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prevent a clinical rebound of inflammatory activity.

Congestive cardiac failure is usually controlled by bed rest and steroids. Occasionally diuretic therapy is necessary, and rarely careful digitalization is required.

Treatment of chorea, a self-limited feature, generally requires more than anti-inflammatory therapy. Most patients benefit significantly from quiet, nonstressful surroundings and administration of phenobarbital or diazepam (Valium) or other tranquilizer. The latter medications must be given on a trial-and-error basis, since patients vary considerably in their responsiveness to treatment and a single drug is not beneficial in all cases.

CHRONIC RHEUMATIC DISEASE

Individuals who have had an attack of ARF with or without cardiac disease or who are found to have chronic rheumatic heart disease (RHD) are at risk for recurrent attacks of ARF following streptococcal pharyngitis. Thus, they should receive *continuous* antistreptococcal prophylaxis to prevent recurrences of ARF. Three standard regimens are considered satisfactory for this purpose, in order of preference: (1) monthly intramuscular injection of 1.2 million units of benzathine penicillin (0.6 million units for those less than 60 pounds); (2) 500-mg tablets of sulfadiazine twice daily; and (3) 250 mg tablets of penicillin V twice daily.

The advantage of parenteral penicillin is that one does not depend upon daily patient compliance; however, the injections may be painful. Strict compliance with this regimen has been shown to result in healing of valvular heart disease (as reflected by disappearance of murmurs) in the majority of patients, in addition to prevention of recurrent attacks of ARF. The advantage of sulfadiazine over oral penicillin relates primarily to the induction of penicillin-resistant oral flora by the latter, which theoretically could predispose a patient to an episode of bacterial endocarditis due to a penicillin-resistant organism. Erythromycin has been suggested for the rare patient who is intolerant of both penicillin and sulfadiazine. A subject of considerable controversy is the optimum duration of rheumatic fever prophylaxis. Most investigators, including the American Heart Association, recommend lifelong prophylaxis for patients with RHD because the risk of recurrent ARF persists long beyond childhood, albeit in a diminished way. In patients without residual cardiac involvement, prophylaxis can probably be safely discontinued at age 21 if at least 5 years has elapsed from the last attack of ARF.

In addition to rheumatic fever prophylaxis, patients with RHD require subacute bacterial endocarditis (SBE) prophylaxis on an episodic basis related to dental or surgical procedures, or gastrointestinal or genitourinary tract instrumentation, as recommended by the American Heart Association.

LYME DISEASE

(Lyme Borreliosis)

method of
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Lyme borreliosis is a recently described spirochetal infection caused by *Borrelia burgdorferi*. It is already recognized as the most common tick-borne infection in the United States. It is transmitted primarily by hard-shelled vegetation inhabiting ticks of the *Ixodes ricinus* complex. These include *Ixodes dammini* in northeastern United States, *Ixodes scapularis* in southeastern United States, and *Ixodes pacificus* in far western United States. This disease has been reported from 43 states, most European countries, Russia, China, northern and South Africa, and Australia. The nymphal stage occurs in spring and summer and accounts for most human attacks. The attachment is recognized in only 25 to 30% of patients, most likely because of the vector's tiny size.

CLINICAL DESCRIPTION

Although the infection often presents in a characteristic manner, many atypical presentations have been described in recent years, often leading to diagnostic confusion. It is a multisystem disorder affecting skin, joints, nervous system, and heart most commonly, but involvement of other systems has also been described. The key to diagnosis is the pathognomonic rash, erythema chronicum migrans. Unfortunately, it is often not present. The disease is described in stages, but considerable overlap between stages has been seen. Its pathogenesis appears to be predominantly immunologic.

Stage I: Early Manifestations

A few days to a month following a tick bite, the central erythematous papule becomes macular and expands gradually, at times to greater than 60 cm. Erythema chronicum migrans is typically flat, annular, with diffuse erythema early. Pain and pruritus are variable but usually not prominent. Central cyanosis leading to vesiculation may occur early. Late central clearing is common, leading to a ring pattern. Slow resolution typically occurs, but similar migrating an-

nuli may occur elsewhere. The rash often does not occur and is especially infrequent in children. Constitutional symptoms, including fever, fatigue, malaise, myalgias, arthralgias, transient and migratory synovitis, tendinitis, bursitis, axial stiffness, pharyngitis, headaches, and lymphadenopathy, are common. Nonproductive cough, hepatosplenomegaly, hepatitis, orchitis, periorbital edema, conjunctivitis, iritis, and panophthalmitis are less common. Symptoms often wax and wane within an individual. They may remit within weeks, even without treatment, or persist for extended periods.

