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CHAPTER 63

Lyme Borreliosis

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KEY CLINICAL POINTS

Definition:
- Tick-borne inflammatory borreliosis

Dermatologic Findings:
- Solitary erythema migrans (EM)
- Borrelial lymphocytoma (BL)
- Multiple erythema migrans–like lesions
- Acrodermatitis chronica atrophicans (ACA)
- Sclerotic and atrophic lesions

Ophthalmologic Findings:
- Conjunctivitis
- Episcleritis
- Keratitis
- Iridocyclitis
- Vitritis
- Retinitis
- Disk edema
- Optic neuritis
- Optic atrophy
- III, IV, VI, VII nerve palsies

Diagnostic Tests:
- Flagellin-ELISA
- Indirect immunofluorescence (IFA)
- Western immunoblot
- Culture
- T-cell proliferation studies
- Polymerase chain reaction (PCR)
- Borreliacidal antibody test

Therapy:
- Oral doxycycline
- Oral amoxicillin
- IV ceftriaxone
- IV penicillin
- Synovectomy
- Temporary pacemaker

Complications:
- Hepatitis
- Heart block
- Myocarditis
- Pericarditis
- Arrhythmias
- Meningitis
- Cranial and peripheral neuropathies
- Radiculopathies
- Encephalopathies
- Arthritis
- Baker's cysts
- Myositis
- Fasciitis
- Fetal and infant death

Prognosis:
- Good, especially if therapy is begun early

DISEASE ENTITY

Definition

Lyme disease is a tick-borne borreliosis with multisystem inflammatory sequelae (1). The preferred terminology is Lyme borreliosis (LB). In its early localized form, skin findings are the most prominent aspect of the disease, especially the erythema migrans (EM) rash. Later stages of LB can feature myocarditis, pericarditis, arrhythmias, meningitis, cranial and peripheral neuropathies, encephalitis, oligoarthritis, and ocular inflammation.

Presentation and Clinical Profile

LB can be separated into three distinct clinical stages. Stage I LB begins with a skin bite by a tick of the genus *Ixodes* that has inoculated the spirochete *Borrelia burgdorferi* (Bb). This is followed by the development of a characteristic EM skin lesion. At least 60% of infected patients manifest EM, despite the fact that only 30% recall a preceding tick bite (2). Soon after the onset of this so-called bull's-eye or annular skin rash, Bb disseminates throughout the bloodstream with subsequent flu-like symptoms. Fever, headache, fatigue, arthralgias, myalgias, and neck and back pain may follow (3). There may be a regional lymphadenopathy. In addition pharyngitis, pneumonitis, hepatosplenomegaly, lymphadenopathy, and orchitis may occur (4).

In stage II LB, annular skin lesions, malar rash, diffuse erythema, urticaria, and lymphocytoma may develop (4). Musculoskeletal problems can evolve into oligoarthritis, bursitis, and myositis. Stage II LB begins weeks to months following the initial infection and can be accompanied by cardiac and neurologic involvement. Lymphocytoma cutis, meningitis, encephalitis, cranial neuropathy (especially 7th-nerve palsy), radiculoneuropathy, myelitis, myocarditis, myositis, and fasciitis have been reported (4). Many ocular findings have been described, including ptosis, interstitial keratitis, nummular keratitis, peripheral corneal ulceration, Horner's syndrome, 3rd-, 4th-, 6th-, and 7th-nerve palsies, iridocyclitis, vitritis, atypical pars planitis, retinitis, retinal vasculitis, optic neuritis, disk edema, ischemic optic neuropathy, optic atrophy, and panophthalmitis (5). Cranial or peripheral radioculoneuropathies frequently occur in stage II LB. Meningitis occurs in about 15% of patients with stage II LB (6).

Stage III LB is the chronic phase, usually beginning months after onset, and lasting many years. The hallmark sign of stage III LB is chronic oligoarthritis. This intermittent arthritis most commonly involves the knee, but also frequently the wrist and shoulder (6). Other findings in stage III LB may include chronic fatigue-like syndrome, vasculopathies, myositis, peripheral neuropathy, acrodermatitis chronica atrophicans, lymphocytoma cutis, localized sclerotic, and atrophic lesions. In addition, progressive encephalomyelitis, peripheral neuropathy, and latent neuroborreliosis are found in stage III LB (7).

