the assessment, treatment and prevention of Lyme disease. The Centers for Disease Control and Prevention (CDC) have endorsed those guidelines. Like other such tools, it is a consensus document based on the best available scientific evidence and meant to assist physicians in individualizing patient care in a scientifically and medically appropriate manner. In November, 2006, Connecticut Attorney General Richard Blumenthal launched an investigation into possible violation of antitrust laws on the part of the IDSA in formulating the guidelines, stating they “may severely constrict choices and legitimate diagnosis and treatment options for patients.” The absurdity of his proposition almost does not warrant comment. How will the story end? It certainly will not be with Mr. Blumenthal’s investigation and perhaps not with the latest iteration of the IDSA guidelines. In an agreement announced in April 2008, Mr. Blumenthal agreed to end the investigation. In exchange, the IDSA will convene a special review panel to conduct a comprehensive and up-to-date evaluation of the scientific literature, in order to determine whether the 2006 guidelines should be revised or updated. As part of the review process, interested individuals will be invited to submit relevant information, and a public hearing will be held. The review panel will consider all the evidence and make recommendations regarding whether the Lyme disease guidelines should be revised. If the panel recommends revisions, they will be carried out in accordance with our normal procedures overseen by the IDSA Standards and Practice Guidelines Committee. The agreement by the IDSA was explicitly to avoid the considerable costs of litigation, and to protect the volunteer authors of the guidelines, with every expectation that the guidelines will stand as written after the review. That the Society would have been vindicated if the matter had gone to court was never in question.

Research continues and our knowledge and experience increase. Ultimately these are matters of biology and medicine and we have every confidence that science will prevail. Toward that end, this edition of Medicine & Health/ Rhode Island is intended to provide insight into the diagnosis and treatment of Lyme disease and other tick-related illnesses and assist the clinician in negotiating the thicket of controversy and misinformation while attempting to help afflicted patients.
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Ticks and Tick-Related Illness
Jerome M. Larkin, MD

There are over 800 described species of ticks all of which share the characteristic of requiring blood meals during their life cycle. They are often adapted to specific seasons and environments and feed on a specific animal or group of animals. Their bites tend to be painless and feeding lasts for hours to days. Affinity for humans is variable. Ixodes damini, the vector of Lyme disease, belongs to the group of hard-bodied or damini ticks. I. damini has three distinct life cycles, larva, nymph and adult, and must take a blood meal once during each cycle. A single nest may harbor as many as 10,000 insects. The tick must itself be infected with the bacterial pathogen in order to transmit infection to humans. Infection in the tick persists across the stages of its life cycle and can be transmitted to offspring.

Two infections other than Lyme disease, ehrlichiosis and babesiosis, are of concern in Lyme-endemic areas. The pathogens of both diseases can be transmitted by the tick Ixodes scapularis and ticks and people can be dually or triply infected. Infection can be asymptomatic for both microorganisms. Presentation, as with Lyme disease, can be non-specific with fever, malaise and an otherwise flu-like syndrome. Similarly, patients often do not recall a tick bite at presentation. Accordingly, ehrlichiosis and babesiosis are in the differential for any patient presenting with a febrile illness in the spring, summer or fall months, and physicians in endemic areas should be familiar with their presentation, diagnosis and treatment.

ERHLICHIOSIS
Ehrlichiosis is caused by three distinct species: Ehrlichia chaffeensis, Ehrlichia ewingii and Anaplasma phagocytophilum. The three species have the capacity to infect a number of mammals other than humans including deer, dogs, coyotes, mice and other rodents. A. phagocytophilum can also infect I. damini. Accordingly it is typically the pathogen of ehrlichiosis in the northeastern United States while E. chaffeensis is more common in the southern United States. Human granulocytic anaplasmosis and human granulocytic ehrlichiosis are synonymous terms. All three pathogens are small, gram negative intracellular bacteria. They exhibit a tropism for white blood cells; A. phagocytophilum for the granulocyte. As a result, infection may be evident by the observation of clusters of bacteria in cytoplasmic vacuoles known as a morula. This is, however, a relatively rare finding.

Human granulocytic anaplasmosis (HGA) follows a seasonal pattern reflecting the activity of the I. damini tick. Peaks of clinical illness occur in July and November with a low level of endemic activity throughout most of the rest of the year. Disease activity drops off after the first hard frost in the fall or early winter. However ticks may still be active in areas which experience less severe cold weather, such as coastal areas, or in years of relatively little freezing weather. 2963 cases of HGA have been reported since 1994 with over 700 in 2005 alone. Although a reportable disease, most surveillance is passive and so the true incidence of infection and or disease is likely underreported. The highest prevalence is reported in Minnesota, Connecticut and Rhode Island, the last with 36.5 cases/million. Infection and disease are more likely to occur in males and in those over the age of 50. As with infection with Borrelia burgdorferi, the majority of patients do not recall a tick bite. A lack of outdoor exposure does not reliably exclude the diagnosis. In one study approximately 1% of Connecticut residents were seropositive with no current or past history of disease. Other studies have reported seroprevalence rates as high as 36%.

Incubation is two to three weeks although shorter periods have been described. The typical patient with ehrlichiosis caused by any of the three pathogens is likely to present with fever and malaise. The fever is often persistent and out of proportion to the typical viral illness and usually striking for its presentation during the summer months. Head-
ache is very common, myalgias and gastrointestinal symptoms frequent. Other reported symptoms include rash, cough and confusion. No single symptom is specific for ehrlichiosis. Physical exam is similarly nonfocal. The classic laboratory finding is leukopenia with thrombocytopenia. Transaminitis is relatively common. Mild anemia may also be present.

More fulminant disease is possible and appears to be relatively more common from infections with E. chaffeensis and in the immunosuppressed, the latter including those with HIV infection and solid organ transplant recipients. Manifestations of more severe disease include meningoencephalitis, adult respiratory distress syndrome, acute renal insufficiency and sepsis. Opportunistic infections with fungal and viral pathogens are possible. Peripheral neuropathies including an isolated facial palsy are also possible.

Diagnosis relies on clinical suspicion in an appropriate epidemiologic setting because no single symptom, physical finding or laboratory value is specific. The spectrum of fever, a nonfocal exam and findings of leukopenia and thrombocytopenia during the summer in an endemic area warrant therapy. More difficult is the patient with fever alone. Cautious observation for 48 to 72 hours is reasonable. Treatment should be initiated in the face of any worsening or if the fever persists and no other diagnosis, such as enterovirus, is apparent. Approximately 25% of patients have positive serologic evidence of infection at the time of presentation; 95-100% of patients are positive within two weeks of the onset of symptoms. Polymerase chain reaction is highly specific but has a sensitivity of only 60 to 85%. The presence of morula on peripheral smear is variable, reported as approximately 7% in infections with E. chaffeensis and 20-80% in infections with A. phagocytophilum. Culture is difficult and currently used only in research.

All forms of ehrlichiosis respond to treatment with tetracycline. Doxycycline at a dose of 100 mg twice daily for seven to ten days is the therapeutic regimen of choice. The use of doxycycline has the advantage of potent activity against B. burgdorferi and so is effective treatment for dually infected patients. Treatment, however, should be extended to 21 days in this instance. Rifampin is an alternative agent at 300 mg bid for 7-10 days for patients intolerant of or allergic to doxycycline. Children should be treated with doxycycline at 3-4 mg/kg/day divided bid. Successful treatment of children with rifampin has been reported but should be reserved for those under the age of eight years and who are judged to be only mildly ill. Beta-lactams, cephalosporins, macrolides, quinolones and chloramphenicol are all ineffective therapy.

The majority of patients do not recall a tick bite.

A recent report describes treatment of nine woman diagnosed with HGA during pregnancy from 1997 to 2006. Gestational age at time of diagnosis ranged from 10 to 39 weeks. Four women received therapy with doxycycline and five received therapy with rifampin. One woman was not treated. None of the woman presented with fulminant disease and all those treated responded promptly to antimicrobial therapy. One perinatal infection occurred. All pregnancies went to term and no adverse outcomes were observed in the children at 21 months of follow-up. Overall prognosis is generally good with the exceptions described above. There is no known chronic syndrome associated with ehrlichiosis. Reinfections have been reported.

**Babesiosis**

Babesiosis is a parasitic infection caused by one of many different species of Babesia. The genus is names for Viktor Babes who first described disease in cattle in 1888. The first case of human disease was described in an asplenic farmer from Yugoslavia in 1957 and the first case in the United States in a resident of Nantucket in 1969. There are more than 100 known species of Babesia infecting many different vertebrates. The two most common species to infect humans are Babesia microti and Babesia divergens. Babesia divergens is primarily seen in Europe, usually results in asymptomatic disease, often in asplenic individuals, and typically presents as a more fulminant disease with a high mortality.

Babesia microti is the more typical pathogen in the United States and many infections are clinically silent. An epidemiologic study in blood donors in Connecticut found a seroprevalence rate of 1.4%. Fifty-three percent of seropositive patients were parasitemic. Other studies in highly endemic areas indicate a relatively high incidence of asymptomatic infection. The parasite can also infect white-footed mice and white-tailed deer which serve as a reservoir of infection in the environment. Infection of ticks is endemic in southern New England and its coastal islands and New York. Cases have also been described in the mid-Atlantic states, the midwest and on the west coast. Several transfusion related cases have been reported in Rhode Island. Distinct species, designated MO-1 and WA-1 have been described as causing disease in Missouri and Washington respectively. Asymptomatic parasitemia can persist for months. Treatment of asymptomatic but parasitic patients results in more rapid clearance and is indicated if the patient remains parasitemic for more than three months. Treatment of a seropositive but not parasitic, asymptomatic patient is not indicated.

Babesia species infect the red blood cell of humans and other species where they undergo asexual reproduction. This results in the classic tetramer or “maltese cross” inclusion seen on examination of the peripheral blood smear. The diagnosis of malaria should be considered in a patient with anemia, red blood cell inclusions and an appropriate epidemiologic risk profile. Eventually hemolysis occurs with subsequent infection of uninfected cells. Patients typically present with non-specific, “flu-like” symptoms: fever, headache, malaise, anorexia. Rash is distinctly unusual. The typical finding on laboratory testing is anemia and thrombocytopenia. It is not unusual for the diagnosis to be made when and automated blood counter mandates review of a smear as a result of thrombocytopenia. Red blood cell inclusions are then noted by the laboratory technician as consistent with either babesiosis or malaria. In suspected cases in which initial smears are negative repeating the smear several times over the course of days or PCR testing may be helpful.