Stage II: Cardiac and Early Neurologic Manifestations

Onset is typically weeks to months following infection. This stage often appears prior to resolution of Stage I. Cardiac affliction affects about 10% of untreated subjects and often presents as syncope due to high-grade atrioventricular (AV) conduction disorders. Most commonly first-degree AV block is seen. It often resolves spontaneously or with therapy but may persist. Cardiomegaly, left ventricular dysfunction, pancarditis, and cardiac death have all been reported.

In untreated patients 20% develop neurologic injury. Cranial palsies, especially facial nerve, often symmetrical, are the most common presentations. Cranial nerves II, III, V, VI, VIII, IX, and XII have also been involved. The triad of cranial neuritis, meningitis, and radiculoneuritis (Garin-Bujadoux-Bannwarth syndrome) is commonly seen in Europe. Encephalitis, myelitis, ataxia, chorea, and mononeuritis multiplex may occur.

Borrelia lymphocytoma, a nodular cutaneous lesion often of the ear lobe, is recognized in Europe.

Stage III: Chronic Arthritis and Neurologic Manifestations

Typically, months to years following infection, inflammatory arthritis appears in 60% of untreated patients. It becomes chronic in 10%. The knees are most commonly affected, but any synovial joint may be affected. Symmetrical polyarthritis may be seen. The radiologic and pathologic findings are indistinguishable from rheumatoid arthritis. Panniculitis, myositis, and dermatomyositis have been described. Ulnar fibrous nodules clinically resembling rheumatoid nodules may be seen.

Acrodermatitis chronica atrophicans is often seen in Europe and has been seen in the United States. The inflammatory phase may resemble lymphedema or venous stasis while the atrophic stage can be confused with other cutaneous sclerosing disorders. Peripheral neuropathies with both axonal and myelin sheath injuries are often associated. Multifocal encephalitis, central nervous system (CNS) demyelination leading to multiple sclerosis presentations, psychoses, and dementia have been recognized.

PREGNANCY

Transplacental infection was recognized in 5 of 19 pregnancies reported in one study. Injuries there included fetal wastage, syndactyly, cortical blindness, prematurity, and neonatal rash. The organism has been cultured from fetal organs and from two neonatal deaths, one resulting from aortic thrombosis.

LABORATORY FINDINGS

Serology remains the mainstay of laboratory diagnosis. Unfortunately, the sensitivity of available tests is exceedingly low in early disease and is too often inadequate in late disease. Of the 19 mothers in the above quoted study on transplacental infection, 80% were falsely seronegative. Threshold for serodiagnosis has been set at three standard deviations (S.D.) above the control mean in some laboratories rather than the customary 2 S.D. This was done to reduce cross-reactivity with other spirochetal infections, but unfortunately, cross-reactivities with treponemal and other borrelia infections occur at and above that higher threshold. T cell stimulation studies support the concept of seronegative disease. T cell assays are not available commercially. Intradermal testing of delayed hypersensitivity may follow this in vitro assay. An antibody capture assay reporting only a 7% false negativity in late disease has recently been described. A urine antigen capture assay is under study. Direct culture of the organism is too often unsuccessful to be useful as a clinical assay. Elevation of serum IgM and transaminases as well as microhematuria is seen at times, especially in early disease. CSF assays often reveal only a mild pleocytosis and elevation of total protein. Lack of evidence for CNS in situ formation of borrelia antibodies should not exclude the diagnosis of neuroborreliosis. Conversely, malignant-appearing cells may be seen in the CSF leading to a misdiagnosis of CNS lymphoma. It is generally agreed that the diagnosis of Lyme borreliosis should be based on clinical factors and not excluded because of negative serology.

TREATMENT

General Considerations

Prevention remains the most important approach. Thorough covering by light-colored clothing whose openings are tightly closed offers the first line of defense. Careful tick checks should be done at the end of an outdoor day and more often if possible. Hairy and crural regions are special targets of the ticks. Gentle traction on the tick near its attachment is the best removal method.