Incidence and Prevalence

LB has been increasing in frequency. It is the most commonly reported tick-borne bacterial disease in the United States, exceeding Rocky Mountain spotted fever by a ratio of almost two to one (8). Over 75,000 case reports from 49 states have been described. LB has a worldwide distribution; it has been reported from every continent except Antarctica (6).

Manifestations of what we now call LB were first reported in the European literature in 1883 (8). Over the years, various signs of LB have been noted as distinct clinical entities, such as EM, acrodermatitis chronica atrophicans, and lymphocytic meningoradiculitis (Bannwarth's syndrome) (8). These various isolated manifestations were synthesized into one single acute infectious illness in 1975 when Steere and coworkers (9) described a cluster of arthritis cases that were preceded by the EM rash along the east bank of the Connecticut river near the towns of Lyme, Old Lyme, and East Haddam, thus prompting the eponymic term *Lyme disease* to encompass these various clinical entities (10).

CLINICAL FEATURES

Dermatologic

Primary (solitary) EM is the hallmark of early LB (Fig. 1). Analogous to the primary chancre of syphilis,

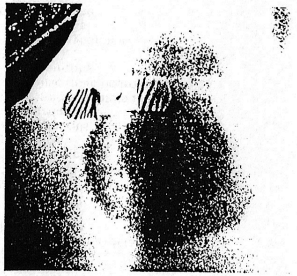

FIG. 1. Classic erythema migrans ("bull's eye") rash on abdomen. The Band-aid covers the biopsy site, where positive culture for Bb was obtained. Note that the biopsy was taken at the leading edge of the rash.

it appears at the site where ticks of the genus *Ixodes* have inoculated spirochetes. This usually occurs within 2 weeks after the bite. Most studies indicate that at least 60% of infected patients manifest EM, despite the fact that only a minority (30%) recall a preceding tick bite (2).

As the nonspecific skin changes of the bite subside, EM classically begins as an erythematous macule or papule that peripherally enlarges in a centrifugal pattern. The advancing border may be either sharply demarcated or hazy. The lesion is usually ovoid, sometimes circinate, and warm to the touch. National surveillance case definitions require diameters of 5.0 cm or larger for epidemiologic reporting, though not for management considerations (11). The cardinal feature of EM is its striking migratory peripheral pattern of enlargement (12). It often spreads several dozen centimeters in diameter within 2 weeks (13).

EM usually disappears spontaneously within 1 to 2 months, leaving residual hyperpigmentation and very mild scaling. Rarely, lesions may last for 6 months to a year or more, at which time they may appropriately be labeled erythema chronicum migrans. Often a confluent erythematous lesion has an intensely reddened center, which may become edematous, indurated, vesicular, encrusted, or hemorrhagic; rarely, it becomes erosive or ulcerated (14). Occasionally, lymphangiitic streaks may accompany the plaque (15). Alopecia in the outline of EM may also result (16). These inflammatory changes, uniquely occurring in the center of the lesion, may indicate a hypersensitivity to antigens of tick parts of saliva (17).

On the other hand, complete central clearing of an expanding lesion may occur. This results in the well-

known diagnostic picture of a complete annulus with an advancing red border and a pale center (13). Another well-known variant is a discoid patch surrounded by relatively normal skin, which, in turn, is surrounded by a red circle (18). Polygonal lesions (13), especially oblong ones, also occur (15).

EM often appears on the body and extremities of adults, whereas children have a tendency for lesions on the scalp, neck, and face. The incidence of EM is much lower in children than in adults (19). Often it is more difficult to diagnose in children, especially when masked by scalp hair. Dysesthesia, lesional or on the scalp, may occasionally be noted (20). Extracutaneous constitutional, nonspecific symptoms and signs, such as headache, sore throat, malaise, malar flush, fever, chills, and fatigue may precede, follow, or appear concurrently with the skin eruption (20).