Patients with significant immunocompromise such as HIV infec-
tion, asplenia, chronic steroid dependence and solid organ transplantation are at risk for more fulminant disease. This can present as rapidly progressive sepsis with multisystem organ failure, particularly acute renal failure and pulmonary edema with respiratory failure. Review of the peripheral smear is critical to diagnosis in this instance. Increased age also appears to be a risk factor for more fulminant disease. 9,10

Treatment is with one of two different antibiotic combinations. Effective therapy was first achieved with clindamycin 600 mg three times daily and quinine 650 mg both three times daily for 7 to 10 days. More recently, a combination of atovaquone 750 mg twice daily and azithromycin 500 mg on day one and then either 250 mg or 500 mg thereafter, both for 7 to 10 days have been shown to be equally effective. The combination of atovaquone and azithromycin is better tolerated with fewer side effects than clindamycin and quinine. Quinine has the advantage of offering treatment for malaria in instances where this diagnosis may be of concern. Additionally, quinine appears to result in a more rapid drop in parasite burden.11

Patients presenting with fulminant disease should be treated in an intensive care unit (ICU). Parasite burden can be as high as 85%. Exchange transfusion is indicated for high levels of parasitemia (>10%), severe hemolysis or evidence of liver, kidney or pulmonary involvement. In such patient, antimicrobial therapy should continue at least until the parasite level is less than .04% or for 10 days, whichever is longer. Repeat exchange transfusion should be considered for patients with a parasitemia persisting over 5% after an initial exchange. Patients who are immune compromised and/or present with fulminant illness should be rechecked for parasites both by smear and PCR at one and three months. Retreatment is indicated for positive results, 12

CONCLUSION

Ticks are ubiquitous arthropods which are highly adapted to specific environments and seasons. They are the vectors of a multitude of human diseases. *Ixodes dammini* is endemic to the coastal northeastern United States, including Rhode Island. It requires a single blood meal during each of its three life stages. During feeding it can transmit infection with *Borrelia burgdorferi*, *Anaplasma phagocytophilum* and *Babesia microti*. Patients with dual and even triple infection have been described. Ehrlichiosis (anaplasmosis) and babesiosis typically present with non-specific, “flu-like” symptoms during the spring, summer and fall. The majority of patients do not recall a tick bite and all residents of endemic areas are at some degree of risk of infection regardless of lifestyle and habits. Diagnosis rests on clinical suspicion and the finding of abnormalities on blood count and smear. Ehrlichiosis is suggested by leukopenia and thrombocytopenia, babesiosis by anemia, thrombocytopenia and intraerythrocytic parasites on peripheral smear. Ehrlichiosis is effectively treated by doxycycline and so is covered when treating with typical regimens of this drug for Lyme disease. Babesia infection while quite common is asymptomatic in more than 95% of cases in otherwise healthy individuals. Symptomatic disease is effectively treated in most cases by a combination of clindamycin and quinine or atovaquone and azithromycin. Fulminant disease in the immune-compromised requires hospitalization, often admission to the ICU and potentially exchange transfusion.

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Disclosure of Financial Interests

The author has no financial interests to disclose.

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Two populations, pregnant women and children under the age of eight, warrant special mention as therapy with the drug of choice for Lyme disease, doxycycline, is contraindicated for both.

CHILDREN

The epidemiology, presentation and clinical course of Lyme disease in children is similar to that in adults. Children between the ages of five and nine years comprise one of the peaks of incidence in regard to age. An intriguing notion is the possibility that children under the age of five may have less incidence of disease despite exposure because children in this age group are often treated with courses of amoxicillin and second and third generation cephalosporins for presumed otitis media. These antibiotics in the doses and courses they are commonly prescribed would constitute effective therapy for early localized and disseminated disease.

As with adults, children may present with erythema migrans in around 15% of cases. Other manifestations of disease include fever, headache, arthritis, arthralgia, myalgia, cranial nerve palsies and meningitis. Approximately 50% of children who do not receive appropriate antimicrobial therapy will develop arthritis. Abnormalities of the cardiac conduction system are possible later. Diagnosis is based on clinical signs and symptoms, appropriate epidemiologic exposure and serologic testing. Antibody testing in early disease may be negative and should not preclude treatment in the appropriate setting. Demonstration of seroconversion by repeated testing may be helpful in selected cases.1

For children under the age of eight, amoxicillin at a dose of 50 mg/kg divided three times a day for 14 to 21 days is the drug choice for early localized and disseminated disease. Alternatives include cefuroxime 30 mg/kg day divided twice daily. Azithromycin 500 mg daily and clarithromycin 500 mg twice daily also have activity but are inferior to amoxicillin and cefuroxime. Doxycycline may be used safely in children over the age of eight. Patients should be advised regarding simultaneous calcium consumption and photosensitivety when taking doxycycline. Central nervous system involvement and third degree heart block should be treated with ceftriaxone 75-100 mg/day daily up to 2 grams total dose for 21-28 days. Isolated cranial nerve palsies and lower degrees of heart block are treated as for early disseminated disease although for longer periods of time i.e. 28 days. Frank arthritis (warmth, redness, swelling, pain, and as opposed to arthralgia) should likewise be treated with a 28 day course of therapy.2

PREGNANCY

The epidemiology, presentation and diagnosis of Lyme disease in pregnant women is the same as for non-pregnant adults. Doxycycline, however, is absolutely contraindicated as therapy. The most appropriate alternatives are amoxicillin 500 mg three times daily or cefuroxime 500mg twice daily for 14 to 21 days.2

In 1985 Schlesinger et al published possible evidence of maternal fetal transmission of B. burgdorferi. Concerns were raised regarding the possibility of fetal malformations and stillbirth.3 Several large studies have not, however, borne these concerns out. A prospective study of 2000 pregnancies and outcomes in an endemic area did not find an increased risk of pregnancy loss or congenital malformation.4 5 A survey of pediatric neurologists in an endemic area did not detect a clinical syndrome or pattern of abnormalities which could be attributed to Lyme disease.6 Finally, there is no evidence that infection is transmitted via breast milk.

REFERENCES


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Disclosure of Financial Interests

The author has no financial interests to disclose.

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In 1977, Dr. Allen Steere and colleagues reported an outbreak of arthritis in children and adults in three small Connecticut comminutes: Lyme, Old Lyme and East Haddam. These cases were first noted in this small geographic region beginning in about 1972 and several of the children were diagnosed with juvenile rheumatoid arthritis (now called juvenile idiopathic arthritis). Steere and colleagues described this syndrome as a previously unrecognized disorder and coined the term “Lyme Arthritis.” There was a strong suspicion that the syndrome was caused by an infectious agent, transmitted by an arthropod vector.

Subsequently, Lyme arthritis was found to be a major feature of a larger multi-systemic illness, Lyme disease, caused by the spirochete Borrelia Burgdorferi transmitted by a bite from the deer tick Ixodes damini. Following the tick bite, the syndrome may involve multiple organs. Musculoskeletal symptoms and findings are noted in the majority of patients with Lyme disease.

Arthritis was, and is, a dominant feature in most patients with Lyme disease; however, the pattern of arthritis varies during different stages of this syndrome. In fact, the pathogenesis of Lyme arthritis is initially related directly to the spirochete infection and later, it is postulated, to immunologic abnormalities. This is particularly true in patients with chronic Lyme arthritis. Lyme disease is said to be an infectious disease that behaves like a rheumatic disease.2

### Prodrome

Erythema migrans (EM), the classic skin manifestation of Lyme disease, is noted in approximately 90% of patients, usually within one month of the tick bite.3 Synchronously with, or subsequently to, the skin rash, a prodrome develops consisting of flu-like symptoms, fever, fatigue, malaise, myalgias and polyarthralgias. Joint pain is typically polyarticular, involving both large and small joints as well as occasionally the back and neck. During this early localized phase of Lyme disease, patients rarely developed frank arthritis and synovial effusions are not evident. At this stage, the patient’s illness resembled a typical viral syndrome.

### Lyme Arthritis

Frank arthritis develops months to a few years following the tick bite in untreated or inadequately treated patients and Lyme arthritis is considered a manifestation of late Lyme disease (previously referred to as Stage 3 Lyme disease). This arthritis affects one or a few joints in two distinctive patterns, intermittent arthritis and chronic arthritis.4

#### Intermittent Arthritis

Intermittent arthritis develops in at least 60% of patients with Lyme disease who are not treated during the early stages. The presence of prodromal symptoms of polyarthralgia does not predict the development of future arthritis. Patients develop episodes of severe joint inflammation that are variable in frequency. The usual pattern of joint involvement is either an asymmetric oligoarthritis or a monoarthritis, primarily affecting large joints. The knee is the most common joint involved and is almost always affected at some point during the illness; the ankle and the wrist are the next most common sites for arthritis.5

During episodes of arthritis the affected joint may become very swollen and warm although the patient usually complains only of mild pain. Patients with episodes of arthritis that are severely painful or associated with fever should be evaluated for other causes of joint inflammation including crystal disease or even septic arthritis; this is true even in patients that have previously proven Lyme arthritis.

The presence of effusions in one or both knee joints is typical of the intermittent arthritis of Lyme disease. Very large knee effusions, and Baker cysts formation and spontaneous rupture in these settings have been described.6

The exacerbations of arthritis usually last weeks to months and typically resolve spontaneously. In general the frequency and duration of arthritis attacks are greater in the early years of the disease compared to more chronic illness. Between the episodes of joint inflammation, the patients typically do not have any joint symptoms.

### Chronic Arthritis

About 10% of untreated patients with recurrent attacks of arthritis lose the typical periodicity of flares and develop chronic arthritis in one to three large joints. This does not resemble the pattern of rheumatoid arthritis, and Lyme arthritis should not be considered in the differential diagnosis of chronic inflammatory polyarthritis, especially if the small joints of the fingers and toes are involved. Chronic Lyme arthritis clinically causes unremitting joint swelling and pain for at least one year and one or both knees are almost always involved.4 Due to the increased awareness of EM in endemic areas and the development of clearer treatment guidelines, the proportion of patients with Lyme arthritis who do not have a history of EM is increasing and the lack of EM should not exclude patients with characteristic arthritis in endemic areas from being tested for Lyme disease.

### Synovial Pathology

Unlike other forms of bacterial infections affecting the joint, Lyme arthritis is indolent and damage is delayed for months or even years. The Borrelia spirochete lacks the enzymatic activity of other bacterial pathogens that may affect the joints and it is believed that joint damage occurs largely due to an exuberant inflammatory response.

The synovial pathologic of patients with Lyme arthritis is similar to that seen in other types of non-bacterial inflammatory arthritis. This includes synovial hypertrophy, vascular proliferation, and infiltration of the synovial membrane with mononuclear cells. However, it may be distinguished from the synovial pathology of rheumatoid arthritis in that germinal centers and follicular hyperplasia are not typically seen.

Synovial fluid analysis shows only mild elevations of white blood cells in the
low inflammatory range. The synovial fluid white blood cell count is usually less than 50,000 cells/cubic millimeter.

**Laboratory**

Virtually all patients with Lyme arthritis have serum immunoglobulin G (IgG) antibodies to Borrelia burgdorferi by Western blotting, but the presence of anti Borrelia antibodies within the synovial fluid by ELISA or Western blot is an accurate and reliable method of proving that arthritis is truly related to Lyme disease.

In patients with chronic Lyme arthritis cultures of the synovial fluid for the causative organism are usually negative but the genomic DNA of B. burgdorferi can be identified in the synovial fluid by Polymerase chain reaction (PCR) with sensitivity about 85%. The conversion of a positive PCR to a negative PCR after antibiotic therapy is used to confirm successful treatment. PCR analysis of synovial tissue has a higher yield than that of synovial fluid for the presence of B. burgdorferi DNA.

