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Treatment of Brucellosis

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Abstract

The goal of brucellosis therapy is to control the illness and prevent complications, relapses and sequelae. Important principles of brucellosis treatment include the use of antibiotics with activity in the acidic intracellular environment (doxycycline, rifampin), use of combination regimens and prolonged duration of treatment.

Keywords: Brucellosis, Treatment

1. Introduction

Human brucellosis is a major zoonosis caused by facultative intracellular Gram-negative bacteria of the genus *Brucella* [1, 2]. Brucellosis is a systemic disease and although less lethal, notoriously hard to eradicate, and relapses are being reported many years after the initial infection. Since global eradication of brucellosis is due to socioeconomic and political factors, it will not be feasible in the near future, and since the evolution of a satisfactory vaccine for human currently seems a utopia, there exists a need for optimal antibiotic treatment schedules [3, 4].

The optimal treatment for brucellosis remains an unsolved medical puzzle, owing to the propensity of the infection for relapses, the universal failure of monotherapy and the absence of multiethnic, randomised trials evaluating possible new regimens for the disease. Current recommended treatment regimens for brucellosis involve the use of two or more antibiotics in order to avoid relapses occurring and to prevent prolonged use of these drugs [4, 5]. The choice of regimen and duration of antimicrobial therapy should be based on whether focal disease is present (e.g. endocarditis, spondylitis, meningitis, paraspinal abscesses) or there

are underlying conditions that contraindicate certain antibiotics (e.g. pregnant patients or children under 8 years old) [6]. In this chapter, we will discuss the effects of various antibiotic regimens, monotherapy or in combination with other antibiotics for treating human brucellosis.

1.1. General principles of therapy

Brucella spp. are facultative intracellular pathogens with a unique ability of escaping phagocytosis by human macrophages. Thus, the first major parameter of successful antimicrobial treatment of brucellosis is the use of antibiotics that penetrate into macrophages and are thus active against the pathogen. The second important parameter is the use of antibiotics that are active in the acidic environment of the macrophages infected with *Brucella* spp. [4, 7].

The third major parameter in the successful treatment of brucellosis is the use of combination regimens, as monotherapy has universally been related to unacceptable percentages of relapse. The identity and number of antimicrobial agents used in each combination is the one major subject of debate on the treatment of brucellosis [4, 7].

The fourth major parameter is the evaluation of the duration of treatment, when applied to cases of uncomplicated brucellosis. The fifth major parameter that should be taken into account is the need for a convenient regimen for countries with poor health resources, that is, the need for a cheap, oral regimen, and this is exactly the philosophy that prompted the guidelines modification by WHO in 1986. Finally, the sixth major parameter is the inconcordance between in vitro studies on antimicrobial susceptibility of *Brucella* spp. and in vivo efficacy or resistance [4, 7].

1.2. Therapeutic regimens

Antimicrobial therapy is useful for shortening the natural course of the disease, reducing symptoms, decreasing the incidence of complications and preventing relapse. Appropriate antibiotics should have high in vitro activity and good intracellular penetration. Thus, the use of appropriate antibiotic combinations is required for the successful treatment of brucellosis [1, 8].

2. Specific compounds

Historically, single-agent therapy due to the relapses after treatment has proved inadequate for brucellosis. This is because of the primarily bacteriostatic effect exhibited by most of these agents (predominantly tetracyclines) and to a lesser extent (or not at all) the emergence of resistance [3].

The use of single-agent therapy with rifampin, oxytetracycline or doxycycline showed high relapse rates of 9–25 %. The duration of therapy (either 3, 5 or 8 weeks) showed no statistically significant difference. In addition, the use of monotherapy with trimethoprim–sulfamethoxa-

zole (TMP–SMX) or ciprofloxacin has led to an unacceptable relapse rate of 30 % and up to 83 %, respectively. Thus, monotherapy is not accepted as a treatment strategy for brucellosis [9].