The disease spontaneously subsides without further progression in about 20% of untreated cases. The remainder may experience progressive disease of the cardiac, skin, musculoskeletal, or nervous systems, individually or in combination (21). At this time, symptomatology such as palpitations, dizziness, chest pain, myalgia, arthralgia, stiff neck, and lack of concentration may point to specific organ involvement. Untreated EM may wax and wane in intensity, usually in the same location. Adequately treated patients very rarely relapse (13). However, cured patients may be reinfected subsequent to additional tick bites (22).

Multiple EM-like (secondary) lesions signal dissemination of the disease through the bloodstream or lymphatics (15). Europeans give transdermal and transneural dissemination some credence (23,24). Multiple lesions have been reported in 17% to 57% of United States cases (15,18). Patients are usually seropositive by the time multiple lesions are well established. They are distinguished from primary lesions by their small size, less tendency to migrate, and lack of an encrusted central punctum or a central erythema. They do not exhibit intense inflammation, nor are they vividly erythematous in color (18). The long axes of these lesions parallel the lines of skin tension. The most common lesion is a homogeneous, erythematous macule (15). However, complete annules with clear centers have appeared with larger lesions (25). They tend to occur in crops of similar-looking macules and usually, but not invariably, spare the palms and soles (18). As these lesions enlarge peripherally, the borders may collide, masking the annular nature of some lesions and forming bizarre patterns that may cover large areas of the body. Anywhere from several to one hundred lesions may form. Cultures are more likely to be positive when obtained from secondary lesions than from primary sites (26).

Borrelial lymphocytoma (BL) is one of a heterogeneous and etiologically diverse group of benign lymphoreticular proliferations (pseudolymphomas) of skin for which a cause has been discovered—namely, an infection with Bb or one of its Eurasian genospecies (Fig. 2) (27,28). This rarest cutaneous manifestation of LB appears to be native to Europe and is more commonly manifested in children. Clinically, it presents as a solitary, deep red, slightly tender nodule, plaque, or area of coalescent papules on skin and/or mucous membranes. Characteristically, BL appears on the pinna, nipple, breast areola, scrotum, and axilla. It develops over several weeks to many months, and may persist for years (29). In fact, it may follow or appear with EM, and may itself be replaced by acrodermatitis chronica atrophicans (ACA) in long-standing cases (27,30). Specific constitutional symptoms are unusual. However, since BL may appear throughout all stages of the infection, it occasionally is associated with meningoradiculitis, cranial neuritis, arthritis, choroiditis, or, rarely, sclerotic or atrophic skin lesions (30–32). Regional lymphadenopathy may be present. Most patients have positive serologies for specific antibodies to Bb (27–29). Positive cultures from lesional skin are rarely obtained (28). The nature of BL is defined by its histopathology and immunohistology (28,32).

FIG. 2. Borrelial lymphocyloma on pinna.

ACA is an outstanding example of prolonged latency and persistent late infection (Fig. 3). Although ACA has been known in the United States for a century (33), our knowledge is scant in comparison to the rich European experience from which much of our knowledge derives. ACA consists of an early inflammatory stage and a later atrophic stage (34). It is usually ushered in with a unilateral, poorly demarcated bluish-red inflammatory dermatitis or edema of a hand, foot, heel, lower leg, elbow, or forearm many months to years after the initial infection has been forgotten, if ever ascertained. The acral extensors and posterior heel are preferred sites (35). Sometimes, a traumatic injury or surgical procedure triggers it (28). A few patients recall a preceding EM located on the same extremity (36). Dissemination to more proximal body parts may occur, but lesions only rarely appear above the buttocks and groin. In the upper extremities, lesions usually become arrested at the elbows, where fibrous nodules frequently develop.

