Update on brucellosis: therapeutic challenges

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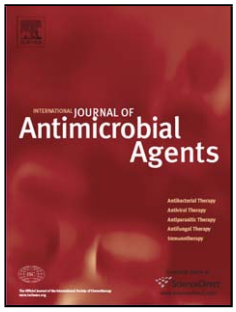

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Update on brucellosis: therapeutic challenges

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Abstract

Brucellosis is an extremely important disease around the world, especially in developing countries. Its clinical manifestations and severity vary with the patient population studied and the species of *Brucella* involved. The choice of regimen and duration of antimicrobial therapy should be based on whether focal disease is present or there are underlying conditions that contraindicate certain antibiotics (e.g. pregnant patients or children under 8 years old). Most individuals with acute brucellosis respond well to a combination of doxycycline plus aminoglycosides or rifampicin for 6 weeks. Monotherapy with doxycycline or minocycline, or a combination of doxycycline plus trimethoprim–sulfamethoxazole, or a quinolone plus rifampicin may be an alternative. Patients with focal disease, such as spondylitis or endocarditis, may require longer courses of antibiotics, depending on clinical evolution. Tetracycline monotherapy, especially with doxycycline, is a good option for patients with brucellosis with no focal lesions and a low risk of relapse. In this clinical situation, practitioners should avoid the use of high-cost or more toxic schedules.

Keywords:

Brucellosis

Doxycycline

Rifampicin

Aminoglycoside

Zoonosis

Emerging infectious disease

1. Introduction

Human brucellosis is a zoonosis caused by facultative intracellular Gram-negative bacteria of the genus *Brucella*. Six classical species exist, of which four cause disease in humans: *B. abortus, B. melitensis, B. suis* and *B. canis*, with the animal reservoirs being cattle, sheep and goats, pigs, and dogs, respectively. More recently, marine mammals have been recognized as additional animal reservoirs for *Brucella* species with zoonotic potential. *B. ceti* and *B. pinnipedialis* are the newly proposed species names. *B. melitensis* is the most virulent *Brucella* sp. for humans, with a few organisms (10–100) being sufficient to cause a chronic infection.

Brucellosis in animals is a chronic infection resulting in abortion and sterility. A large bacterial load is present in milk, urine and the products of pregnancy. In humans it is usually contracted either by the ingestion of unpasteurized dairy products or from direct contact with the secretions or blood of diseased animals. Brucellosis is an extremely important disease around the world, especially in developing countries [1]. This is because the domestic or semi-domestic species it afflicts are widely used for meat, milk, hair, wool, hides, fertilizer, fuel, carrying burdens or cultivating the soil. Moreover, these animals are generally in parts of the world where animal and/or human health services are scarce or non-existent. Therefore most cases of brucellosis will be in developing countries and we must considerer the cost and availability of the antibiotic to be used to treat patients.

The successful management and treatment of any infectious disease rests mainly upon early and accurate diagnosis. The absence of specific symptoms or signs makes the clinical diagnosis of brucellosis difficult. In areas of endemic

disease, a fever without evident cause that lasts more than 1 week should be considered possible brucellosis, and a history of exposure to *Brucella* (risk jobs, unpasteurized dairy products) should be sought. For patients in countries where brucellosis is not endemic a travel history is crucial.

The clinical manifestations and severity of brucellosis vary with the patient population studied and the species of *Brucella* involved. Not everyone who has contact with *Brucella* specimens develops active brucellosis. In endemic areas many people have a positive serological test for brucellosis but no history of recognized clinical infection. Patients who develop acute symptomatic brucellosis can manifest a wide spectrum of symptoms, including fever, headache, arthralgia, myalgia, fatigue and weight loss. In general, antibiotic therapy can reduce the duration of the symptoms [2].

In some patients, acute and chronic brucellosis may lead to complications covering a wide spectrum of focal disease affecting the reticuloendothelial system (i.e. bone, liver and spleen). The cardiovascular, gastrointestinal and neurological systems may also be affected [2]. Complications are relatively frequent but, fortunately, only a few cases are severe.

The mortality rate of brucellosis is very low (0.1% in a recent cohort) [3] and is associated with late diagnosis and late therapy, especially when *Brucella* damages the endocardium, producing endocarditis, or when it affects the central nervous system, resulting in meningitis or cerebral abscess. Therapeutic intensity is obviously higher in focal disease, some cases requiring surgery and/or a longer duration of antibiotic therapy.

