do not occur with the cell-surface antigens of rough *Brucella* strains such as *B. canis* or *B. ovis*; serologic tests for these nomen species must employ an antigen prepared from either one. The live *B. abortus* vaccine strain RB51 does not elicit antibody responses in serologic tests that use smooth antigens, and this fact must be taken into account if serologic tests are employed in attempts to identify or follow the course of infections in persons accidentally exposed to the vaccine.

TREATMENT BRUCELLOSIS

The broad aims of antimicrobial therapy are to treat and relieve the symptoms of current infection and to prevent relapse. Focal disease presentations may require specific intervention in addition to more prolonged and tailored antibiotic therapy. In addition, tuberculosis must always be excluded, or—to prevent the emergence of resistance—therapy must be tailored to specifically exclude drugs active against tuberculosis (e.g., rifampin used alone) or to include a full antituberculous regimen.

Early experience with streptomycin monotherapy showed that relapse was common; thus dual therapy with tetracyclines became the norm. This is still the most effective combination, but alternatives may be used, with the options depending on local or national policy about the use of rifampin for the treatment of nonmycobacterial infection. For the several antimicrobial agents that are active in vivo, efficacy can usually be predicted by in vitro testing. However, numerous *Brucella* strains show in vitro sensitivity to a whole range of antimicrobials that are therapeutically ineffective, including assorted β-lactams. Moreover, the use of fluoroquinolones remains controversial despite the good in vitro activity and white-cell penetration of most agents of this class. Low intravacuolar pH is probably a factor in the poor performance of these drugs.

For adults with acute nonfocal brucellosis (duration, <1 month), a 6-week course of therapy incorporating at least two antimicrobial agents is required. Complex or focal disease necessitates ≥3 months of therapy. Adherence to the therapeutic regimen is very important, and poor adherence underlies almost all cases of apparent treatment failure; such failure is rarely due to the emergence of drug resistance, although increasing resistance to trimethoprim-sulfamethoxazole (TMP-SMX) has been reported at one center. There is good retrospective evidence that a 3-week course of two agents is as effective as a 6-week course for treatment and prevention of relapse in children, but this point has not yet been proven in prospective studies.

The gold standard for the treatment of brucellosis in adults is IM streptomycin (0.75–1 g daily for 14–21 days) together with doxycycline (100 mg twice daily for 6 weeks). In both clinical trials and observational studies, relapse follows such treatment in 5–10% of cases. The usual alternative regimen (and the current World Health Organization recommendation) is rifampin (600–900 mg/d) plus doxycycline (100 mg twice daily) for 6 weeks. The relapse/failure rate is ~10% in trial conditions but rises to >20% in many non-trial situations, possibly because doxycycline levels are reduced and clearance rates increased by concomitant rifampin administration. Patients who cannot tolerate or receive tetracyclines (children, pregnant women) can be given high-dose TMP-SMX instead (two or three standard-strength tablets twice daily for adults, depending on weight).

Increasing evidence supports the use of an aminoglycoside such as gentamicin (5–6 mg/kg per day for at least 2 weeks) instead of streptomycin, although this regimen is not approved by the U.S. Food and Drug Administration. Shorter courses have been associated with high failure rates in adults. A 5- to 7-day course of therapy with gentamicin and a 3-week course of TMP-SMX may be adequate for children with uncomplicated disease, but prospective trials are still needed to support this recommendation. Early experience with fluoroquinolone monotherapy was disappointing, although it was suggested that ofloxacin or ciprofloxacin, given together with rifampin for 6 weeks, might be an acceptable alternative to the other 6-week regimens for adults. A substantial meta-analysis did not support the use of fluoroquinolones in first-line treatment regimens, and these drugs are not recommended by an expert consensus group (Ioannina) except in the context of well-designed clinical trials. However, a more recent meta-analysis is more supportive of the efficacy of these drugs, and an adequately powered prospective study will be needed to resolve their role in standard combination therapy. A triple-drug regimen—doxycycline and rifampin combined with an initial course of an aminoglycoside—was superior to double-drug regimens in a meta-analysis. The triple-drug regimen should be considered for all patients with complicated disease and for those for whom treatment adherence is likely to be a problem.

Significant neurologic disease due to *Brucella* species requires prolonged treatment (i.e., for 3–6 months), usually with ceftriaxone supplementation of a standard regimen. *Brucella* endocarditis is treated with at least three drugs (an aminoglycoside, a tetracycline, and rifampin), and many experts add ceftriaxone and/or a fluoroquinolone to reduce the need for valve replacement. Treatment is usually given for at least 6 months, and clinical endpoints for its discontinuation are often difficult to define. Surgery is still required for the majority of cases of infection of prosthetic heart valves and prosthetic joints.

There is no evidence base to guide prophylaxis after exposure to *Brucella* organisms (e.g., in the laboratory), inadvertent immunization with live vaccine intended for use in animals, or exposure to deliberately released brucellae. Most authorities have recommended the administration of rifampin plus doxycycline for 3 weeks after a low-risk exposure (e.g., an unspecified laboratory accident) and for 6 weeks after a major exposure to aerosol or injected material. However, such regimens are poorly tolerated, and doxycycline monotherapy of the same duration may be substituted. (Monotherapy is now the standard recommendation in the United Kingdom but not in the United States.) Rifampin should be omitted after exposure to vaccine strain RB51, which is resistant to rifampin but sensitive to doxycycline. After significant brucellosis exposure, expert consultation is advised for women who are (or may be) pregnant.

PROGNOSIS AND FOLLOW-UP

Relapse occurs in up to 30% of poorly compliant patients. Thus patients should ideally be followed clinically for up to 2 years to detect relapse, which responds to a prolonged course of the same therapy used originally. The general well-being and the body weight of the patient are more useful guides than serology to lack of relapse. IgG antibody levels detected by the standard agglutination test and its variants can remain in the diagnostic range for >2 years after successful treatment. Complement fixation titers usually fall to normal within 1 year of cure. Immunity is not solid; patients can be reinfected after repeated exposures. Fewer than 1% of patients die of brucellosis. When the outcome is fatal, death is usually a consequence of cardiac involvement; more rarely, it results from severe neurologic disease. Despite the low mortality rate, recovery from brucellosis is slow, and the illness can cause prolonged inactivity, with domestic and economic consequences.

The existence of a prolonged chronic brucellosis state after successful treatment remains controversial. Evaluation of patients in whom this state is considered (often those with work-related exposure to brucellae) includes careful exclusion of malingering, nonspecific chronic fatigue syndromes, and other causes of excessive sweating, such as alcohol abuse and obesity. In the future, the availability of more sensitive assays to detect *Brucella* antigen or DNA may help to identify patients with ongoing infection.

PREVENTION

Vaccines based on live attenuated *Brucella* strains, such as *B. abortus* strain 19BA or 104M, have been used in some countries to protect high-risk populations but have displayed only short-term efficacy and