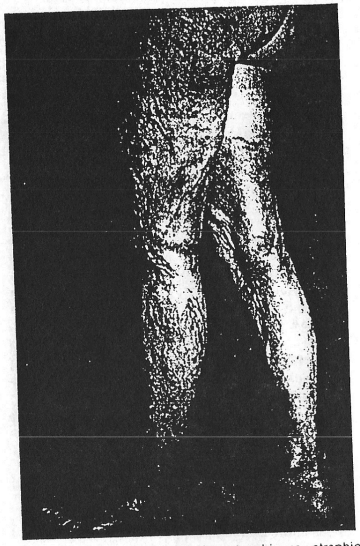

FIG. 3. Acrodermatitis chronica atrophicans, atrophic form, manifesting prominent venous pattern on legs.

The atrophic stage may take years, even decades to develop, or it may never occur at all. When it does occur, it leaves the skin appearing parchment-like, through which an underlying vascular pattern may be seen (35). Ulceration and malignancy may be complications. Cutaneous and systemic manifestations characteristic of earlier stages of LB may or may not have preceded the onset of ACA. Eventually, fatigue, lymphadenopathy, and weight loss may be noted (36).

ACA, unlike EM, does not spontaneously resolve. In Europe, associated findings of earlier or concomitant large joint arthritis, polyneuropathies, periostitis, bursitis, tendinitis, and luxations of the phalanges of the hands and feet are noted with some frequency (35). Less frequently, personality changes are seen (36). Partial and complete luxations often occur below areas of atrophic dermatitis, suggesting direct extension from the skin for many years (35). Researchers have obtained positive cultures for Bb from such cases (37). Luxations, severe neuropathies, and personality changes have not been associated with ACA reported recently in the United States, but the pool of American cases is too small to draw valid conclusions at this time. Serologic tests for antibodies to Bb are usually strongly positive in most European cases (27).

Ophthalmologic

Every part of the eye and ocular adnexa can be involved in LB (Table 1). In early LB, approximately 11% of patients were found to have a follicular conjunctivitis and 6% had photophobia (3). Periorbital edema and subconjunctival hemorrhage have also been noted (3). The most common corneal involvement is a keratopathy characterized by diffuse, nummular, bilateral,

TABLE 1. *Ocular findings in Lyme borreliosis*

Conjunctiva
Follicular conjunctivitis
Sclera
Episcleritis
Cornea
Interstitial keratitis
Exposure keratitis (2° to 7th-nerve palsy)
Nummular keratitis
Peripheral ulcerative keratitis
Uvea
Iridocyclitis
Choroiditis
Exudative retinal detachment
Vitreous
Vitritis
Pars planitis
Retina
Retinitis
Retinal vasculitis
Optic nerve
Optic neuritis
Papilledema
Atypical pseudotumor cerebri
Ischemic optic neuropathy
Optic atrophy
Pupil
Horner's syndrome
Tonic pupils
Orbit and globe
Periostitis
Panophthalmitis

nonstaining opacities that can involve the entire corneal stroma and can reduce vision if in the visual axis (38–40) (Fig. 4). Flach and Lavoie (41) described episcleritis, conjunctivitis, and keratitis in stage II LB. deLuise and O'Leary (42) described peripheral ulcerative keratitis in LB similar to that seen in immune-mediated vasculitis. Inferior exposure keratitis of the cornea from facial nerve palsy can occur (6). Interstitial keratitis resembling that seen in syphilis has been described (6,39).

Many ocular inflammatory syndromes have been reported including granulomatous iritis, iridocyclitis, diffuse choroiditis with exudative retinal detachments, orbital myositis, chronic vitritis with vitreous snowballs, and an atypical pars planitis syndrome with cystoid macular edema (43,44). A patient with unilateral diffuse panophthalmitis was reported by Steere et al. (45) and subsequently by Kauffman and Wormser (46). The eye became severely inflamed and in spite of vitrectomy, phthisical. Review of the vitreous specimen using a Dieterle stain showed Lyme spirochetes. In a review of patients with uveitis without any history of LB, it was found that routine screening for Lyme titers was an ineffective way of diagnosing LB (46).

Neuro-ophthalmic involvement includes papilledema secondary to meningitis with elevated intracranial pressure. Other findings reported include optic atrophy secondary to an ischemic optic neuropathy-like picture (48–51).