Diagnosis depends on keen awareness of possible infection and a thorough occupational and travel history. A definitive diagnosis requires isolation of the

organism from blood culture or other clinical samples. However, a diagnosis of brucellosis is often made serologically, most frequently by standard tube agglutination measuring antibody to *B. abortus* antigen. The Rose Bengal test and lateral flow assay are faster and inexpensive diagnostic methods [4].

2. Standard treatment of human brucellosis

Antimicrobial therapy is useful for shortening the natural course of the disease, decreasing the incidence of complications and preventing relapse. Appropriate antibiotics should have high in vitro activity and good intracellular penetration [2].

There is strong evidence that the tetracyclines (especially doxycycline and minocycline) are the most effective drugs for brucellosis treatment [5]. These drugs are inexpensive, widely available and rarely associated with side effects. In randomized controlled trials these drugs have proven safe in all age groups. They produce rapid relief of symptoms, with defervescence usually occurring within 2–7 days; however, ≥6 weeks of treatment are required and adherence over this period may be low. The rate of treatment failure is 1–5%, the relapse rate is 5–10% and the cure rate exceeds 80% when an appropriate duration is used. Tetracyclines are usually combined with aminoglycosides, rifampicin, trimethoprim–sulfamethoxazole (TMP–SMZ) or quinolones.

The choice of regimen and duration of antimicrobial therapy should be based on whether focal disease is present or there are underlying conditions that contraindicate certain antibiotics (e.g. pregnant patients or children under 8 years old) [2]. Most individuals with acute brucellosis respond well to a combination of doxycycline plus aminoglycosides or rifampicin for 6 weeks. Monotherapy with doxycycline or minocycline, or a combination of doxycycline

with TMP–SMZ, a quinolone and rifampicin may be an alternative (Table 1). Patients with focal disease, such as spondylitis or endocarditis, may require longer courses of antibiotics, depending on clinical evolution.

[Table 1 here]

Patients with persistent symptoms following extended antibiotic therapy, for whom focal disease or relapse have been ruled out, pose a difficult clinical management problem. This disabling syndrome, sometimes called chronic brucellosis, is similar to chronic fatigue syndrome and must be treated symptomatically.

3. Special clinical problems

3.1. Pregnancy

Increased rates of spontaneous abortion, premature delivery and intrauterine infection with foetal death have been described among pregnant women with clinical evidence of brucellosis. Women who received early diagnosis and adequate treatment had successful maternal and foetal outcomes. Tetracyclines and streptomycin should be avoided during pregnancy. Rifampicin 900 mg once daily for 6 weeks is considered the regimen of choice. TMP–SMZ plus rifampicin is an alternative. However, TMP–SMZ should not be used in pregnancy, either before 13 weeks because of the risk of teratogenic effects or after 36 weeks because of the risk of kernicterus.

3.2. Children under 8 years old

Children often have fewer or milder symptoms than adult patients. Tetracyclines are generally contraindicated for children under 8 years old. The preferred regimen is rifampicin plus TMP–SMZ for 6–8 weeks. An alternative regimen is

rifampicin or TMP–SMZ for 8 weeks plus gentamicin 5 mg/kg/day for the first 5 days. Treatment over prolonged periods (>6 months) with TMP–SMZ has produced favourable results in some cases.

3.3. Therapy for relapses

Relapse occurs in 5–30% of patients, usually 1–6 months after initial infection, and tends to be milder than the original attack. The bacteria isolated from a relapsed patient usually demonstrate the same antibiotic susceptibility pattern as the isolate obtained during the original episode. Consequently, nearly all relapse cases respond to a repeated course of antimicrobial therapy.

4. Is monotherapy convenient in brucellosis?

Monotherapy with doxycycline or minocycline may be a cost-effective therapy (Table 2). These tetracyclines have few adverse effects, are effective and allow a convenient therapeutic schedule. Moreover, they are cheap, widely available and may be administered orally. However, there are only a few clinical trials comparing monotherapy with combination therapy.

[Table 2 here]

Two randomized therapeutic trials that included monotherapy as a branch of the treatment were conducted by Lubani et al. [6] (1100 children with brucellosis in Kuwait) and Montejo et al. [7] (330 patients aged 14–82 years, treated in Spain).

In Lubani's trial, monotherapy with oxytetracycline, doxycycline, TMP–SMZ or rifampicin was compared with these antibiotics combined with each other or with aminoglycosides. The duration of therapy was divided into three periods: 3 weeks, 5 weeks and 8 weeks. In the 8-week treatment group the relapse rate

in patients treated with oxytetracycline, doxycycline and rifampicin ≤9% and it was clearly noticed that the results were not different from those from the combination therapy during the same period of treatment. TMP–SMZ alone had a relapse rate of approximately 30% in all three durations of treatment.