2.1. Tetracyclines

Tetracyclines are the cornerstone of successful antibiotic regimens for the treatment of brucellosis. The two regimens suggested by WHO both include a tetracycline, and most of the subsequently proposed regimens also include a member of this antibiotic class. Tetracyclines are inexpensive antimicrobial agents, easy to obtain and easy to adhere to; side effects are unusual and of mild severity; and dosage, in the form of doxycycline administered twice daily – the tetracycline currently employed in almost all regimens – is convenient. There is strong evidence that the tetracyclines (especially doxycycline and minocycline) are the most effective drugs for brucellosis treatment. The rate of treatment failure in tetracyclines is 1–5 %, the relapse rate is 5–10 % and the cure rate exceeds 80 % when an appropriate duration is used [4, 6].

Doxycycline exhibits excellent activity in the acidic phagolysosomal environment where the compound interfaces with *Brucellae*, and its bactericidal activity has been repeatedly proven. Doxycycline has also been used as adjunctive monotherapy in cases of residual focal brucellosis for a protracted period, although there are no official data supporting its effectiveness when used as a single agent after an initial combination with another compound. The suggested adult dose of doxycycline employed in the various therapeutic combinations is 100 mg b.i.d. [4, 6].

Of the other tetracyclines, minocycline has also been favoured as the tetracycline of choice in several trials. Moreover, tigecycline is a glycylcycline antibiotic, related to tetracyclines, that exhibits a similar but fivefold enhanced mode of action compared with tetracyclines while also avoiding the emergence of antimicrobial resistance. The enhanced effectiveness of tigecycline may allow for its use as a single agent in brucellosis, even with decrease in treatment duration. Studies have shown that tigecycline can be a therapeutic alternative option for the treatment of brucellosis [3].

2.2. Streptomycin and other aminoglycosides

Streptomycin has been the second cornerstone in the treatment of brucellosis for the last 50 years and remains a popular antibiotic choice, especially by senior specialists. The need for parenteral administration, the significant percentage of toxicity (mainly ototoxicity) and difficulty in obtaining the drug in certain countries are parameters responsible for a lack of interest in the use of streptomycin in the last 25 years, especially as an acceptable all-oral regimen had been applied in clinical practice [4, 9].

Streptomycin is an example of the discrepancy between in vitro studies and in vivo effectiveness, as it has been proven that the drug does not survive in the acidic phagolysosomal environment, but it has also been proven that it is the only compound exhibiting bactericidal activity in the first 24 h after administration. Streptomycin is usually administered at a dose

of 15 mg/kg body weight/day for 2 or 3 weeks. Further administration would significantly increase the rate of unwanted effects [4, 6].

The need of combining an equally effective, but less toxic, compound with doxycycline switched interest to other members of the antibiotic class of aminoglycosides. Of these, gentamicin is the most extensively studied compound, and various studies have proven that its combination with doxycycline is an excellent regimen. The suggested dose is gentamicin 5 mg/kg/day, administered intravenously or intramuscularly, and the usual period of administration does not exceed 1 week. Netilmicin has also been employed in various combination regimens, but it is less well studied than gentamicin [2, 4, 6].

2.3. Rifampicin

In the early 1970s, it was determined that rifampicin in combined treatment regimens is effective for brucellosis, and by the early 1980s, this compound gradually replaced streptomycin as the complementary agent of choice to doxycycline in the treatment of the disease, culminating in the 1986 WHO guidelines, which advocated its use in the optimal treatment of the disease. Moreover, various therapeutic combinations have recently preferred the use of rifampicin over doxycycline, making rifampicin the cornerstone of modern antibiotic treatment [4, 6].

Rifampicin survives in the acidic environment of the infected macrophages and exhibits bactericidal activity 48 h after administration. One potential problem that could arise with the use of rifampicin-containing regimens for the treatment of brucellosis involves the concurrent high incidence of tuberculosis in areas endemic for brucellosis, due to the pertaining socioeconomic status. Fear that extended use of rifampicin would increase population resistance to the compound in the treatment of tuberculosis exists but has not been validated in clinical practice. The suggested dose for rifampicin in the treatment of brucellosis is 600–1200 mg/day [4, 6].