Optic neuritis, perioptic neuritis, and neuroretinitis have also been reported (Fig. 5) (48,51–54). Isolated cranial neuropathies include cranial nerves VII, VI. III, and IV, in order of most frequent involvement. In endemic areas, bilateral 7th nerve palsies are most commonly caused by LB. Of 38 patients reported by Pachner and Steere (55), one-half had facial nerve palsy with one-third having bilateral involvement. Sixth-nerve involvement is secondary either to elevated intracranial pressure in association with meningitis, or in some cases due to direct infection. One case of a

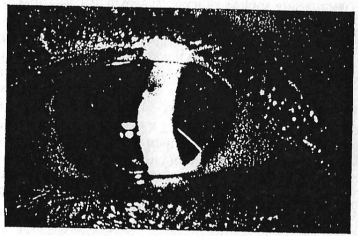

FIG. 4. Nummular corneal infiltrates in LB keratitis.

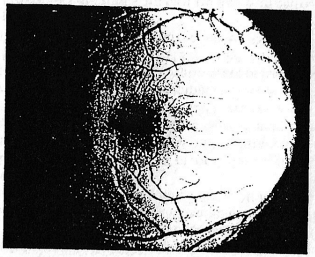

FIG. 5. Exudate seen in LB neuroretinitis.

fascicular abducens nerve palsy has been reported (56). Neuro-ophthalmic signs and symptoms often occur from as early as 1 week to months and occasionally years after the onset of LB. Most patients have associated systemic symptoms such as fatigue, headache, lethargy, and depression.

Criteria used to attribute eye findings to LB include lack of evidence of other disease, occurrence in patients living in endemic areas, positive serology for LB, and clinical findings of LB in other organs (48). Eye findings may develop secondary to direct infection, vasculitis, or may be immune mediated.

ETIOLOGY AND PATHOGENESIS

It is now well established that LB is caused by a systemic borreliosis from the Bb spirochete obtained from the bite site of the *Ixodes ricinus-persulcatus* complex. Although other ticks have been reported to be infected with Bb, they have not been shown to transmit it (8). Bb enters the skin at the site of the tick bite and replicates very slowly (only every 24 to 36 hours) (6). After 3 days to a month, the spirochete may begin to cause symptoms. Bb has been cultured from skin, blood, cerebrospinal fluid, and synovial fluid. Recent studies from Europe postulate that Bb can bind host-derived enzymes, cleave extracellular matrices, and activate B cells, T cells, and inflammatory mediators (57). The pathogenicity of Bb is mainly due to its capacity to extravasate and escape from the host's immune system and directly interact with the host's vasculature and affected organ systems (57).

HISTOPATHOLOGY AND DERMATOPATHOLOGY

The histology of an advancing border of EM shows a superficial and deep perivascular lymphohistiocytic infiltrate with a normal epidermis. Sometimes, the infiltrate is located interstitially. Clusters of plasma cells may be present. The histologic changes of the central area of EM are indistinguishable from an arthropod or insect bite (58). Bb microorganisms may be visualized in dermal papillae, and the reticular dermis adhering to collagen fibers. They may also appear in vessel walls (58). Monoclonal and polyclonal antibody stains may be invaluable to specifically distinguish the microorganisms. Immunohistology has shown that the lymphocytic infiltrate is composed of many T cells with a preponderance of helper/inducer subsets (59). Epidermal and dermal Langerhans cells increase in number (60).

BL is composed histologically of a diffuse lymphocytic infiltrate with or without follicular structures resembling germinal centers in lymph nodes. It may extend deeply throughout the dermis into the subcutaneous fat. Spirochetes may be stained in large germinal centers using silver stains (58). The interfollicular areas show an infiltrate of lymphocytes, plasma cells, eosinophils, mast cells, and macrophages. The inflammatory infiltrate is characterized by polyclonal proliferations of mostly B cells, and CD4 and CD8 cells (32).

