Antimicrobial agents in Lyme disease

The later complications of Lyme disease have been increasingly recognized, and can be divided into those that occur shortly after the diagnostic skin rash, erythema migrans, and those that may develop a decade after the initial infection, such as acrodermatitis chronic atrophicans. A parallel has been drawn between erythema migrans and primary syphilis and between the organ involvement of Lyme disease (as of nervous system, joint and periarticular tissue, heart and liver) and secondary syphilis. Lyme disease differs from syphilis in that there may be a considerable temporal overlap between skin and organ involvement in any particular patient, person to person transmission has not been reported in early Lyme disease, and spirochaetes may be readily isolated in the late stages of the illness.

A particular problem of Lyme disease is that the clinical outcome cannot always be predicted from the sensitivity of the causative bacterium to antimicrobial agents in vitro. *B. burgdorferi* is sensitive to a variety of common antibiotics; characteristic MICs (and MBCs, where available) in mg/l are: benzylpenicillin 4-0 (80), erythromycin 0.06 (2-17), tetracycline 0.36 (4-1), amoxycillin 0.5, ceftriaxone 0.06 (3-8) and cefotaxime 0.12 (Johnson, Kodner & Russell, 1987; Mursic et al., 1987). MICs comparable with those obtained with erythromycin have been reported with the macrolides, azithromycin, clarithromycin and roxithromycin, for ten strains of European borreliae (Preac-Mursic et al., 1989).

In borrelia-infected gerbils, erythromycin, despite its very low MIC, was found to be inferior to penicillin and tetracycline. A criticism of this model is that the borreliae are allowed to multiply and produce a seemingly continuous bacteraemia, without reproducing the histopathological features of Lyme disease. The disappointing results with erythromycin may be due in part to the development of resistance. In experimental *B. duttoni* infections in mice, resistance had developed in 7.5% (3/40) and 5.2% (2/38) of reisolated strains after relapse of infection following treatment with erythromycin and clindamycin, respect-
severity of the illness: ten days therapy is thought to be adequate in mild cases with skin manifestations but twenty days may be more appropriate in cases with underlying organ involvement (Berger, 1988). The earlier the disease is treated the more rapidly it resolves and the less likely is the occurrence of late sequelae.

The isolation of *B. burgdorferi* from the blood has raised the possibility of transplacental transfer of the organism. To date, borreliae have been isolated from one stillbirth and one newborn infant, but congenital abnormalities resulting from Lyme disease during pregnancy have not been unequivocally demonstrated (Schlesinger et al., 1985). The abnormalities that have been recorded were associated with serological evidence of infection in retrospective studies (Nadal et al., 1989). Antibiotic therapy is therefore indicated for the pregnant patient with antibodies to borreliae, combined with comprehensive developmental surveillance of the baby, once born.

In pregnant and lactating patients penicillin therapy is the most appropriate regimen. If patients are penicillin hypersensitive, erythromycin is a possible alternative, but if erythromycin is used, the newborn should be fully treated with penicillin because of the unpredictability of placental transfer of erythromycin (Phillipson, Sabath & Charles, 1973; Fenton & Light, 1976). For this reason, hospital admission and monitoring of erythromycin concentrations have been recommended. An attractive alternative treatment in pregnancy, imipenem, must await clarification of animal studies of imipenem's possible fetotoxicity, in which newborn rats were of lower birth weight than controls and testicular descent was also delayed (Clarke et al., 1989).

It is probably best to avoid prophylactic antibiotics for people who have been bitten by ticks, as the likelihood of individuals' developing Lyme disease is small and there is always a risk of unexpected allergic reactions to antibiotics. Insect repellents to discourage the attachment of the tick would be more practical. Nursing and medical staff attending patients with Lyme disease do not require prophylaxis as person to person transmission is unknown.