**Radiology**

In a study of 25 patients with Lyme arthritis' who had active arthritis in the knees for a median of 9 months (range 2 to 24 months), 20 patients (80%) were found with radiographic abnormalities. The most frequent findings were: soft tissue changes including knee effusions, synovial hypertrophy, edema of the infrapatellar fat pad and enthesitis. Other findings included symmetrical articular cartilage loss, juxta-articular osteoporosis and erosions at bare areas at the margins of the cartilage. However, radiographs of involved joints in the early stages of Lyme arthritis are typically normal. No studies specifically evaluate the role of magnetic resonance imaging in Lyme arthritis.

**Treatment of Lyme Arthritis**

Antibiotic treatment early in the course of Lyme disease is very effective in preventing arthritis, and when started after the presence of arthritis, shortens the duration of attacks with resolution of arthritis within weeks to months. Oral antibiotic therapy is preferred over intravenous antibiotic therapy because both treatments are equally effective, but oral treatment is cheaper and probably associated with fewer side effects. Oral antibiotics (doxycycline or amoxicillin) are usually given for 30 to 60 days; this is effective in about 90% of patients. Other recommendations are that patients who did not respond to 30-60 day course of oral antibiotics should be treated with a 30 day course of intravenous ceftriaxone. These strategies are generally extremely effective in treating chronic Lyme arthritis.

**Lyme arthritis, whether intermittent or chronic, is a hallmark of late Lyme disease.**

**Antibiotic-Refractory Lyme Arthritis**

Approximately 5-10% of patients with Lyme arthritis do not respond to either oral or intravenous antibiotic therapy according to the prescribed recommendations. These patients are felt to have antibiotic-refractory (or slowly resolving) arthritis. This condition is defined by persistent joint swelling for 3 or more months after the start of at least 4 weeks of IV antibiotic therapy or at least 8 weeks of oral antibiotic therapy or both. This condition could, theoretically, result from persistent infection, but the identification of either spirochetes or spirochetal DNA in these patients is rare.

It is believed that persistent arthritis in these patients results from immunologic abnormalities. Patients with this condition have a higher incidence of HLA-DRB1 alleles (similar to the alleles associated with rheumatoid arthritis) and are thought to have greater immune reactivity to Borrelia burgdorferi Outer-Surface Protein A (OspA).

Once the patients in this category have a negative PCR for Borrelia Burgdorferi, the general recommendation is to treat these patients with oral non-steroidal anti-inflammatory drugs, hydroxychloroquine, sulfasalazine or intraarticular steroids. Intraarticular steroids should not be used for Lyme arthritis if the patient has not previously been treated with adequate antibiotic therapy.

Methotrexate and even tumor necrosis factor a inhibitors have been considered for patients in this category. A treatment strategy which is usually effective in patients with persistent arthritis is arthroscopic synovectomy. Although it is difficult to achieve a complete synovectomy with arthroscopy this should still be considered as a treatment option. It should be further emphasized that although chronic Lyme arthritis may be associated with joint erosions and cartilage loss, the arthritis resolves eventually in all patients.

**Post-Lyme Disease Syndrome**

Lyme disease at any stage may have associated nonspecific symptoms of fatigue, myalgia, malaise, and wide spread body pain. A fibromyalgia-like symptom is well described in some of these patients even in those who received adequate antibiotic therapy for Lyme disease. These patients have been referred to as having post-Lyme disease syndrome. Additional symptoms include not only fatigue, arthralgias, myalgias, and malaise but symptoms of cognitive dysfunction including difficulty concentrating, poor attention and memory deficit. Headaches, poor sleep and irritability also comprise this syndrome in many patients.

Although those patients have significant symptoms and functional disability, they lack the objective findings of active inflammation, such as synovitis, on physical examination.

The etiology of this syndrome is still unclear and the actual incidence is very variable. However, it does not seem to represent chronic active infection and it does not benefit from prolonged courses of antibiotics, whether orally or intravenously.

**Other Manifestations**

Based on case reports, Lyme disease could be associated with myositis, osteomyelitis, and panniculitis. Patients with myositis may develop weakness and muscle pain. The patients in this category have been found to have elevated muscle enzymes and other inflammatory markers in their serum. In one report a muscle biopsy showed tissue invasion with B. burgdorferi and an immune response to this organism.
SUMMARY

Musculoskeletal symptoms in Lyme disease are very common at all stages of the disease. Lyme arthritis, whether intermittent or chronic, is a hallmark of late Lyme disease. This may cause severe joint pain and swelling especially confined to one or a few joints, most notably the knee. Antibiotic therapy is very effective in treating Lyme arthritis in the majority of cases. However, a small proportion of individuals will develop persistent chronic arthritis which is likely mediated through immunologic mechanisms. In these patients treatment strategies should include anti-inflammatory medications and possibly immunosuppressive treatments. Arthroscopic synovectomy may be very helpful in some of these patients. Post Lyme disease syndrome and Lyme myositis are two other sequelae that are associated with Lyme disease.

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Disclosure of Financial Interests
The authors have no financial interests to disclose.

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Neurological Complications of Lyme Disease

Syed Rizvi, MD, and Amanda Diamond, MD

A tick-bite associated rash with later neurological manifestations, including paralysis and meningitis, had been documented in Europe for several years before Lyme arthritis was recognized in the 1970s. The illness was later understood to be part of a multisystem disease caused by spirochetes and transmitted by *Ixodes* ticks. *Borrelia burgdorferi,* although initially thought to be a single species, has been found to have several sub-species. These subgroups may be responsible for the variation in clinical symptoms observed in different parts of the world.

The pathophysiology of neuroborreliosis is difficult to demonstrate, but mimics other spirochetal infections. Infection is local with subsequent dissemination. During this time spirochete numbers are high. *B. burgdorferi* components that induce cytokine production by T and B cells produce immune activation and indirect cell damage. Central nervous system involvement is common and clinical syndromes tend to occur in stages.

Lyme disease has been implicated in a variety of peripheral and central nervous system disorders. The neurological syndromes are often accompanied by more general complaints (arthralgias, fatigue, myalgias). Earlier neurological symptoms, or those occurring during dissemination within weeks to months, tend to be more clinically obvious and develop in an estimated 15% to 20% of patients. Lyme arthritis was recognized in the United States in the 1970s, although it was not until the 1980s that the disease was well characterized. Lyme arthritis is usually self-limited and may be easily mistaken for nerve-impingement syndromes, with segmental symptoms of weakness, sensory or reflex changes. The symptoms may not occur in the region of the tick bite. Electrodiagnostic testing usually shows multifocal mild sensorimotor involvement.

**Cranial neuropathies.** Involvement of cranial nerves, particularly the seventh nerve, may be present in up to 50%-75% of all patients experiencing neurologic symptoms. Multiple cranial nerves may be involved simultaneously. Reports include symptoms of every cranial nerve except the olfactory nerve. The facial nerve involvement is reported to be bilateral in up to one third of cases. Facial nerve symptoms may not affect taste or hearing, indicating that involvement may be outside the subarachnoid space. Additionally, CSF analysis in isolated Lyme disease facial palsy may be normal. Complete recovery occurs in 80-90% of patients within weeks to months.

The same patients have been discovered to develop an axonal neuropathy in the affected limb. In the case of chronic infection, it has been estimated that one in four patients may have peripheral nerve involvement. These patients may present with mainly sensory symptoms.

**Neuroborreliosis of the central nervous system**

**Meningitis.** Although many syndromes involving the central nervous system remain controversial, several have been well-defined. Certainly, the early appearance of lymphocytic meningitis is well recognized. Mildly increased CSF pressure with headache and papilledema may occur. The lymphocytic pleocytosis usually includes tens to hundreds of lymphocytic cells per mL. A mild elevation of protein may also be seen, with CSF glucose usually remaining within a normal range to minimally decreased. The ‘typical’ symptoms that usually occur with ‘aseptic’ meningitis, such as photophobia, headache and neck stiffness, are extremely variable with Lyme meningitis.

**Intracranial hypertension syndrome.** A rare complication of Lyme disease resulting in headache and potential papilledema, this syndrome seems to be associated more often with children and adolescents. CSF abnormalities may occur. There does not appear to be a correlation with female sex or obesity, as with pseudotumor cerebri.

**Encephalomyelitis.** A chronic manifestation of Lyme disease, encephalitis is rare in North America (nearly all cases have been reported in Europe). On MRI there is evidence of parenchymal involvement. This can include hemispheric or brainstem abnormalities and is usually nonspecific, although may mimic ischemic patterns.

**Myelopathy.** Patients may present with symptoms of transverse myelitis so that Lyme disease should be considered in the diagnosis of these patients. Rarely, a transverse myelopathy may accompany Lyme radiculoneuritis. This...
typically occurs at the same level as radicular involvement and may be preceded by a leptomeningitis. 

Lyme encephalopathy. This may be the most common late neurologic manifestation of Lyme disease. Patients express difficulties with concentration, sleep disturbance, emotional lability, memory and attention. 

Despite studies including requirements for CSF abnormalities and SPECT imaging, the definitive diagnosis of Lyme encephalopathy remains elusive. 

In the consideration of acute encephalopathy, one should note that persons with Lyme-induced cognitive changes likely have a mild encephalitis; these patients should not be confused with mental status changes associated with systemic symptoms. Such patients are likely to have objective findings on neuropsychiatric testing and such a diagnosis should only be made in the presence of appropriate findings after testing has been performed by a qualified professional. This is distinct from the more subjective symptoms often experienced for weeks to months following an episode of acute infection with B. burgdorferi (discussed below).

Post-Lyme disease. Several patients who have had Lyme disease have been noted to have other psychiatric and cognitive symptoms, such as fatigue, cognitive slowing and depression. These patients are sometimes diagnosed with post-Lyme disease. It is unlikely that these symptoms indicate persistent neurologic infection, and studies have not shown that antimicrobial therapy is helpful in these patients.

Diagnosis of neurologic Lyme disease

The crucial element for the consideration of neurologic Lyme disease is the presence of an indicative neurologic symptom. Laboratory data should be complimentary and supportive of clinical findings. In evaluating response to therapy, the clinician must remember that many neurologic illnesses improve with time, regardless of treatment. Unfortunately, sensitivity of culture in nervous system infections is low (only about 10% in CSF in Lyme meningitis). The sensitivity of PCR testing appears to be low as well. Confirmation of the diagnosis, therefore, relies largely on serologic testing. Spinal fluid can, however, be tested for the presence of anti-B. burgdorferi antibodies.

The American Academy of Neurology (AAN) guidelines for the diagnosis of neurologic Lyme disease include the consideration of exposure to ticks in an endemic region, clinical abnormalities other than those affecting the nervous system (including cardiac, rheumatologic and dermatologic symptoms), and adequate laboratory support (proof of the presence of B. burgdorferi or immunologic evidence of exposure) in addition to the causally-related neurologic disease or syndrome.