Early ACA manifests a patchy, bandlike, or diffuse lymphocytic infiltrate with varying amounts of plasma cells involving the entire dermis and sometimes subcutaneous fat. Striking features include telangiectases of blood and lymph vessels with lymphedema (60). With progression, epidermal atrophy, reduction of elastic fibers, and collagen degeneration occurs. Eventually, after many years, advanced atrophy of the dermis, including all appendages, follows the inflammation. Later, the inflammation disappears, and a pronounced thinning of the entire dermis and subcutis develops. A rich admixture of plasma cells, if present, may be the only feature differentiating sclerotic and atrophic ACA from idiopathic morphea and LSA, except for the presence of the spirochete (60). Immunohistologic staining shows a predominance of CD4 lymphocytes. Many lymphocytes and keratinocytes express human leukocyte antigens (HLA) DR and DQ (60,61).

Fibrotic nodules exhibit the same pattern, and, in addition, display fibrosis of the deep dermis and subcutis, leading to dermal thickening and disappearance of fat lobules. Researchers have also reported epithelioid cell granulomas and foreign body giant cells. In some cases, hyalinization of collagen bundles occurs deep in the dermis and subcutis (60).

DIAGNOSTIC TESTS

Unfortunately, laboratory testing for LB is not standardized, and because there is overlap and cross-reactivity with other diseases, serologic testing must be interpreted with caution. To make the diagnosis, a combination of clinical findings usually in association with a positive titer from a reliable laboratory is needed. Most researchers have accepted the standardized flagellin enzyme-linked immunosorbent assay (ELISA) serologic test available from state health departments. ELISA testing has improved the sensitivity and specificity over commonly available whole-cell sonicate tests, but still yields false-positive results with other spirochetal diseases such as syphilis, tick-borne relapsing fever, and leptospirosis (8). In addition, ELISA is insensitive very early in the disease, since it takes 2 to 3 weeks for antibodies to form in response to Bb (8). It may take up to 6 to 8 weeks before antibody levels are measurable (8). In addition, patients who take antibiotics early in the course of their disease may have a subclinical production of borrelial antibody causing a false-negative reaction.

Another serologic test is indirect immunofluorescence assay (IFA) (62). Because IFA interpretation is subjective, this may often yield false-positive results (62). The Western blot (immunoblot) analysis is widely available and may be used to confirm or negate a borderline positive or false-negative ELISA. It detects antibody bands specific for Bb and is more useful later in the disease when multiple bands may appear (62). Western immunoblot techniques are still not standardized, and therefore this test is also not as useful as the standardized flagellin ELISA (8). Direct culture of Bb can provide information about current infection, but requires up to several weeks of incubation and is not readily available (62). The organism can be cultured from biopsy of the advancing margins of the EM lesions in over 50% of patients (8).

Polymerase chain reaction (PCR) testing may be helpful in detecting specific DNA from Bb even in the early phases of the disease (62). PCR only indicates that an organism is or was present, but does not confirm an active infection. Other tests include borreliacidal antibody test and T-cell proliferation studies (62). Urine antigen testing of Bb has been used without success to date.

DIFFERENTIAL DIAGNOSIS

EM may be distinguished from arthropod or insect bites by its delayed onset and progressive course. Cellulitis with its abrupt high fever, leukocytosis, and painful adenitis contrasts with chronic, progressive Lyme disease. Tinea corporis, pityriasis rosea, and some persistent figurate erythemas are characterized by scaling. Scaling is ordinarily not a feature of the expanding border of EM. Eczema uniformly displays epidermal changes, which only appear in the central area of EM lesions. Histopathology excludes fixed drug eruptions and Sweet's syndrome.

Immunohistochemical staining distinguishes the polyclonal BL infiltrate from its monoclonal counterparts in malignant lymphoma (32). The stable, solitary, primarily B cell lymphocytoma contrasts with the peripherally migrating, multiple papules of Jessner's lymphocytic infiltrate, a T-cell disease. Routine histopathology distinguishes BL from sarcoidosis, lupus vulgaris, lupus erythematosus, arthropod bite granuloma, polymorphous sunlight eruptions, granuloma annulare, and facial granuloma with eosinophils. The distinctive plasmacytic infiltrate, clinical features, and serologic findings distinguish ACA from a large number of vascular diseases, such as venous and arterial insufficiency, acrocyanosis, and livedo reticularis. Fibrotic nodules histologically are distinguished from gouty tophi, calcinosis cutis, and rheumatoid nodules.