Standard treatment for early disease (Stage I) has typically consisted of common oral antibiotics administered over a 2-week period. Penicillin V 500 mg, tetracycline 250 to 500 mg, or erythromycin 250 mg, all given four times a day, has been the usually recommended regimen. Recently, the adequacy of these as well as standard regimens for later stages has been questioned. This has been stimulated by numerous reports of

treatment failure or late relapses following all available forms of oral and parenteral treatment. According to a sizable European dermatologic study, 27% of early and 47% of late disease patients later developed extracutaneous signs and symptoms following standard treatment. The causes of these difficulties are likely manifold. Surely the very slow reproduction rate of this microbe in vitro (12 to 20 hours) and its suspected much slower reproduction rate when the microbe has become established in host parenchyma are probable contributors. Evidence for long asymptomatic intervals of many years is accumulating. This latency is reminiscent of lues.

B. burgdorferi is sensitive to common spirochetal antibiotics including the penicillins, tetracyclines, some cephalosporins, erythromycin, and chloramphenicol (Chloromycetin). Erythromycin's benefit in vivo is far less than its in vitro sensitivity would indicate. Rifampicin, sulfonamides, aminoglycosides, and quinolones appear to have no role in this infection.

Stage IA: Hematogenous

This is the earliest and usually asymptomatic stage when parenchymal infection has not yet occurred. It accompanies the tick bite and likely lasts for only a few days during which a low-grade spirochetemia exists. Treatment with the above noted standard oral agents may be adequate. The use of doxycycline at 2.5 to 3 mg per kg per day or amoxicillin at 25 to 30 mg per kg per day in divided doses for 2 weeks is preferred. Tetracycline should not be used in children under age 8 years. Erythromycin at 30 mg per kg per day in divided doses for 20 days may be used in penicillin-allergic children, although its efficacy is likely less than the agents it replaces.

Stage IB: Parenchymous

Experience with hamsters indicates that parenchyma is invaded within 7 days of experimental infection. Too often patients are seen initially weeks following spirochetal inoculation; therefore, the likelihood of parenchymous infection becomes high. Once systemic symptoms and signs are present, parenchymous infection likely exists. Antibiotics that cross the blood-brain barrier are then required. Doxycycline (Vibramycin) at 2.5 to 3 mg per kg per day or minocycline (Minocin) at 2 to 2.5 mg per kg per day or amoxicillin (Amoxil, Polymox) 1500 mg with probenecid (Benemid) 500 mg (in adults) three times a day appears to adequately penetrate CNS tissues and offer acceptable antibiotic effect. Children under age 8 should receive amoxicillin 60 mg per kg per day in divided doses. Those who are penicillin allergic may receive erythromycin at 30 mg per kg per day in divided doses, but its weaker effectiveness should be kept in mind. Studies of various oral third-generation cephalosporins and a new erythromycin class drug are in progress. These should be considered in this penicillin-allergic age group when they become available.

Persistent symptoms including fatigue, headaches, myalgias, and arthralgias have been noted in about half of all patients with this disease. These symptoms have been considered immunologically based by many. Molecular mimicry, where natural host proteins mimic spirochetal antigens, has been offered as one such mechanism promoting ongoing immune response. Longer antibiotic therapy has been beneficial to a number of these patients in uncontrolled observations suggesting that persistence of the infection in parenchymous sites may be the cause of these ongoing symptoms. Borreliae have been shown in deep tissues following 2 months of accepted oral antibiotic treatment. Such findings strongly support suspicion that parenchymal infection is probably not eradicable with short-term treatment. Treatment well beyond clearance of the last symptoms seems appropriate until controlled studies define optimal type and duration of therapy to achieve bacteriologic cure. To date there is no evidence of the spirochete's developing resistance to established antibiotics.

Stage II: Cardiac and Neurologic Treatment

This stage clearly implies parenchymous infection. It is also the stage of potentially dramatic and organ-threatening presentations. When cardiac signs are limited to mild PR interval prolongation, then the oral antibiotics and dosing mentioned for Stage IB parenchymous disease above should be applied. Duration of treatment should be at least 4 months, pending results of controlled studies. Nonsteroidal anti-inflammatory drugs (NSAID) such as high-dose aspirin (3 to 4 grams daily in adults) or equivalent should also be applied in the early weeks. Temporary restriction of physical activity may be appropriate.