Weeks to months after the initial infection, specific skin rashes, such as lymphadenosis benigna cutis, or neurological, cardiac or joint disease predominate (Asbrink & Hovmark, 1988). The neurological signs respond to high dose parenteral penicillin (Baumhackl et al., 1987). The use of tetracyclines in such patients has been very limited. In a Swedish study doxycycline was used to treat nine patients with neurological Lyme disease. Doxycycline concentrations of 0.2–1 mg/l were obtained in the CSF during a regimen of 100 mg twice daily. All patients had a favourable outcome (Dotevall et al., 1988). On a treatment schedule of 200 mg twice daily CSF concentrations of 0.6–1.9 mg/l were achieved. The MIC for *B. burgdorferi* was exceeded in the CSF after the first day of this dosage, but three to five days' therapy was needed to achieve comparable concentrations on the lower dosage regimen (Dotevall & Hagberg, 1989). In future ceftriaxone, cefotaxime and imipenem may have a useful role in these patients. The low MIC values obtained with these antibiotics in laboratory, and the results of animal studies, are encouraging but will have to be confirmed in therapeutic trials (Mursic et al., 1987).

Patients who are inadequately treated in the early stages may develop acrodermatitis chronica atrophicans or eosinophilic fasciitis, stigmata of 'tertiary' Lyme disease. As many as 30% of patients do not demonstrate erythema migrans or other signs of early disease before presenting with late complications (Steere et al., 1983). Parenteral penicillin in doses of 12 g (20 mega units) daily for ten days have been used as standard therapy for neuroborreliosis and arthritis. Results have been disappointing, with failure rates as high as 50% reported in patients with arthritis (Steere et al., 1985). The isolation of *B. burgdorferi* from the cerebrospinal fluid of a patient who was being treated with penicillin underlines the inability of penicillin to kill spirochaetes when they survive under suboptimal conditions (Baranton et al., 1989). In syphilis, the persistence of treponemes despite adequate penicillin therapy has been well documented, both in man and in the laboratory (Dunlop, 1985). Borreliae are known to remain dormant in the central nervous system of experimental animals for considerable periods of time and it is possible that under poor nutritive conditions a 'vegetative' non-dividing persistor may remain unaffected by penicillin.

In a search for alternative agents, ceftriaxone was used to treat seven patients with central nervous system Lyme disease who had failed to respond to penicillin (Dattwyler et al., 1987a). Most patients had both neural and joint disease and all improved rapidly. Ceftriaxone has a half-life of 8.5 h (Wise, 1987). In the absence of meningitis it crosses the blood-CSF barrier to give CSF concentrations 1-5% of those in serum. Two to four
hours after an intravenous infusion of 2 g ceftriaxone, CSF concentrations three to four times the MIC for B. burgdorferi may be obtained (Chandrasekar et al., 1984). These findings were reinforced by results of a randomized comparative trial of penicillin 24 mega units daily, and ceftriaxone 4 g daily. Twenty-three patients were studied. Treatment failures in the penicillin treated group were more common, 5 of 10, in comparison with 1 of 13 in the ceftriaxone treated group (Dattwyler et al., 1988), a statistically significant difference (chi: P < 0.02). This investigation was extended, with treatment of a further 31 patients with either 4 g or 2 g ceftriaxone daily, and symptomatic and objective responses were excellent and equal in both groups. Patients did significantly worse on glucocorticoids, implying that the pathogenesis is not related to the inflammatory response. Patients with extensive joint damage were less likely to respond favourably. An association has been demonstrated between the use of ceftriaxone and the development of biliary concretions (Schaad, Wedgewood-Krucko & Tschaep-pler, 1988), and this antibiotic is as yet unlicensed in the United Kingdom. As an alternative cefotaxime was used with good effect to treat a case of borrelial encephalitis (Preac-Mursic et al., 1987). Meptazinol may be useful to treat a case of borrelial encephalitis (Berger, 1988). Treatment of early Lyme disease. They occur within 2-4 h of starting therapy and are more common in 14% of patients treated for Lyme disease involving vital organs. Pregnant patients should receive penicillin. In the late stages, ceftriaxone is more effective than penicillin. The role of other third generation cephalosporins has yet to be assessed.

References


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