Additionally, the US Centers for Disease Control and Prevention (CDC) has recommended a two-tier system to test for anti-B. burgdorferi antibodies. Serologic testing starts with enzyme-linked immunosorbent assay (ELISA), with usually high sensitivity depending on acuity of infection and organ systems involved, and low specificity due to cross-reacting antigens. Seropositivity may remain for years and can occur in up to 10% of the asymptomatic population in endemic areas. The antibody may not be detected within the first 2 to 6 weeks after exposure, so retesting (or treatment without testing in cases with Erythema migrans) may be important in cases of high clinical suspicion. Borderline or positive results are then confirmed by Western blot. IgM testing is recommended only acutely in disease, when clinical history is limited to 1 to 2 months, and requires 2 of 3 possible bands (sensitivity 32%). Confirmatory testing of IgG presence requires 5 of 10 possible bands (sensitivity 83%). Given lower sensitivities, clinical judgment should in used in patients with positive ELISA whom do not meet Western blot criteria. Also, positive Western blot performed without ELISA may be deceptive and should not be used.

Given the high incidence of B. burgdorferi antibody in the CSF of patients who are seropositive but without neuroborreliosis, other tests for the diagnosis of central nervous system disease have been evaluated. A recent study by Blanc, et.al. suggested the use of an anti-Borrelia antibody index (AI). The AI is the ratio of anti-Borrelia IgG in CSF to anti-Borrelia IgG in the serum and is considered positive if greater than or equal to two. The study noted 74 patients with diagnoses of other neurologic diseases all had positive CSF Lyme antibodies; only two of those patients had a positive AI (specificity of 97%). The sensitivity of positive AI was determined to be 75%. The authors suggested the following criteria for diagnosis of neuroborreliosis: presence of four of the following five items, 1) no past history of neuroborreliosis, 2) positive CSF anti-Borrelia antibodies, 3) positive anti-Borrelia antibody index, 4) favorable outcome after specific antibiotic treatment, 5) no other etiologic diagnosis.

Researchers have also described a B-cell-tropic chemokine, CXCL13, which appears abnormally elevated in CSF of patients with Lyme neuroborreliosis. If confirmed, this cytokine might serve as a marker to assist in the confirmation of the diagnosis of neuroborreliosis.

Treatment of neuroborreliosis

Although the general recommendation in the US is to use parenteral antibiotics whenever the nervous system is involved, there is considerable evidence in the European literature suggesting oral doxycycline (200-400 mg/day) may be equally effective in most patients. At the recommended doses it appears that the CSF concentrations of doxycycline exceed minimum inhibitory concentration for most strains. Although there are strain differences between United States and Europe, there probably is not a significant difference in antimicrobial susceptibility. Also, prolonged courses of antibiotics do not improve outcomes and are not recommended. The duration of parenteral treatment suggested is 2 to 4 weeks, with no data showing any definite advantage of prolonged treatment. Oral regimens are generally given for 30 days.
The AAN published practice parameters for the treatment of nervous system Lyme disease in March, 2007. It recommended:

1) Parenteral penicillin, ceftriaxone, and cefotaxime are probably safe and effective treatments for peripheral nervous system Lyme disease and for CNS Lyme disease with or without parenchymal involvement (Level B recommendation).

2) Oral doxycycline is probably a safe and effective treatment for peripheral nervous system Lyme disease and for CNS Lyme disease without parenchymal involvement (Level B recommendation). Amoxicillin and cefuroxime axetil may provide alternatives but supporting data are lacking.

3) Prolonged courses of antibiotics do not improve the outcome of post-Lyme syndrome, are potentially associated with adverse events, and are therefore not recommended (Level A recommendation).

Treatment regimens are listed in Table 1.

Table 1. Antimicrobial regimens for the treatment of nervous system Lyme disease

<table>
<thead>
<tr>
<th>Medication</th>
<th>Oral regimens</th>
<th>Adult dose</th>
<th>Pediatric dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxycycline</td>
<td>100 (-200) mg BID</td>
<td>Aged = 8 years: 4 mg/kg/day in 2 divided doses; max 200mg/dose</td>
<td></td>
</tr>
<tr>
<td>Amoxicillin (when doxycycline contraindicated)</td>
<td>500 mg TID</td>
<td>50 mg/kg/day in 3 divided doses; max 500 mg/dose</td>
<td></td>
</tr>
<tr>
<td>Cefuroxime (when doxycycline contraindicated)</td>
<td>500 mg BID</td>
<td>30 mg/kg/day in 2 divided doses; max 500 mg/dose</td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>2 g IV daily</td>
<td>50-75 mg/kg/d in single dose, max 2 g</td>
<td></td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>2 g IV Q4H</td>
<td>150-200 mg/kg/day in 3-4 divided doses; max 6 g/day</td>
<td></td>
</tr>
<tr>
<td>Penicillin G</td>
<td>18-24 MU/day, divided doses Q4H</td>
<td>200-400,000 U/kg/day divided Q4H, max 18-24 MU/day</td>
<td></td>
</tr>
</tbody>
</table>

The AAN published practice parameters for the treatment of nervous system Lyme disease in March, 2007. It recommended:

1) Parenteral penicillin, ceftriaxone, and cefotaxime are probably safe and effective treatments for peripheral nervous system Lyme disease and for CNS Lyme disease with or without parenchymal involvement (Level B recommendation).

2) Oral doxycycline is probably a safe and effective treatment for peripheral nervous system Lyme disease and for CNS Lyme disease without parenchymal involvement (Level B recommendation). Amoxicillin and cefuroxime axetil may provide alternatives but supporting data are lacking.

3) Prolonged courses of antibiotics do not improve the outcome of post-Lyme syndrome, are potentially associated with adverse events, and are therefore not recommended (Level A recommendation).

Treatment regimens are listed in Table 1.
Lyme disease is the most commonly reported vector-borne disease in the United States, with approximately 20,000 cases diagnosed each year. A majority of these cases occur in the Northeast and upper Midwest, with a significant number of cases each year in Rhode Island. According to the Rhode Island Department of Health, 736 cases were reported in 2003, the last year for which it has published data. Because patients with Lyme disease can present to primary care providers, subspecialists or providers in urgent care centers and emergency departments, all Rhode Island physicians should understand the diagnosis and management of Lyme disease. Similarly, they should have knowledge of the controversies surrounding diagnosis and the use of antimicrobial therapy. Lyme borreliosis is caused by a spirochete, *Borrelia burgdorferi*, which is transmitted by the *Ixodes scapularis* tick, commonly known as the deer tick. The disease consists of three stages. The first stage is usually localized, and presents as *erythema migrans* (EM), the characteristic “bullseye rash.” This rash is an expanding skin lesion that appears at the site of the tick bite, presents within 7-14 days after removing the engorged tick, and is usually at least 5cm in largest diameter. Although helpful for diagnosis when present, not all patients develop a rash. Additionally, some patients may have an atypical rash; i.e., smaller and without central clearing. Relatively few patients recall a tick bite. Stage 2 or disseminated infection may begin several days or weeks after the rash, as the spirochete spreads hematogenously. Manifestations of disseminated infection include multiple erythema migrans, meningitis, cranial or peripheral neuritis, carditis, atrioventricular nodal block, or migratory musculoskeletal pain. Stage 3, the late stage disease, may present as chronic arthritis or chronic neurologic disturbances.

Two national organizations, the Infectious Diseases Society of America (IDSA) and the International Lyme and Associated Diseases Society (ILADS), have published treatment guidelines for Lyme disease. The guidelines, which differ significantly, can be confusing to patients and providers. The IDSA guidelines have generally been derived from controlled clinical trials especially with regard to choice of antibiotic and duration of treatment. Conversely, the ILADS guidelines are largely symptom-based and eschew the use of diagnostic testing to confirm cases, relying on physician judgement on when, with what and how long to treat a given patient.

### Diagnosis

Both the IDSA and ILADS guidelines agree that the presence of an *erythema migrans* type rash is highly suggestive of Lyme disease and, when present, constitutes sufficient evidence to make a diagnosis of acute infection. Yet such a rash is not present in all cases. Accordingly, the IDSA guidelines maintain that in the absence of *erythema migrans*, a positive serologic test is necessary to make a diagnosis of Lyme disease. The joint and other systemic symptoms of infection are too nonspecific, and overlap with other types of, usually viral, infections. Additionally, the majority of patients presenting with *systemic symptoms*, i.e. early disseminated disease, are seropositive at the time of presentation. Those patients who still may not have seroconverted may be reasonably treated empirically, especially if the case is highly suggestive and in an area of high endemicity, with follow-up testing used to demonstrate seroconversion and confirm the diagnosis. The ILADS guidelines, in contrast, hold that clinical judgment alone stands as the only alternative basis for the diagnosis of Lyme disease.

In terms of late stage Lyme, where the time from initial bite to presentation is relatively long, a diagnosis per the IDSA guidelines requires a positive blood *enzyme-linked immunosorbent assay* (ELISA) confirmed with a Western blot. A lumbar puncture or joint aspiration yielding a positive *polymerase chain reaction* (PCR) may be helpful in confirming the diagnosis. Conversely, the ILADS guidelines rely on physician judgement coupled with a list of symptoms, of which most, if not all, can be present in other infectious and non-infectious disease states. Per the ILADS guidelines, antibody assays are not sensitive enough to be used clinically and Lyme disease is a suspected diagnosis in many circumstances. This is especially true when there are both musculoskeletal and neuropsychiatric symptoms, and when there is no evidence to indicate another illness. Accordingly, many patients may be treated with antibiotics without clear lab-based or objective physical evidence of a specific disease. This can lead to overuse of antibiotics and the resulting complications of drug reactions and the development of resistant bacteria, with the attendant negative impact on both the patient and the community.

### Laboratory Testing

IDSA and Centers for Disease Control and Prevention (CDC) recommendations consist of a two-test approach using a sensitive ELISA or *immunofluorescent assay* (IFA) followed by a confirmatory Western blot test. If the ELISA or IFA is negative, these guidelines state that a Western blot should not be performed. The need for confirmatory Western blot is supported by the results of a study by Engstrom et al. where 29% of positive ELISA tests were recorded in persons with illnesses other than Lyme disease. Although the western blot is highly specific, false positives do exist, particularly in the IgM immunoblot. The one exception to this algorithm is in the acute phase of infection. Most of the current tests are too insensitive to be helpful diagnostically, given the time lapse in developing an immune response to the spirochete antigens.

The ILADS guidelines state that a seronegative patient may present with Lyme disease, especially if evidence does not indicate another disease. Citing unpublished surveillance data, the ILADS guidelines state that laboratory testing advocated by the CDC fails to
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identify up to 90% of cases of Lyme disease. ILADS proposes to increase sensitivity of the test by registering a seropositive case when only 2 of the immunoblot bands are positive rather than the CDC recommended 5 IgG bands. ILADS maintains that other tests, including antigen capture, urine antigen, and PCR on fluids other than CSF and synovial remain options for Lyme diagnosis. Although the ILADS guidelines acknowledge that these tests have not been standardized, the CDC has taken this a step further and put out an advisory warning against the use of these tests, as the accuracy and clinical usefulness of these assays have not been adequately established.