In addition to minor conduction defects, this infection is known to cause major conduction defects (PR interval $\geq$ 0.3 seconds), which often present as syncope or as inflammation of any or all three layers of the heart (endocardium, myocardium, pericardium). Death may ensue. Hospitalization is often indicated, and temporary pacemaker placement may be required. In this setting of acute threat to vital organs, intravenous antibiotics appear to have their greatest applicability. High-dose penicillin, 20 million

units per day in divided doses, has been favored until recently. Ceftriaxone (Rocephin) 2 grams intravenously per day for 14 days now seems more appropriate based upon its superior tissue penetration and spirochetal sensitivity. It is also more easily administered in the home setting, allowing shorter hospital stays. Continued oral antibiotic treatment as previously described for Stage IB parenchymal infection should follow for at least 4 months or until resolution of symptoms, whichever is longer. NSAID treatment may be beneficial, but a rapidly tapering course of corticosteroids over 1 week is preferred for these life-threatening presentations. Prednisone starting at 1 mg per kg the first day is suggested.

Acute CNS presentations (meningitis, encephalitis, myelitis) typically require hospitalization. Intravenous ceftriaxone at 2 grams daily for 14 days has become favored for reasons mentioned above. In addition, its penetration of the blood-brain barrier is far superior to that of penicillin. Treatment with oral antibiotics as described for Stage IB parenchymal infection should follow for at least 4 months or until resolution of symptoms, whichever is longer. Less dramatic CNS presentations, e.g., headaches and memory difficulties, also are usually adequately treated by this oral regimen.

Peripheral nervous system afflictions should be treated according to the method suggested for Stage IB parenchymal infection. Duration should also be at least 4 months or until resolution of symptoms, whichever is longer. A rapidly tapering course of corticosteroids over 1 week, e.g., prednisone starting at 1 mg per kg the first day, may be additionally beneficial to patients presenting with recent onset (less than 2 weeks) cranial neuropathy, e.g., facial palsy or sudden deafness.

Stage III: Chronic Arthritis and Neurologic Disorders

A general consensus is arising among clinicians most familiar with this disorder that late disease is the most difficult to treat and refractoriness to various treatment modalities is often seen. Intravenous ceftriaxone 2 grams per day for 14 days has recently been favored in publications for this stage. Unfortunately, its long-term efficacy in practice falls below what has been published. It is conceivable that late disease represents the greatest adaptation of the microbe to its host environment. In turn, its reproduction rate may be far slower than its in vitro rate, leading to greater need for prolonged therapy as well as optimal antibiotic tissue penetration. Treatment of the kind outlined in Stage IB parenchymal disease is at times more efficacious than a short course of intravenous ceftriaxone. Unfortunately, symptomatic flares as a result of treatment are often seen. This likely represents tissue deposition of immune complexes formed as a result of antibiotic-induced release of antigen from its parenchymous sites. Interruption of treatment typically aborts the flares. A treatment approach that allows for ongoing clearance of immune complexes via scheduled interruption of treatment seems to be most efficacious when flares recur as a function of prolonged oral therapy. Using amoxicillin 1500 mg and probenecid 500 mg twice a day or even daily seems to offer the greatest comfort, especially in the case of chronic arthritis. Doxycycline or minocycline can similarly be interrupted by giving doses as described in Stage IB parenchymal disease on an every-other-day schedule. Treatment should be continued beyond clearance of symptoms or at least 4 months, whichever is longer.

In a 1981 report, hydroxychloroquine (Plaquenil) was shown be beneficial for chronic Lyme arthritis. It appears to improve the efficacy of prolonged oral antibiotic treatment in cases where antibiotics alone are insufficient. Standard dosing at 6 mg per kg per day is recommended along with the usual ophthalmologic precautions.

Pregnancy

Maternal treatment to prevent transplacental infection is not established. A standard, short course of oral penicillin given to the mother soon after appearance of erythema migrans did not prevent fetal infection and neonatal death in the only reported case of this circumstance. Two weeks of ceftriaxone 2 grams intravenously per day in early pregnancy and amoxicillin 1 gram three times a day for 6 weeks in late pregnancy have been protective to offspring in recent uncontrolled observations on eastern Long Island, N.Y. Six weeks of amoxicillin 500 mg four times a day given at various gestational times has resulted in no apparent fetal injuries in 12 pregnancies in Wisconsin.

The likelihood of placental infection is highest early in the disease when hematogenous spread is active. Very low-grade spirochetemia likely occurs in later stages and may continue for indefinite periods. Protection against this phenomenon should require lower serum antibiotic levels than those required for CNS penetration. Amoxicillin 500 mg orally four times a day should be adequate. Continuation throughout gestation would seem to offer the greatest protection, pending results of studies defining optimum treatment.

Maternal immunologic reaction to treatment of

the Jarisch-Herxheimer type could be acutely injurious to the fetus and could lead to fetal wastage, but this has not been reported.