The conjunctivitis of LB is nonspecific. It may mimic the follicular conjunctivitis of viral disease. Lyme keratitis is protean in its manifestations. Herpes simplex, herpes zoster, and syphilis need to be ruled out. LB should be included in the workup of any unexplained uveitis. Facial nerve palsy (Bell's palsy) is usually idiopathic, but may be due to herpes zoster, other viral diseases, tumors, or diabetes mellitus. The differential diagnosis of optic neuritis and optic atrophy is legion. Lyme optic neuropathy is indistinguishable from other causes as a solitary ophthalmologic finding.

EXTRACUTANEOUS AND EXTRAOCULAR COMPLICATIONS

The systemic infection caused by Bb may be so widespread that practically any organ system may be involved. During the past decade, many case reports have enlarged the clinical spectrum. Some are not convincing. The most convincing sites of involvement, however, include the cardiac, nervous, musculoskeletal, and reticuloendothelial systems.

Early LB is often associated with mild hepatitis, splenitis, and lymphadenopathy (20,63). A fluctuating, usually remitting, high degree of heart block, myocarditis, pericarditis, and arrhythmias may appear, alone or concomitantly in early disease in less than 10% of patients (64). A somewhat larger percentage of patients experience nervous system involvement. Meningitis, cranial and peripheral neuritis, painful radiculitis, diffuse neuropathies, plexopathies, and entrapment neuropathies may occur during early, subacute, and chronic disease. Encephalitis, leukoencephalitis, myelitis, and encephalopathy have been well documented on both sides of the Atlantic (65–67).

Large joint oligoarthritis, especially of the knees, fluctuating with localized, intermittent musculoskeletal pain, has been the principal defining feature of this disease in the United States since its inception (68). Ruptured Baker's cysts are common. Chronic, potentially erosive joint changes refractory to antibiotic therapy may be seen in individuals with the class II HLA phenotypes DR4 and/or DR2 (69). Cases of focal, nodular, and occasionally interstitial myositis and/or fasciitis are occasionally reported in the United States and Europe (70). They are seen in early or late disease. One noteworthy case has been reported in Germany with diffuse edematous erythema on the face, with distinctive bluish edema of the eyelids resembling dermatomyositis (71). Fetal infection with stillbirths and early infant death are infrequently seen (72).

MANAGEMENT

Although amoxicillin, doxycycline, ceftriaxone, and penicillin G have emerged as the therapeutic mainstays (Table 2), newer macrolides and cephalosporins are being evaluated. Failures have occurred with all these drugs. Duration of treatment remains controversial. Occasionally, courses of therapy are repeated in extremely symptomatic patients. Recent trends are to administer antibiotics in higher dosages and for longer duration than in the past (8). Neuroborreliosis requires antibiotic therapy that must cross the blood-brain barrier in sufficient concentration to affect cure (60). Early disease responds to less-intense therapy than later disease (73).

Doxycycline (100 mg, twice daily) for 10 to 21 days is the preferred regimen for adults and older children. Amoxicillin (500 mg, three times daily) for 10 to 21 days is the alternate choice for localized early disease in pregnant or lactating women, or in children younger than 8 years of age (pediatric dose 30 to 40 mg/kg/day) (73). Most authorities favor ceftriaxone (2 g intravenously) for 2 to 4 weeks for all but the mildest cases of LB in pregnancy (73). Erythromycin is seldom used for LB, except as an alternative for patients allergic to amoxicillin and tetracycline. When administered, it is usually given 500 mg, four times daily, 50 mg/kg/day in children.

BL requires 2 to 4 weeks of oral doxycycline or amoxicillin treatment depending on the duration of its presence. Its total disappearance may require many weeks to months. Doxycycline (100 mg, twice daily) for 21 days is suitable for uncomplicated ACA. If neurologic and/or arthritic manifestations are present, benzyl penicillin intravenously (12 g daily) for 14 days, followed by 14 days of oral doxycycline (200 mg daily) is preferred (8,60).

