Failure of short antimicrobial treatments for human brucellosis.

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Failure of Short Antimicrobial Treatments for Human Brucellosis

We read with interest the recent article by Solera et al., in which the safety and efficacy of two treatment protocols for patients with brucellosis, mostly adults, were compared (5). The results of the study showed that the relapse rate of patients receiving a 30-day treatment with oral doxycycline, combined with a single daily dose of intramuscular gentamicin, was as high as 22.9%.

Because of the inconveniences of prolonged antimicrobial therapy, the potential toxicity of prolonged tetracycline exposure, and the need for parenteral administration of aminoglycosides, shorter antimicrobial treatments for pediatric brucellosis are required. In 1989, Lubani et al. reported that no relapses among 71 children receiving gentamicin twice daily for 5 days combined with either doxycycline, oxytetracycline, rifampin or co-trimoxazole for 3 weeks were observed, suggesting that short antimicrobial regimens can also be efficacious (2).

We have recently evaluated the efficacy of treating children with brucellosis with 5 mg of gentamicin per kg of body weight per day (maximum 300 mg) given intramuscularly as a single daily dose for 5 days, combined with (i) 3-week therapy of doxycycline (5 mg/kg/day in two divided doses, maximum 200 mg) in children older than 8 years of age or (ii) co-trimoxazole (10 and 50 mg/kg/day in two divided doses) in children younger than 8 years. Diagnostic criteria included a positive blood culture with the BACTEC 9240 Peds Plus medium (Becton & Dickinson Diagnostic Instrument Systems, Towson, Md.) and/or the Isolator 1.5 Microbial Tube (Wampole Laboratories, Cranbury, N.J.) or clinical signs (at least two of the following: fever, arthralgia and/or arthritis, organomegaly, leukopenia, and thrombocytopenia) together with serological evidence of brucellosis (antibruccella titers by the standard tube agglutination test of ≥1/160 or a fourfold rise in titers by day 21).

Surveillance protocols included clinical assessment, performance of cultures of blood and other normally sterile body fluids when indicated, and serological tests on days 1, 5, 21, 60, 120, and 180. Therapeutic failure was defined as persistence of clinical signs or a positive sterile body fluid culture after completion of antimicrobial therapy. Relapse was defined as recurrence of clinical signs, a fourfold increase in serological titer or seroconversion, and/or positive blood and/or other normally sterile body fluid culture after completion of therapy. Compliance was assessed by nurse’s records, peak and trough gentamicin levels, and bottle reclamation after oral therapy.

Fifteen children aged 2 to 16 years (median, 10.5 years) were diagnosed with brucellosis during the study period. According to age, 10 patients received gentamicin and doxycycline and 5 patients were treated with gentamicin and co-trimoxazole. All patients responded to treatment with defervescence within 3 to 5 days. One of the five children who received the combination of gentamicin and co-trimoxazole failed to eradicate the organism from the blood in the course of treatment, and two other patients showed relapse of bacteremia despite a clinical cure and declining serologic titers. In the gentamicin-doxycline treatment group, 2 of 10 children showed a bacteriologic relapse; only 1 of these 2 children was symptomatic. The failure rate of both regimens combined was then 33.3% (95% confidence interval [CI] 9.5 to 57.2%).

The failure rate found in our study is higher than that found by Solera et al. after 30 days of doxycycline and is substantially different from the experience reported by Lubani et al. (2). It should be pointed out that the use of sensitive blood culture methods resulted in the detection of relapse in three of our patients and treatment failure in another that would have gone unnoticed by clinical or serologic surveillance. It is then possible that a fraction of patients considered to be treatment successes in other studies in which less sensitive bacteriological methods were used in fact failed to eradicate the organism (3, 4).

Nowadays, treatment strategies based on short antibiotic courses are being developed for infectious diseases to reduce costs and inconveniences of prolonged hospitalizations (1). The ultimate goal, however, is to achieve cure rates comparable to those observed with traditional therapeutic modalities (1). The preliminary results of our study, as well as those of Solera et al., preclude the recommendation of gentamicin as a single daily dose combined with short courses of either doxycycline or co-trimoxazole for adult and pediatric patients with brucellosis. Furthermore, when treatment protocols for brucellosis are evaluated, sensitive blood culture methods should be used, since persistent bacteremia can occur in asymptomatic individuals.

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Authors’ Reply

We thank Abramson et al. for their comments. We believe that there are too few data to “preclude the recommendation of gentamicin as a single daily dose combined with short courses of...doxycycline...for patients with brucellosis.” As we indicate in our study, determination of the most convenient duration of doxycycline in the doxycycline-gentamicin regimen requires prospective randomized trials.

We disagree that the failure rate found in their study was
higher than that found in our study. Abramson et al. observed two relapses in 10 children aged 8 to 16 (20%; 95% CI, 2.52 to 55.6%) treated for 3 weeks with doxycycline and 5 days with gentamicin. We observed a 22.9% relapse rate (95% CI, 10.4 to 40.1%) in 35 patients who were treated with doxycycline for 30 days and gentamicin for 7 days, a rate similar to theirs.

Our study did not include children under 8 years who were treated with co-trimoxazole for 3 weeks and gentamicin for 5 days. We therefore cannot determine the efficacy of this therapy regimen. Previous studies with co-trimoxazole used as monotherapy resulted in a high rate of relapse (6). For instance, in a controlled study (3) that tested the efficacy of co-trimoxazole for 6 weeks versus that of tetracycline for 3 weeks and streptomycin for 2 weeks, 13 of the 28 patients (46.4%) treated with co-trimoxazole relapsed versus 4 of 27 patients (14.8%) treated with the classic tetracycline-streptomycin combination. However, other studies which have administered co-trimoxazole for 6 months have shown better results (7).

Antibiotic therapy of human brucellosis continues to be controversial. The intracellular parasitism of Brucella species predisposes patients to relapse and may complicate therapy (9). Prolonged therapy is required after apparent successful treatment of infection to avoid relapse. Nonetheless, the prolonged antimicrobial therapy necessary to prevent relapse increases the potential of toxicity, and at the present time, the optimal duration of therapy is unknown (9). The tetracyclines are at present the antibiotics of choice for brucellosis (9). Brucellae continue to be exquisitely susceptible to tetracyclines (MICs are generally <1 mg/liter), and numerous studies have demonstrated the clinical efficacy of tetracyclines in treating most Brucella species infections (6). However, relapse after short courses of therapy remains a significant problem (5). Prolonged treatment for 6 weeks reduces the rate of relapse (7). On the other hand, the addition of intramuscular streptomycin to tetracycline decreases the incidence of relapse compared with monotherapy with tetracycline for the same duration (5, 7). This regimen has been used widely and successfully since the 1950s, with a relapse rate ranging between 0 and 8% when tetracycline was given for 30 days or more and streptomycin was given for 14 days or more (1, 4, 6, 7, 10).

Treatment of children with brucellosis poses a problem since tetracyclines are generally contraindicated for children aged <8 years (9). The preferred regimen is rifampin for 45 days combined with co-trimoxazole 45 days, gentamicin for 7 days, or netilmicin for 7 days (9). Some authors stress the importance of treatment lasting more than 45 days (2).

We agree that when treatment protocols for brucellosis are evaluated, sensitive blood culture methods should be used, since persistent bacteremia can occur in asymptomatic individuals. The occurrence of patients with positive blood cultures despite an absence of clinical signs or symptoms during follow-up is a phenomenon that has already been described (7, 8, 9) and underlines the need for routine checks of this kind in the follow-up of patients with brucellosis.

REFERENCES


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