TREATMENT

The IDSA guidelines recommend doxycycline, amoxicillin, or cefuroxime axetil for 14 days for adult patients with early Lyme disease associated with an EM, and state that macrolides should only be used when the patient has contraindications for all of the medications listed above. These recommendations are based on the results of randomized controlled trials. Late Lyme disease should be treated with a full 28 days of the oral antibiotics listed or parenteral therapy with ceftriaxone, cefotaxime, or penicillin G for 14-28 days. In cases where symptoms such as arthritis persist, a second cycle of antibiotics may be given. However, clinicians are advised by the IDSA to wait several months to allow for the slow resolution of inflammation associated with this disease. As a general rule, these guidelines state that response to treatment is slow, and re-treatment in most cases is not recommended unless objective measures indicate relapse. In contrast, ILADS states that giving antibiotics for a fixed amount of time based on recommendations is “arbitrary.” Instead, the patient’s symptoms and clinical response should guide the duration of the treatment. ILADS defends this ambiguity by stating that in an ideal situation treatment would be halted when the Lyme spirochete is cleared from the body; however, without such a test clinicians must rely on symptom based diagnosis and treatment. The ILADS panel writes that treatment should be initiated at once upon suspicion of a diagnosis, even without objective values. To support their recommendations, the authors cite 2 non randomized studies: one involves 43 acute psychiatric patients with a positive Lyme serology who improved after 90 or more days of concurrent antibiotic and antipsychotic pharmacologic therapy, and another, where 18/23 patients previously treated for Lyme had better outcomes in cognition, but similar improvement in depression and anxiety as compared to the 5 who were not retreated with antibiotics.

To summarize, IDSA proposes a fixed treatment course for each stage of Lyme disease based on the results of controlled studies, while ILADS avoids specific recommendations, arguing to treat the patient, often with long courses of antibiotics, based on clinical response. Given the growing concern of antibiotic resistance, and the substantial morbidity and even mortality associated with persistent antibiotic usage, physicians and patients should understand that at this time there are no randomized controlled studies that show a sustained benefit of long term antibiotics.

LATE STAGE VS. CHRONIC VS. POST-LYME DISEASE SYNDROME

Often the terms late stage, chronic, and post-treatment Lyme disease are used interchangeably; however, it is important to note that they describe very different disease states, and that there is disagreement regarding the presence of chronic Lyme disease. Late stage Lyme disease is generally a point of consensus between IDSA and ILADS and is defined as the late manifestations of the disease such as arthritis, encephalopathy, encephalomyelitis, and peripheral neuropathy. This stage of Lyme can arise from a spirochete infection that has gone untreated for months, or even years. Chronic Lyme and Post-Treatment Lyme Disease Syndrome refer to a set of non-specific symptoms that can occur after initial treatment for Lyme disease. The real question is whether these symptoms are due to active spirochetal infection, or a post-infectious disease state.

ILADS describes Chronic Lyme as a set of permanent symptoms that include fatigue, cognitive dysfunction, headaches, sleep disturbance, demyelinating disease, neuropsychiatric presentations, cardiac presentations, and musculoskeletal problems that seems to be a growing epidemic. ILADS maintains that chronic Lyme and its symptoms may continue despite a 30 day treatment course (persistent), may relapse in the absence of a new tick bite (recurrent), and may be poorly responsive to antibiotic therapy (refractory). In these cases, ILADS guidelines state that the Lyme disease is often resistant to treatment and may require higher and longer doses of antibiotics to produce clear evidence of improvement.

In an exhaustive review of the literature, the authors of the IIDSA guidelines found no convincing biologic evidence of the persistence of the spirochete in humans following recommended treatment regimens for Lyme disease. Instead, they propose that the symptoms following treatment of Lyme be entitled Post-Treatment Lyme Disease Syndrome. Chronic symptoms following Lyme disease most likely represent either an autoimmune phenomenon or stem from the slow resolution of the initial immune response to the infection. They also note that there are a high rate of similar complaints in the general population, as is supported by population-based surveillance data.

The concept of a post-infectious state is supported by a landmark study that randomized individuals with a history of Lyme disease and persistent symptoms to placebo or an additional 90 days of antibiotic therapy; in this study, extended antibiotic therapy showed no additional benefits but did have slightly increased adverse events over the placebo group. Two recent studies, published since the IDSA guidelines in November 2007, also argue against the use of long term antibiotics. A randomized, placebo-controlled trial of 10 weeks of IV...
Ceftiraxone showed slight cognitive improvement in patients on intravenous antibiotics versus the intravenous placebo at 12 weeks, but this difference was not maintained at 24 weeks post-treatment; and more than one quarter of the patients experienced adverse effects attributed to IV ceftiraxone. Another double-blind, randomized, placebo controlled study, from Finland, demonstrated that an additional 100 days of oral amoxicillin showed no benefit over placebo after both groups were treated with 3 weeks of IV ceftiraxone. Based on the results of these studies, physicians should explore other treatment modalities, similar to those used for patients with fibromyalgia, such as increased physical activity, antidepressants and alternative/complementary medicine.

**Conclusion**

The nature of the spirochete that causes Lyme disease has to date prevented the development of laboratory testing that would allow us to accurately monitor disease activity. Controversy stems from differing interpretations of the available data. Whereas the ILADS guidelines rely primarily on small, clinically based studies, the IDSA guidelines were evidence-based, using data from randomized, controlled, and open-label trials. Given the non-specific symptoms of many patients, following the ILADS recommendations could lead to a rise in the misdiagnosis of Lyme disease with a resultant overuse of antibiotics. Therefore, it is important that we educate our patients (Table 1) regarding the significant negative effects of prolonged antibiotics, and the lack of convincing scientific data at this time that support their use. Through education, patients can understand the risks of prolonged antibiotics, and through such understanding, can embrace alternative forms of treatment for symptoms that can often be quite disabling. Physicians in Lyme endemic areas can play a central role helping patients negotiate the controversies and choose safe and studied treatments.

**References**


**Disclosure of Financial Interests**

The authors have no financial interests to disclose.

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**Table 1. Web Sites That Provide Information for Patients and Clinicians on Lyme Disease**

- www.cdc.gov
- www.idsociety.org
- www.tickencounter.org
- www.nih.gov
- www.familydoctor.org
A 76-year-old woman comes to your office for her routine annual visit. She’s been doing well since you last saw her, has no complaints, and is in her usual state of health. She has a history of hypertension that has been well controlled on hydrochlorothiazide. She attends the local senior center weekly, participates in Tai Chi every morning and volunteers at the local elementary school on weekdays. You have seen her regularly and she is up to date with influenza and pneumococcal vaccines, had a normal colonoscopy 4 years ago, and normal yearly mammograms, which she has decided to continue as long as she is active and independent. Today, she asks you about dementia screening, because her best friend was just diagnosed with Alzheimer’s and is now on donepezil. You ask her targeted questions about her memory, functional status and ask whether she or her family have noted any deficits or problems; she reports none.

Dementia is a major cause of morbidity and mortality in the older patient population, as well as in younger, more active adults, who are just beginning their “leisure years”. It is estimated that about 8% of adults over 65 years old have dementia; for those over 85 years old, the number jumps to 30-40%. This translates to more than 4 million people.

Dementia care is estimated to exceed $100 billion per year. The per person, per year cost for formal health care (long term care, medications, acute care and emergency visits) is estimated at $27,672, and the cost of informal care (caregiver and private home care) ranges from $10,400 to $34,517. These figures do not include the social costs of a debilitating disease that can ravage a family, and almost always results in permanent nursing home placement and loss of independence, personality and the most basic of functional activities. Due to dementia’s dramatic impact, many are considering instituting screening programs. Screening programs would involve asking asymptomatic patients questions about their memory and functional status, and performing cognitive assessment tests (e.g., Mini Mental Status Exam, 7 minute screen, Mini-Cog).

The discussion of screening is difficult, because the treatments we can offer are not curative. The purpose of a screening test is early identification to permit early initiation of therapy that will improve outcomes. Data indicate that cholinesterase inhibitors at best temporarily slow or delay progression of disease and improve measures of cognition on some scales. Most experts describe a delay in progression of approximately 6 to 12 months with use of cholinesterase inhibitors. Studies of donepezil, for example, have demonstrated mixed results. A 24-week, placebo controlled trial demonstrated significant improvements in cognition as measured by several rating scales (Alzheimer’s disease Assessment scale and Clinician’s global ratings). There was no effect on quality of life scores. A second placebo controlled trial, AD2000, showed a small but significant improvement in cognition (Mini Mental Status Exam score up by an average of 0.8 points). These effects are consistent with several other studies. However, the study did not demonstrate a delay in institutionalization. Other studies have demonstrated delays in the decline of performance of activities daily living. More consistently demonstrated is that cholinesterase inhibitors have a positive effect on the behavioral complications of dementia.

An additional argument in favor of dementia screening is that there are conditions, albeit rare, that cause dementia but are not due to underlying neurodegeneration or stroke. These rare situations result from an array of metabolic disorders, CNS infections, nutritional deficiencies, drug toxicities and even psychiatric conditions. But even if these “reversible dementias” are rare, the more common circumstance is that the dementia due to neurodegeneration or stroke is made worse by the effects of the superimposed comorbidity.

The question to the patient then becomes a personal one: “when would you want to know”? As discussed above, the argument for screening is colored by the fact that we cannot alter the outcome, only delay it at best. However, allowing patients and families to do advance care and estate planning in the earlier, more functional stages is often argued as a large benefit of earlier detection. There are people who prefer to know, regardless of the answer, and who would worry more about the chance of the disease than the disease itself. But some might be crippled by the knowledge and lose day-to-day enjoyment and quality of life due to their anxiety about the future. No studies demonstrate psychosocial benefits to patients or their caregivers through earlier detection.

A good screening test is evaluated by its sensitivity and specificity for the disease or condition. Many of the cognitive tests that are routinely used to evaluate for cognitive impairment have met the desired sensitivity and specificity cut offs. However, a valuable screening test must also have a high positive predictive value to be sure that patients are correctly identified as having the disease. The positive predictive value should be higher than the disease prevalence, a criterion on which identified as having the disease. The positive predictive value should be higher than the disease prevalence, a criterion on which
health care system. No evidence supports the hypothesis that earlier diagnosis will ameliorate costs to our health care system. In fact, many speculate that early detection will increase costs due to increased physician and support staff time, longer duration of use of medications (6 month cost of Aricept is almost $1000 $), and longer use of community and health care resources. For many of the reasons discussed, the current recommendation by the US Preventative Services Task Force is an “I” recommendation, indicating insufficient evidence to recommend for or against dementia screening. 