ASYMPTOMATIC TICK BITE

As we learn more about the potential severity of late disease and the difficulties with effecting adequate treatment, consideration for treatment at the earliest time becomes rational. In the first days following a bite by an infected tick, potential for eradicating the infection is highest because the infection is presumed to be only hematogenous. In regions of high endemic tick infection, early treatment of asymptomatic tick bites by the method previously described for Stage IA hematogenous seems prudent. Serologic reactivity will likely not occur, but late disease should be prevented. In regions of low endemic infection, such prophylactic treatment offers no benefit statistically.

ROCKY MOUNTAIN SPOTTED FEVER

method of
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Rocky Mountain spotted fever (RMSF), an acute infectious disease, is the most prevalent and severe of the rickettsioses. The etiologic agent is *Rickettsia rickettsii*, an obligate intracellular parasite of several species of ticks and rodents and possibly of mammals. It is transmitted to man by the bite of the adult tick. A variety of ixodid (hard-shelled) ticks serve as both reservoir and vector for the disease. The western wood tick, *Dermacentor andersoni*, and the eastern dog tick, *D. variabilis*, are the principal vectors. RMSF of the United States is identical to Sao Paulo fever, Colombian spotted fever, fiebre maculosa, fiebre petequial, and the fiebre manchada of Mexico.

Despite its name, the disease is more common in the southern, southwestern, and eastern United States. Since 1960 the number of reported cases in the United States has increased steadily, and the increase has been particularly striking since 1970. The true incidence is likely higher than the reported incidence. Persons of all ages are susceptible to the disease, but most of the cases occur in children. There is a striking seasonal distribution, with most cases occurring during the spring and summer. This parallels both the activity of ticks and the behavior of individuals that brings them in contact with the ticks.

The incubation period in man is 2 to 12 days, with a mean of 7 days. Since about one-fourth of patients have no history of a tick bite or of the presence of ticks on the body, the absence of such a history should not prevent the physician from suspecting the disease.

The severity of the disease ranges from cases that are clinically quite mild to fulminant forms. In untreated patients the mortality rate ranges from 10 to 40%. Appropriate treatment has reduced this to between 5 and 10%. Prognosis is influenced by age and other factors, but the most important influence in successful treatment of the infection is early diagnosis and institution of therapy.

CLINICAL ASPECTS

The most prominent clinical features of RMSF are headache, fever, rash, and edema. However, many patients have nonspecific features such as nausea, vomiting, abdominal pain, diarrhea, arthralgia, myalgia, and neurologic manifestations. The onset of symptoms may be either abrupt or gradual. The neurologic manifestations, particularly when alterations in mental status and vomiting are present, may suggest a diagnosis of meningoencephalitis.

The rash of RMSF is the earliest dependable and most important diagnostic sign. It typically begins on the ankles and wrists and spreads centrally. In the early stages it is maculopapular but in many cases (more than half) assumes a petechial character. Some patients do not have a typical rash, and in others, the rash may not appear until later in the disease. Variability in the nature of the rash is common, and failure to recognize this may result in a delay in diagnosis, which can be catastrophic. When looked for, many patients show generalized nonpitting edema. Conjunctivitis, splenomegaly, and a variety of neurologic manifestations may occur.

RMSF may be confused clinically with other infectious diseases, including meningococcal infections, enteroviral infections, atypical measles, infectious mononucleosis, and others. The rash of drug eruptions may be confusing. A newly recognized rickettsial disease, ehrlichiosis, may clinically resemble RMSF. It is caused by *Ehrlichia canis*, an intraleukocytic parasite that infects a variety of wild and domestic animals, including dogs. The clinical findings are similar to those of RMSF, except that rash is usually absent.

RMSF cannot be clearly identified in the early stages on the basis of routine laboratory procedures. Urinalysis is usually normal, but specimens may contain traces of albumin and, sometimes, casts. Leukopenia, present in the first week, evolves into moderate leukocytosis in the second. There may be mild to moderate normochromic normocytic anemia, thrombocytopenia, and multiple coagulation disturbances, including hypofibrinogenemia and evidence of disseminated intravascular coagulation.

Serial determinations of serum proteins usually show a progressive decrease, particularly of the albumin fraction. Serum electrolyte measurements frequently demonstrate hyponatremia and hypochloremia. These abnormalities may be associated with increased aldosterone excretion.

Mild CSF mononuclear pleocytosis with slight elevation of the protein content is common. The leukocyte count almost never exceeds 300 per mm^3. The glucose concentration is normal.

Liver function abnormalities include decreased