In Montejo's trial the relapse rate with TMP–SMZ as monotherapy was only 3%, but the duration of therapy was 6 months. This suggests that TMP–SMZ could be considered a good option for monotherapy, but only when used for long periods. By contrast, in Montejo's trial doxycycline monotherapy showed a relapse rate higher than in Lubani's trial, but similar to the doxycycline plus rifampicin combination (the World Health Organization regimen) [8].

In conclusion, tetracycline monotherapy, especially with doxycycline, is a good option for patients with brucellosis with no focal disease and a low risk of relapse [9] (Table 3). Experts in brucellosis have a clear responsibility to educate physicians on the pros and cons of the different options in the treatment of patients with brucellosis. Practitioners must avoid the excessive use of high-cost or toxic schedules.

[Table 3 here]

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[1]

Table 1

Recommended treatment for brucellosis according to patient group[a]

Patient group	Recommended therapy	Alternative therapy
Acute brucellosis (adults and children >8 years old)	Doxycycline 100 mg PO twice daily for 45 days plus either streptomycin 15 mg/kg IM daily for 14–21 days, or gentamicin 3–5 mg/kg IV or IM daily for 7–14 days Or Doxycycline 100 mg PO twice daily for 45 days plus rifampicin 600–900 mg PO daily for 45 days	Rifampicin 600 mg PO daily for 42 days plus quinolone (ofloxacin 400 mg PO twice daily or ciprofloxacin 750 mg PO twice daily) for 42 days Or Doxycycline 100 mg PO twice daily plus TMP–SMZ one double-strength tablet twice daily for 2 months Or Monotherapy with doxycycline or minocycline PO daily for 6–8 weeks
Children <8 years old	TMP–SMZ 5 mg/kg (of trimethoprim component) PO twice daily for 45 days plus gentamicin 5–6 mg/kg IV daily for 7 days Or Rifampicin 15 mg/ kg PO daily for 45 days plus gentamicin 5–6 mg/kg IV or IM daily for 7 days	
Brucellosis during pregnancy	Rifampicin 600–900 mg PO daily for 45 days	Rifampicin 600 mg PO daily for 45 days plus TMP–SMZ one double-strength tablet twice daily for 45 days
Focal infections (endocarditis, spondylitis, meningitis, paraspinous abscesses)[b]	Doxycycline 100 mg PO twice daily and rifampicin 600 mg PO daily for 6–52 weeks plus either streptomycin 1 g IM daily or gentamicin 3–5 mg/kg IV or IM daily for 14–	Consider TMP–SMZ, ciprofloxacin 750 mg PO twice daily or ofloxacin 400 mg PO twice daily as a substitute for doxycycline or rifampicin

abscesses)[b]	21 days

[a] The choice of regimen/duration should be based on the presence of focal disease and whether there are underlying conditions that may contraindicate certain antibiotic therapy. Aminoglycoside and quinolone dosage should be adjusted in patients with poor renal function.

[b] Patients with focal disease, such as spondylitis or endocarditis, may require long courses of therapy depending on the clinical evolution. Surgery should be considered for patients with endocarditis, cerebral or epidural abscess, spleen or hepatic abscess, or other abscesses that are antibiotic resistant.

IM, intramuscularly; IV intravenously; PO, orally; TMP–SMZ, trimethoprim–sulfamethoxazole.

Table 2

Advantages and disadvantages of monotherapy versus combination therapy in human brucellosis

Antimicrobial	Advantages	Disadvantages
First-line		
Tetracyclines (doxycycline or minocycline)	Shorten clinical duration of disease Low cost Few adverse effects	More relapse with short courses (<6 weeks)
Second-line		
Rifampin Trimethoprim–sulfamethoxazole	Convenient therapeutic schedule	Antimicrobial resistance

Table 3

Treatment of patients according to the risk of relapse[a] [9]

Relapse risk group	Risk factors (*N*)	Risk of relapse (%)	Treatment
Low risk	0–1	4.5	Monotherapy (doxycycline 6–8 weeks)
Medium risk	2	32	Combination therapy (doxycycline plus streptomycin/gentamicin or rifampicin)
High risk	3	67	Combination therapy, long courses of antibiotics

[a] Independent predictors of relapse: temperature >38.3°C at baseline, duration of symptoms before treatment <10 days and positive culture at baseline.