“Rationale: The USPSTF found good evidence that some screening tests have good sensitivity but only fair specificity in detecting cognitive impairment and dementia. There is fair to good evidence that several drug therapies have a beneficial effect on cognitive function (equivalent to delaying the natural progression of Alzheimer’s disease from 2 to 7 months), but the evidence of their beneficial effects on instrumental activities of daily living is mixed, with the benefit being small, at best. There is insufficient evidence to determine whether the benefits observed in drug trials are generalizable to patients whose disease would be detected by screening in primary care settings. The accuracy of diagnosis, the feasibility of screening and treatment in routine clinical practice, and the potential harms of screening (e.g., labeling effects) are also unknown. The Task Force therefore could not determine whether the benefits of screening for dementia outweigh the harms.”

Using objective criteria to evaluate a screening test, dementia screening does not pass the bar. However, many professional organizations recommend screening and early intervention. As better treatments emerge, a concerted screening effort will follow. For now, individualized conversations with patients, discussing the evidence for screening, the likely results of treatment and the impact on quality of life are the best course of action.

What to do with our patient? She has no symptoms of cognitive impairment, and is high functioning and active. Reassurance with a discussion of the rationale above, and plans to follow closely with screening if she strongly desires, or develops any symptoms or concerns would be a reasonable approach.

Further reading and practice guidelines:

- USPSTF rationale: http://www.ahrq.gov/clinic/3rduspstf/dementia/dementrr.htm

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Disclosure of Financial Interests

The author has no financial interests to disclose.
Rituximab In Treating Refractory Thrombotic Thrombocytopenic Purpura: Three Case Reports

Samir Dalia, MD, Brendan McNulty, MD, Gerald A. Colvin, DO

Thrombotic thrombocytopenic purpura (TTP), previously often fatal, today is managed effectively with corticosteroids and plasma exchange (PE); but a subset of patients will require further treatment. Though the classic pentad characteristic of TTP includes microangiopathic hemolytic anemia, thrombocytopenia, neurological deficits, fever, and renal impairment, only one sixth of cases have all these features. Treatment is often initiated based on the findings of microangiopathic hemolytic anemia, including significant schistocytes on peripheral blood smear, in combination with thrombocytopenia unexplained by disseminated intravascular coagulation or other processes.

The additional therapy may include immunosuppressive agents, including vincristine, cyclophosphamide, and cyclosporine, which have been used with variable success. Rituximab, a chimeric monoclonal antibody against CD20, a phosphoprotein that is expressed on the surface of all mature B-cells, has increasingly been shown to induce remission in refractory TTP. In fact, a retrospective review of TTP cases treated with rituximab demonstrated a decrease in the titer of antibodies of ADAMTS13, a metalloproteinase that regulates the biological breakdown of Von Willebrand factor (vWF), a platelet aggregation regulator.

We report three cases of refractory TTP in which the early use of rituximab, combined with PE and corticosteroids, led to favorable outcomes.

**Case 1**

A 28 year-old woman with no significant medical history presented with a two-week history of worsening, spontaneous bruising of her limbs and left breast. She reported malaise and generalized abdominal pain with nausea, but denied any history of fever, diarrhea, or numbness. She had mild diffuse abdominal tenderness, truncal petechiae, and ecchymoses on the extremities and left breast. She was alert, oriented and had no neurologic deficits. Imaging of the abdomen by CT revealed no abnormal findings. Initial laboratory studies showed a hemoglobin of 10.5 g/dL, a platelet count of 11,000/µL, and normal renal function, PT/PTT, and fibrinogen levels. Hemolysis studies were notable for an LDH of 892 IU/L, an undetectable haptoglobin, and an elevated indirect bilirubin of 1.6. Review of a peripheral blood smear revealed numerous schistocytes supporting the diagnosis of TTP. An assay for ADAMTS13 was at <5% (reference range > or = 67%) with a protease inhibitor level >8.0 inhibitor units.

The patient was transferred to the medical intensive care unit where once daily PE was initiated with prednisone 100mg. Due to suboptimal platelet response the patient was started on twice daily PE on hospital day five with subsequent improvement in platelet count. After one week of twice daily PE, her platelet count fell again, and a rituximab course of four weekly doses of 375mg/m² was initiated in addition to a prednisone taper. Her platelet count normalized within a week. On hospital day twenty-one she was discharged home following her third dose of rituximab with close follow-up and a weaning course of PE. After twelve months, she had no signs of relapse without any medications.

**Case 2**

A 23 year-old woman with history of hydrocephalus, treated at age 8 with a VP shunt, presented to the emergency department with a week of progressive spontaneous bruising, dizziness, blurry vision, headache, and intermittent numbness on the right side of her body. Her roommate noticed a right-sided facial droop on the day prior to her admission. On admission, the patient’s physical exam was notable for diffuse truncal petechiae with multiple ecchymoses on the legs. Her neurologic exam was normal. A CT scan of the head revealed no acute abnormalities, as did a subsequent MRI. She had an initial hemoglobin of 9.2 g/dL, a platelet count of 16,000/µL, haptoglobin was <5.83 mg/dL and normal renal function. Coagulation studies and fibrogen level were within normal limits. An assay of ADAMTS13 was <5% with an inhibitor unit level of 1.0. Review of the peripheral blood smear revealed multiple schistocytes.

Daily PE with prednisone 100mg daily was started, and her platelet count rapidly improved along with her symptoms. She was weaned to every other day PE when her platelet count reached 173,000 on hospital day four. However, her platelet count decreased again and daily PE was restarted. Her disease became refractory to once daily exchange, and the patient was then transferred to the intensive care unit for twice-daily PE on hospital day nine because of falling platelet counts. By hospital day fifteen her platelet count response remained poor so weekly rituximab was initiated with a prednisone taper. Her platelet count increased to the low normal range within the first week of treatment with rituximab and this trend continued after the second dose. She was discharged home for outpatient PE three times per week, and two further doses of weekly rituximab therapy. PE was weaned slowly and after six months of follow-up, she remained relapse-free on no medications.

**Case 3**

A 25 year-old man with a history of schizophrenia, hypertension and pancreatitis secondary to hypertriglyceridemia presented initially to an outside hospital with renal failure and
The patient had a hemoglobin of 9.1 g/dL, platelet count of 8,000/µL and multiple schistocytes on peripheral smear. He was transferred to our institution for management of TTP. An assay of ADAMTS13, drawn during PE therapy, revealed proteases activity level >67%.

The patient received twice daily PE with Solu-Medrol 125mg intravenous every 6 hours for one week. The patient was tapered to once daily PE and the Solu-Medrol was changed to a prednisone taper. The patient’s hospital course was complicated by an intra-abdominal infection and continued worsening of his renal function. The week prior to discharge the patient was tapered to prednisone 10mg once a day receiving thrice weekly PE.

His platelets stayed between 160,000-190,000/µL with slight improvement in his renal function and on post hospital day six rituximab therapy was started for continued renal failure thought to be from the TTP. After four doses of weekly rituximab therapy the patient’s creatinine improved to 1.3 mg/dl from a high of 5.0 mg/dl with a stable platelet count. He has been disease free for four months on no medications.

**DISCUSSION**

Treatment of TTP with PE has been accepted since PE was compared with plasma infusion for treatment in 1991. In refractory cases immunosuppression is often utilized based on the rationale that TTP may be caused by autoantibodies that inhibit ADAMTS13 activity. Several different immunosuppressant medications have been tried but none seem as promising and safe as rituximab. Rituximab’s efficacy as an adjunct to plasma exchange and corticosteroids in the treatment of TTP is described in multiple case reports. One case study demonstrated the use of rituximab as a first line treatment in TTP. Another study demonstrated that prophylaxis with rituximab in patients with previous TTP was beneficial. Unlike other immunosuppressants, rituximab is generally safe and well tolerated though it does have a common adverse effect of infusion reactions.

Our case reports illustrate that early intervention with rituximab may provide rapid improvement of refractory TTP. In these cases use of rituximab may have contributed to a decrease in length of hospital stay as well as the associated morbidity and mortality of refractory TTP. The benefits of early rituximab therapy in TTP management will need to be established through a prospective clinical trial. The Transfusion Medicine and Hemostasis Clinical Trials Network, sponsored by the National Heart, Lung and Blood Institute (NHLBI), has initiated a multi-center, randomized clinical trial, designed to determine whether rituximab, in addition to standard treatment of PE and corticosteroids, decreases initial treatment failure rates as well as subsequent relapses of TTP over three years. Data from this study will establish rituximab’s role in the first line treatment in TTP.

Data are mounting in regard to the efficacy of rituximab in TTP management. In our experience rituximab has provided considerable benefit for patients with refractory TTP by facilitating the rapid wean of PE and systemic corticosteroid therapy. It shows promise for reducing the morbidity and mortality of this dangerous immune-mediated disorder.
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Disclosure of Financial Interests

The authors have no financial interests to disclose.

Discussion of use of off-label or investigational product:

Rituximab

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Lyme disease (LD), a tick-borne illness caused by the bacterium *Borrelia burgdorferi*, is prevalent along the northeastern seaboard of the US and in Wisconsin and Minnesota. It is reported with much less frequency in other parts of the nation. (Figures 1 and 2.) According to the Centers for Disease Control and Prevention (CDC):

Typical symptoms include fever, headache, fatigue, and a characteristic skin rash called *erythema migrans*. If left untreated, infection can spread to joints, the heart, and the nervous system. Lyme disease is diagnosed based on symptoms, physical findings (e.g., rash), and the possibility of exposure to infected ticks; laboratory testing is helpful in the later stages of disease.

Because laboratory tests are not definitive for the diagnosis of LD, public health agencies must rely on reports from clinicians containing detailed information on symptoms, physical findings (e.g., rash), and the possibility of exposure to infected ticks in order to establish the burden of LD in a defined population. Obtaining timely, accurate, and complete reporting of LD is labor intensive for both clinician reporters and public health agencies; and the result, to no one’s surprise, has been significant under-reporting of new onset LD.

Connecticut is a case in point, as revealed in the results of a study undertaken by the Connecticut Department of Public Health (CDPH) from 1998 through 2002. By means of labor-intensive investigation during those five years, the CDPH identified an average of 3755 new onset cases of LD per year, of which only about half (approximately 1830 per year) were identified through “physician-initiated” reporting. The rest of the cases were identified by following up on every positive laboratory test for LD reported to the CDPH. Of more than 10,000 positive tests per year reported to the CDPH by mandate, “only 36% of reports received through required laboratory surveillance resulted in identification that met the national surveillance case definition [as defined by the CDC] for LD.” The CDPH could not sustain this intensity of effort for the long term, and dropped mandatory laboratory reporting for LD in 2003. The number of cases reported to the CDC from Connecticut dropped from a high of about 4600 in 2002, the last year of intense case finding, to an average of about 1500 per year in 2003, 2004, and 2005.