Most cases of carditis are best treated with ceftriaxone (2 g daily) intravenously for 14 days (8). Hemodynamically unstable patients with Mobitz 2 heartblock or severe bradycardia may require a temporary pacemaker.

TABLE 2. *Treatment of Lyme disease*[a]

Symptom	Drug	Adult dosage	Pediatric dosage[b]
Erythema migrans	Doxycycline[c] (Vibramycin, and others)	100 mg PO b.i.d.	
	or		
	Amoxicillin (Amoxil, and others)	250–500 mg PO t.i.d.	25–50 mg/kg/day divided t.i.d.
	Alternative: Cefuroxime axetil (Ceftin)	500 mg b.i.d.	250 mg b.i.d.
Neurologic disease	Doxycycline[c]	100 mg PO b.i.d.	
Facial nerve palsy	or		
	Amoxicillin	250–500 mg PO t.i.d.	25–50 mg/kg/day divided t.i.d.
	Ceftriaxone (Rocephin)	2 g/day IV	75–100 mg/kg/day IV
More serious CNS disease[d]	or		
	Penicillin G	20–24 million units/day IV	300,000 units/kg/day IV
Cardiac disease	Doxycycline[c]	100 mg PO b.i.d.	
Mild	or		
	Amoxicillin	250–500 mg PO t.i.d.	25–50 mg/kg/day divided t.i.d.
	Ceftriaxone	2 g/day IV	75–100 mg/kg/day IV
More serious[e]	or		
	Penicillin G	20–24 millin units/day IV	300,000 units/kg/day IV
Arthritis[d]	Doxycycline[c]	100 mg PO b.i.d.	
Oral	or		
	Amoxicillin	500 mg PO t.i.d.	50 mg/kg/day divided t.i.d.
	Ceftriaxone	2 g/day IV	75–100 mg/kg/day IV
Parenteral	or		
	Penicillin G	20–24 million units/day IV	300,000 units/kg/day IV

[a] Recommendations are based on limited data and should be considered tentative. The duration of treatment is not well established for any indications; it is usually based on severity of disease and rapidity of response. Clinicians generally recommend 10 to 30 days for oral drugs and 14 to 21 days for intravenous treatment.
[b] Should not exceed adult dosage.
[c] Or tetracycline HCl (achromycin, and others), 250–500 mg q.i.d. Neither doxycycline nor any other tetracycline should be used for children less than 8 years old or pregnant or lactating women.
[d] In late disease, the response to treatment may be delayed for several weeks or months.
[e] A temporary pacemaker may be necessary.

Lyme arthritis is usually treated with month-long courses of oral doxycycline or amoxicillin (8,73). If unsuccessful, penicillin G or ceftriaxone may be administered intravenously in 14- to 21-day courses in the doses described above. Arthroscopic synovectomy may be offered to individuals with persistent synovitis. This has been fairly successful in the small number of cases in which it was tried (73).

Routine prophylactic antibiotic treatment for *Ixodes* tick bites is usually not recommended except for pregnant females, where the threshold for treatment is lower (73).

Conjunctivitis may be treated symptomatically with topical erythromycin or Polytrim. These antibiotics are not effective against Bb, but are protective against any microbial superinfection.

The use of topical corticosteroids in LB is controversial. Topical and periocular steroids have been helpful in treating Lyme keratitis, vitritis, and retinitis (6,38, 40,44). Preferably, topical steroids should be reserved for the immune manifestations of the disease, including symptomatic episcleritis, nummular or interstitial keratitis, vitritis, and retinitis. Peripheral ulcerative keratitis is best treated with oral prednisone 60 mg a day under oral doxycycline or intravenous ceftriaxone cover (42). Topical steroid treatment of peripheral ulcerative disease is inappropriate, since it may potentiate collagenase formation and corneal melting (43). The treatment of facial nerve palsies, beyond intravenous or oral antibiosis for LB, is similar to that for any etiology and includes the careful use of bland ointments to protect the exposed corneal surface from lagophthalmos secondary to facial nerve palsy, or lateral tarsorrhaphy. Optic neuropathy from LB has been treated with oral prednisone and penicillin (50).

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