2.4. Macrolides

Ideally, macrolides should exhibit excellent efficacy against a facultative intracellular pathogen, as in various other zoonotic infections and various atypical respiratory pathogens. Thus, the newer macrolides and azithromycin, a relative compound of the class of azalides, were considered ideal candidates for the treatment of brucellosis, in certain combination regimens. Erythromycin was used instead of tetracycline in combination with streptomycin as early as 1961; however, the high doses necessary for achieving a clinical response similar to that of the combination of tetracycline and streptomycin were accompanied by unacceptable high rates of adverse reactions [4, 10].

The use of azithromycin in combination with gentamicin was also evaluated in a small clinical trial but resulted in a disappointingly high percentage of treatment failure (either relapse, frank failure or withdrawal due to side effects). Although the planned treatment duration was only 21 days, the cases of frank failure preclude the favourable approach to the use of azithromycin

in brucellosis. Azithromycin does not survive in the acidic environment of the infected macrophages [4, 10].

2.5. Quinolones

The evolution of fluoroquinolones and the successful use of these compounds in various infections, including certain zoonotic diseases and numerous intracellular pathogens, led to the development of what amounted to a scientific obsession in proving their efficacy in the treatment of brucellosis [4, 11].

Laboratory and clinical studies regarding using quinolone in the treatment of human brucellosis suggest that there is a lack of evidence supporting the use of quinolones in the initial therapeutic regimen. In vitro studies show that activity of quinolones decreased at pH 5 compared to pH 7 and there is lack of synergistic activity with the older antibiotics against brucellosis. Trials with ciprofloxacin as a single agent for the treatment of brucellosis have yielded disappointingly high percentages of treatment failure. However, recent studies with the combination of ofloxacin and rifampicin have yielded promising results [4, 11, 12].

Newer quinolones have also been interesting candidates. A trial of moxifloxacin monotherapy is underway in our institution. Their use in various combination regimens is promising and should be evaluated but will eventually be hampered, as with ofloxacin and ciprofloxacin, by cost restrictions, in the presence of a significantly more cost-effective combination regimen such as the one advocated by WHO [1, 11].

2.6. Trimethoprim–sulfamethoxazole

Trimethoprim–sulfamethoxazole has long been a popular agent in the treatment of brucellosis and remains the most popular choice for monotherapy trials. It has been extensively studied in the paediatric population, and its clinical efficacy, when compared to in vitro studies of *Brucellae* susceptibility, underlines the inconcordance between in vitro studies and clinical reality. However, trimethoprim–sulfamethoxazole cannot be viewed at present as more than a convenient third drug in a complex therapeutic regimen for focal brucellosis [4, 6].

2.7. β -Lactams

β -Lactams are active in vitro, and ampicillin was a popular therapeutic choice in the early 1950s. The in vitro susceptibility, however, does not translate to in vivo efficacy, due to the specific in vivo environmental conditions [4, 6].

The efficacy of ceftriaxone in the treatment of a variety of infectious diseases led certain investigators to study its possible use as a monotherapy in the treatment of brucellosis. The results of some studies indicate failure of ceftriaxone in the treatment of acute brucellosis. There are reports of excellent in vitro activity of cefotaxime and meropenem for treatment of brucellosis, but these agents have not been tested clinically [4, 13].

3. Combined regimens

Treatment of brucellosis is still far from ideal, the major problem being identification of the most practical and affordable double or triple antimicrobial combination to prevent relapse which is very common after treatment with single agents [13].

In 1971, the World Health Organization (WHO) suggested a 21-day regimen of tetracycline plus streptomycin as the treatment of choice for treatment of human brucellosis. Although this regimen was successful in reducing the early symptoms, it failed to treat the disease completely, and immediate relapse was seen in some patients. Accordingly, in 1986, the joint Food and Agriculture Organization of the United Nations (FAO)/WHO Expert Committee on Brucellosis suggested two new regimens: rifampicin (600 to 900 mg/day orally) plus doxycycline (200 mg/day orally) for 6 weeks and doxycycline (200 mg/day orally) for 45 days plus streptomycin (1 g/day intramuscularly) for 2 to 3 weeks. However, later studies showed a treatable but high rate of relapse for the mentioned regimens [3, 5].