New Jersey provides another documented illustration of the difficulties associated with LD surveillance. Between 2002 and 2006 (inclusive), the New Jersey Department of Health (NJDH) mandated electronic reporting of all positive laboratory tests for LD among New Jersey residents. Compared to the year preceding mandated laboratory reporting (2001), the average annual number of LD reports quintupled in 2002-2006, creating a significant strain on human resources in local health departments. Nonetheless, the results of this natural experiment are quite instructive, and may be compared—albeit roughly—with Connecticut’s experience. Laboratory reporting increased the average annual incidence of confirmed LD in New Jersey by 18%, less than Connecticut’s increase (~50%). About 29% of New Jersey’s laboratory reports yielded confirmed LD cases, slightly less than Connecticut’s yield (36%). Thus, even though the net yield of confirmed LD cases from laboratory-initiated reports (the yield over and above physician-initiated reports) was lower in New Jersey than Connecticut—18% versus ~50%—the gross yield was roughly the same—29% versus 36%. Ultimately, New Jersey changed its surveillance practices to conserve human resources. It now follows up only on those laboratory reports that are linked to physician-initiated reports.

Like its neighbors in the northeastern United States, Rhode Island has struggled to muster sufficient resources to follow up on mandated laboratory reports for LD. In common with virtually all jurisdictions in which LD is prevalent, cases of new onset disease are known to be undercounted and under-reported to the CDC. Nonetheless, from 1992-1998, Rhode Island had the second highest state LD incidence rate in the United States. Between 1992 and 1998, the Rhode Island Department of Health estimated the incidence of new onset Lyme disease in Rhode Island as 130 cases per 100,000 population. This estimate is based on a review of laboratory reports and clinical charts of patients with confirmed LD, and is consistent with other estimates of the incidence of LD in Rhode Island.

Figure 1. Number* of newly reported Lyme disease cases by county** – United States, 2006

*N=23,174; county not available for 131 other cases. **One dot placed randomly within the county of patient residence for each reported case. 
nation, 44.8 per 100,000 population, and by 2004, had surpassed all other states in new onset cases of LD per capita: 68.39 per 100,000 population.1

Just how high is the actual LD incidence rate in Rhode Island? Can it be estimated? It can, because Rhode Island mandates reporting of positive LD laboratory tests, and because two of Rhode Island’s sister states (Connecticut and New Jersey) have evaluated the yield of confirmed LD cases from positive laboratory reports. It is reasonable to employ the findings of Connecticut’s and New Jersey’s LD reporting evaluations to Rhode Island because the three states share similar geographic features and LD history (Figures 1 and 2), and because the LD case yields from positive LD laboratory tests were roughly similar in Connecticut and New Jersey.4,6

METHODS

Positive LD laboratory reports transmitted to the Rhode Island Department of Health (HEALTH) in 2005 were carefully evaluated for address (of the patient, or, lacking that, of the ordering clinician), test (several tests for other tick-borne illnesses were discovered in this manner and removed), and positivity of result. 2881 contained an authentic Rhode Island address and at least one of several positive test results for LD.

The number of positive test results was multiplied by proportions of yield (for confirmed LD) as reported by the States of Connecticut (for the 1998-2002 reporting years) and New Jersey (for the 2002-2006 reporting years) to estimate the number of new onset LD cases meeting the CDC’s case definition, as used in the 1998-2002 and 2002-2006 periods.

RESULTS

In 2005, an estimated 835-1037 cases of new onset LD (meeting CDC’s case definition for that year) occurred in Rhode Island, yielding crude incidence rates of 78-96 per 100,000 population.

The estimates have good face validity. The number of estimated cases approximates (or exceeds) the highest annual LD counts recorded for Rhode Island in previous years – 789 cases in 1998, 852 cases in 2002, and 736 cases in 2003.1,2 As well, the estimated Rhode Island rate of 96 per 100,000 population (computed from Connecticut’s yield) compares favorably with Connecticut’s rate for the 1998-2002 period, 109 per 100,000 persons (an average of 3730 confirmed LD cases per year, with a mid-period population of 3,409,549).4 On the basis of all LD surveillance information collected to date, it is reasonable to expect similar LD rates in the two states, with Connecticut having a marginally higher rate than Rhode Island.

If the high-end estimate for Rhode Island is roughly correct – 96 LD cases per 100,000 per year in 2005 (the estimate computed from Connecticut’s 1998-2002 experience) – then at best (e.g., in 2002, when Rhode Island confirmed 852 cases) Rhode Island has been able to confirm and report about 83% of LD cases meeting CDC’s case definition.

DISCUSSION

Surveillance for LD is costly, because it is necessary to obtain clinical information on signs and symptoms from clinician’s records, and because so many clinicians are involved. In Rhode Island, more than 400 physicians were responsible for generating the 2881 LD laboratory reports transmitted to HEALTH in 2005. Connecticut, New Jersey, and Rhode Island all tried to enhance surveillance by mandating LD laboratory reporting, and found it too labor-intensive to sustain the follow-up necessary to identify LD cases meeting the CDC’s case definition. In the recently published evaluation of its LD surveillance system, New Jersey public health officials reported that “LD investigations required a median of 2 months to complete follow-up and classify the report… representing approximately 1 hour of active information collection per case.”6 This experience closely parallels informal observations of the same activity as undertaken in Rhode Island. Applying New Jersey’s “1 hour of active information collection per case” finding to Rhode Island, 835-1037 cases would consume one well-trained, full-time employee for the entire year – for just one of many reportable diseases. Furthermore, because LD activity is much more common in the warmer months, it would actually require more than one full-time employee to keep pace with clinical practice. Keeping pace with receipt of laboratory tests is an important time-saver for clinicians, especially the many who see one or two possible LD cases per year, so that they may respond to public health requests for case information without having to search through old records. Keeping pace also assures timely reporting of confirmed cases to the CDC. Every year, public health agencies have a window of opportunity to report calendar year cases to the CDC. Cases that are confirmed outside the window are never counted in national statistics. From its evaluation of LD surveillance activities in 2001-2006, New Jersey concluded that 24% of its LD cases were confirmed outside the window of opportunity for reporting, and therefore were omitted from statistics published by the CDC.6
The CDC has recently attempted to address the costliness of LD surveillance by permitting public health agencies to report LD cases in several categories:

**Case classification**

- **Confirmed:** a) a case of EM [erythema migrans] with a known exposure, or b) a case of EM with laboratory evidence of infection* and without a known exposure or c) a case with at least one late manifestation that has laboratory evidence of infection.*
- **Probable:** any other case of physician-diagnosed Lyme disease that has laboratory evidence of infection.*
- **Suspected:** a) a case of EM where there is no known exposure and no laboratory evidence of infection,* or b) a case with laboratory evidence of infection but no clinical information available (e.g. a laboratory report).

[Lyme disease reports will not be considered cases if the medical provider specifically states this is not a case of Lyme disease, or the only symptom listed is “tick bite” or “insect bite.”]


Using this convention (the 2008 Case Definition) allows public health agencies to report all information to CDC without having to confirm each individual case. This, in turn, will allow the CDC to estimate the true burden of Lyme disease incidence, much as Rhode Island has done by applying estimates of LD yield (and other measures) to numbers of positive LD laboratory reports. Nonetheless, individual clinician reporting of LD cases remains the backbone of LD surveillance. Therefore, health care providers in Rhode Island are strongly urged to report all new onset LD to the Center for Epidemiology and Infectious Diseases on the standard reporting form. (http://www.health.ri.gov /disease/communicable/lyme/LymeReportForm2005.pdf)

**REFERENCES**


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**Disclosure of Financial Interests**

The author has no financial interests to disclose.
Few professions involve the unique privileges and responsibilities that medicine and osteopathy require of practitioners in modern American society. So extraordinary is this role and so necessary is this commitment, that every state operates a governmental agency to monitor and enforce the professional conduct of physicians. These Boards of Medicine in turn have the obligation to be open to performance review by the physician community and society at large.

**The Rhode Island Board of Medical Licensure and Discipline**

The Board is an agency of state government established, by law, to protect the public and to assure high practice and professional standards in the nearly 4000-member physician community. The Board discharges these responsibilities primarily through the licensing process, receiving and investigating complaints, and serving as a disciplinary body. Chapter 5-37 of the RI General Laws describes the Board’s composition, the appointment of members, its mandate, powers and functions. The 12-member Board includes equal appointment of physicians and public members. The Governor appoints members with input from the medical or osteopathic societies and the Health Department.

The Director of the RI Department of Health (HEALTH) serves as Chair. The Board’s Physician Chief Administrator and Legal Counsel serve in vital support roles.

**Board Activities**

**Licensing**

A license to practice medicine in the State of Rhode Island is considered a privilege, not a right. The essential requirements include: graduation from a school of medicine, successful completion of no less than two years of postgraduate training or three years of postgraduate training for ECFMG (Education Commission for Foreign Medical Graduates) certified international graduates, successful completion of the USMLE licensing examination (no greater than 3 attempts per section, all complete in 7 years), evidence of a high moral and ethical standard and payment of the application fee. The Board endeavors to render a decision on a complete license application within 30-90 days.

In 2006 the Board adopted electronic licensing renewal. In 2008 the Board plans to adopt web-based licensing with a common application recognized by other states and linked with nationally accepted credentials verification via FCVS (Federation Credentials Verification Service), testing, USMLE and ECFMG certification to further speed processing.

In 2007 the State legislature increased the licensing fee structure to: $570 for initial license, $650 for the two-year renewal, and $140 for the RI controlled substances registration.

In 2007 a total of 332 completed applications were processed: 320 MD and 11 DO licenses granted with 1 rejection.

**Complaints and discipline**

The Board serves as a clearinghouse for written complaints regarding unprofessional conduct. Complaints may come from individuals, institutions, public officers, other physicians, healthcare professionals or anyone who has contact with medical professionals—including the Board itself. All complaints and investigations remain confidential prior to final Board action.

The Board reviews all complaints and refers those meriting further investigation to a three-member subcommittee. The subcommittee—including at least one physician and one layperson—investigates and makes a recommendation to the full Board. Written Board decisions include findings of fact and law. A majority of Board members must concur for an individual to be found guilty of unprofessional conduct. A variety of sanctions may be administered, including: a reprimand; a suspension; limitation or restriction to practice medicine; probation subject to conditions and requirements; indefinite revocation of the medical license; mandatory participation in a remedial continuing medical education program; compelled submission to care, counseling or treatment; and assessment of fees to cover the administrative costs of proceedings. Appeals receive judicial review by the RI Superior Court. In cases of egregious misconduct constituting an immediate danger to the public, the Director of Health may immediately suspend the individual’s license.

The law speaks in terms of negative examples, i.e. behaviors or activities that constitute “unprofessional conduct.” Examples include: conviction of a crime arising from the practice of medicine; patient abandonment; medical practice while under the influence of alcohol or illicit drugs; volitional falsification or misrepresentation of medical reports records or treatments; fee splitting; willful overcharging for professional services; deceptive billing practices or collection of fees for services not rendered; malpractice or incompetence; negligent or willful misconduct in the practice of medicine; sexual contact in the context of a physician/patient relationship; and failure to comply with requests from the Board or its agents.

The national advocacy group Public Citizen ranks State Medical Boards according to the number of sanctions made per 1000 licensed physicians. For years 2004-2006, RI ranked 38 out of 51 jurisdictions with a serious action rate of 2.75. The range for jurisdictions was Alaska at 7.30 through Mississippi at 1.41. [http://www.citizen.org/publications/release.cfm?ID=7525] In 2007, 279 new complaints were received and reviewed; 182 were opened for investigation; 126 investigations were closed, with an average time-to-close of 117 days.
In 2007 the Board issued 23 public orders regarding physicians. Six orders related to medical negligence, 4 to drugs or alcohol, 3 to reciprocal actions recognizing unprofessional conduct findings in another State on a RI licensed physician, 2 to medical/psychiatric illness rendering a physician unable to practice safely, 2 to Boundary violations (e.g. inappropriate relationship with a patient or key third party), 3 to crime in the practice of medicine, 3 to falsification of records, 2 to inappropriate prescribing – 1 via the internet, and 1 to facilitating the medical practice of an unlicensed physician.*

Below are short summaries. These orders are public documents. [http://www.health.state.ri.us/hsr/bmld/disciplinary.php]

- Two physicians were relicensed on probation and required to comply with a treatment and monitoring program. They are each required to have a chaperone present for all examinations of female patients.
- A physician voluntarily surrendered his medical license while under investigation for inappropriately purchasing approximately 50,000 Vicodin tablets, not for patient use.
- A physician voluntarily surrendered his license while under investigation by the RI Attorney General.
- A physician voluntarily surrendered his medical license owing to medical illness. It was found that his continued practice posed a significant risk to his patients.**
- A physician voluntarily surrendered his license due to health-related problems. He was subsequently reinstated with a 5-year treatment and monitoring contract with the Physician's Health Committee.
- A physician previously suspended by the Director of Health for failing to comply with a Board Consent Order settled the outstanding case with a revocation retroactive to 1998. Of note, a physician who has been revoked may reapply after 5 years.
- A physician previously revoked by the State of Massachusetts, who had also been imprisoned for crimes related to healthcare fraud, was suspended for one year by order of a hearing committee for moral unfitness, inappropriate prescribing, making false statements to the Board, and falsification of a medical record.
- A physician first voluntarily consented to cease all surgical cases while under investigation for his role in a wrong-site surgery. He subsequently consented to a retroactive suspension of surgical privileges to the date of the initial order and was allowed to resume full and unrestricted practice.
- A physician was placed on probation for three years and required to undergo a skills and competency assessment in his area of specialty surgery. He was required to discontinue all surgery in the interim. Conditions were placed upon his supervision of physician assistants and nurse practitioners.
- A physician with undergraduate training as a pharmacist received a reprimand for approving prescriptions for an Internet pharmacy.
- A physician involved with the Physician's Health Committee received a reprimand for willfully making a false report when applying for hospital privileges.
- A physician received a reprimand and was placed on probation for prescribing a medication for one family member using the insurance member identification number of another. No physician-patient relationship existed.
- A physician received a reprimand and was directed to complete an ethics program for facilitating the unlicensed practice of another physician who had previously had his license revoked by the Board.
- Three physicians were issued reciprocal actions to reflect sanctions and findings of unprofessional conduct by other State medical boards for their practice outside of RI.
- An immediate compliance order was issued to a physician to prohibit the prescription of sublingual midazolam as treatment for agitation in unmonitored nursing home patients. This was not associated with any sanction against the physician.
- An immediate compliance order was issued to a physician to discontinue the operation of an illegal physician operatory. The physician was subsequently sanctioned with a 3-month suspension and reinstated on probation.

* Total greater than the 23 orders issued due to several relating to multiple categories
** N.B. physicians are not generally required to surrender their medical license upon retirement or infirmity. Unfortunately the nature of some illness occasionally forces the Board to intervene with a public order for the protection of both the physician and the public.

Policy Statements
The Board is empowered by statute to identify the Standard of Care in the practice of medicine. In the course of case investigation the Board occasionally finds areas of practice where there is a perceived need for clear articulation of the Standard. The Board issues ‘policy statements’ to disseminate this standard. Statements are on the web [ http://www.health.state.ri.us/hsr/bmld/positions.php]. RI licensed physicians are expected to review these statements at least biannually with their license renewal.

In 2007 the Board articulated 3 new statements.

12/12/2007 - Physician or Advanced Practice Clinician Patient Visits in a Hospital Setting – In general, when caring for inpatients in an acute general medicine/surgical hospital, at least daily visits by either the attending physician, his/her physician cross-coverage, or advanced practice clinician should occur and be documented in the medical record.

12/12/2007 - The Physician/Patient Relationship – “It is inappropriate to prescribe medications via the Internet or similar venue without an appropriate physician/patient relationship that would typically include: 1) patient history, 2) physical and/or mental health assessment, 3) legitimate records kept, 4) licensed and trained practitioners, 5) ele-
ments of informed consent wherever appropriate and reasonable, and 6) AMA/AOA code of ethics followed.”

12/12/2007 - Physician Self-Treatment or Treatment of Immediate Family Members

The Board endorses the AMA Statement E-8.19 [http://www.ama-assn.org/ama/pub/category/8510.html]. Specifically, the Board emphasizes that, “Except in emergencies, it is not appropriate for physicians to write prescriptions for controlled substances for themselves or immediate family members.”

CONCLUSION

The Board of Medical Licensure and Discipline continues to protect the high standards of professionalism and ethics that characterize medical practice, to safeguard the public welfare, to provide an efficient yet thorough licensing process, and to provide balanced review and investigation of complaints. The challenges associated with new technologies, telemedicine, emergency preparedness and an increasingly international physician workforce have fostered improved collaboration across State jurisdictions and led to recognition that there are national standards for practice and licensure. The Board’s role in patient safety continues to evolve.

REFERENCES

5. RI BMLD website http://www.health.state.ri.us/hst/bmld/positions.php

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Disclosure of Financial Interests

The authors have no financial interests to disclose.

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Capitate: From the Latin, *capitatus*, meaning headlike in shape; cognate words include capitation, decapitation, capital and Capitol [originally, Jupiter’s Temple in Rome.]

Hamate: From the Latin, *hamatus*, meaning hook-shaped.

Pisiform: From the Latin, *pisium*, meaning pea-like.

Scaphoid: From the Greek, *scaphos*, meaning boat-like [an older term for a submarine is a bathyscaphe]; and from an older Greek term, *scaphoi*, meaning shaped like a shovel [which led to the anatomic name, scapula and the name of a short cloak, scapulary.]

Sesamoid: Shaped like a sesame seed. Derived from the Aramaic, *shimshim*. Why a street has also been named Sesame is unclear, but perhaps related to the Ali Baba tale wherein the secret message, “Open Sesame!” unlocks the cave holding the treasures of the forty thieves.

Trapezium: From the Latin meaning a four-sided plane figure with no two sides parallel. Earlier from a Greek word, *trapezion*, meaning a table with four legs. Cognate words include trapeze and the voluntary muscle, trapezius.

Trapezoid: Shaped like a trapezium.

Triquetrum: From the Latin, *triquestris*, meaning having three corners or angles.

The other bones of the hand and wrist employ such terms as phalanx [From the Greek, meaning a trunk or log; and the Latin describing an infantry unit]; and metacarpal [*meta* from the Greek meaning after or beyond or above; and *carpus*, meaning wrist].

— STANLEY M. ARONSON, MD
NINETY YEARS AGO, JULY 1918

John Champlin, MD, in the President’s Annual Address, briefly discussed Society business, then turned “to the consideration of patriotic and medical questions concerning the war.” The usual agenda was not appropriate, “when we have been participants in the most destructive war the world has ever known, when our country is calling for more and still more medical men for its service.” In 1918 the Medical Society had 460 members (dues: $10.00); the total number of physicians in Rhode Island came to 751; 18.2% of physicians in the state accepted military commissions.

W. Louis Chapman, MD, in “Roentgen Method of Gastrointestinal Investigation,” cautioned that patients’ histories were often unreliable: “The patient’s story should be elicited with as little coaching as possible. It should be verified by questions on succeeding days and will often be found to change with surprising frequency.” The Roentgen examination was essential to understanding the patient’s complaint. He suggested clinicians begin investigating gastrointestinal concerns with mouth x-rays: “The first step ought to be a study of the mouth, and in any case that is at all obscure this should be an x-ray study…if one takes a set of x-rays of the teeth in…cases of arthritis and gastric ulcer the results may be surprising.” He judged subjective symptoms “misleading.”

An Editorial, “The Surgeon General of the Army,” praised General Gorgas, who was nearing retirement age. “No one realizes that he is old, for in reality he is young in body as well as in mind.” The Editorial urged physicians “as a patriotic measure” to lobby the President, their Congressional representatives, and their state legislators to urge the reappointment of General Gorgas.

FIFTY YEARS AGO, JULY 1958

Shields Warren, MD, Professor of Pathology, Harvard Medical School, delivered the 17th Charles Value Chapin Oration: “The Prevention of Somatic and Genetic Radiation Injury.” He stressed the persistence of radiation in normal life. Providence had 4.5r per generation “at least since the days of the Narragansett Indians. Radioactive fallout to date is adding about 1/40 of that amount. The amount added by industrial utilization of atomic energy…is at present insignificant, and appears likely to be adequately controlled.” As for why deaths from radiation still occurred, he cited “ignorance.” For instance, he cited a professor who carried in his vest pocket a piece of radium. As for bomb testing, he reassured readers: “…radioactive fallout at the present time is not likely to cause harm from continued bomb testing, because it is less significant than the changes in background radiation that are produced from changes in altitude alone. Thus the move from Providence to Denver involves the receipt of an increased amount of background radiation compared to which radioactive fallout is of very minor significance.”

The Honorable John D. Pastore, in “The Atom – Its Ultimate Promise,” reflected: “We know that all power God shares with man is power for good. We know that the power and the promise of the atom is — peace.”

Johannes Virks, MD, and Baruth B. Motola, MD, in “Megimide and Daptazole in Treatment of Barbiturate Poisoning,” reviewed 4 cases: all recovered, with no serious side effects from the treatment.

TWENTY-FIVE YEARS AGO, JULY 1983

Thomas C. McOsker, in “Subdural Hematomas in Subteens,” declared: “A subteen child with mild to moderate trauma to the head is unlikely to develop a subdural collection.” He drew his conclusion from chart review of 64 cases of children, aged up to 12, admitted with intracranial bleeding at Rhode Island Hospital, 1973-82. For 47 cases, the cause was not trauma. One 11 year-old child, an “exceptional case,” had struck his head on frozen ground, but not lost consciousness. For five weeks he had no symptoms, then he developed headaches, which was attributed to migraines (his family had had migraines). A CT scan, though, showed a “large left frontotemporal mass which proved at craniotomy to be hygroma.” After the operation, the CT scan still showed subdural collection, but it finally was reabsorbed.

Duane Golomb, MD, in “Attitudes toward Pelvic Examinations in Two Primary Care Settings,” found that the exams “…are tolerated, but not with enthusiasm.”


Norman A. Baxter, PhD, Executive Director, RI Medical Society, in Special Report: “The RIMS Federation: A Necessary Step Forward,” explained the decision of the Medical Society (a 501c6 organization) to create a separate 501c3 organization focused on education.
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