The rifampicin plus doxycycline regimen is the most popular treatment for brucellosis and favourable to the more effective regimen of streptomycin plus doxycycline, possibly due to its lower price and ease of administration. Streptomycin requires parenteral administration in a hospital setting or in an appropriately set up primary care network. The plasma levels of doxycycline in patients treated with rifampin were significantly lower than those in the plasma of patients treated with doxycycline and streptomycin. Furthermore, bacterial clearance in patients treated with rifampin was significantly higher than that in patients treated with doxycycline and streptomycin [4, 5].

According to the suggestions of WHO, only the combination of doxycycline with gentamicin can be considered an acceptable (albeit not ideal) novel regimen for brucellosis [3]. Giving doxycycline plus gentamicin to people with brucellosis may reduce the incidence of total treatment failure compared to administration of doxycycline plus streptomycin. Thus, the combination of oral doxycycline plus gentamicin appears to be as effective as the traditional therapy of streptomycin plus doxycycline [2, 5, 14].

A longer duration of gentamicin plus doxycycline or netilmicin plus doxycycline for at least 14 days followed by doxycycline alone for a further 30–60 days is associated with less therapeutic failure and a lower relapse rate than a regimen containing aminoglycoside for only 7 days [15].

Significant geographical variations in clinical practice, even among different areas of the same country, exist, and in general, the treatment regimen of choice reflects the traditional approach by each institution and the clinical experience of each specialist. The combination of doxycycline for 45 days with gentamicin for the first 5–7 days is gaining acceptance as a first-line treatment regimen, whereas multiple regimens are also applied in various countries. This is particularly important in endemic areas, where many patients exhibit a mild form of the disease and diagnosis and prescription can be readily made at the emergency department. Thus, the all-oral regimen of doxycycline and rifampicin for a period of 45 days still seems a reasonable, inexpensive and convenient first-line treatment for most endemic areas [4, 9].

Alternative treatments for brucellosis include other antibiotics, such as fluoroquinolones and co-trimoxazole and their combinations with rifampicin. Combinations of streptomycin with trimethoprim–sulfamethoxazole, or rifampicin with trimethoprim–sulfamethoxazole, are variably reported in some series [4, 16]. Some studies have suggested that fluoroquinolones in combination with rifampin or doxycycline can be used for the treatment of acute uncomplicated brucellosis as an alternative to the doxycycline plus rifampin combination [12, 13].

The use of ofloxacin plus rifampicin for the treatment of human brucellosis is as effective as the standard doxycycline plus rifampicin regimen. Although ofloxacin in combination with rifampicin decreased the duration of the therapy and provided shorter course of fever, these superiorities are not sufficient for declaring this treatment as treatment of choice. The cost of ofloxacin plus rifampicin treatment is higher than doxycycline plus rifampicin treatment [12, 17].

The use of triple antimicrobial therapy is not widely implemented except in selected situations and in patients with focal disease. However, triple combinations, utilising trimethoprim–sulfamethoxazole or both streptomycin and rifampicin in addition to a tetracycline, remain popular in certain endemic regions [3, 14].

Amikacin plus doxycycline and rifampicin regimen for the treatment of human brucellosis had a higher efficacy and more rapid action in terms of relief of symptoms compared to the doxycycline in combination with rifampicin regimen, and no significant difference in drug side effects and disease relapse existed in the patients of either group; adding amikacin to the doxycycline plus rifampicin standard treatment regimen seems beneficial [18].

Nevertheless, there are still a number of obstacles to overcome, such as the need for parenteral administration of aminoglycosides, the danger of inducing emergence of resistance to rifampicin in countries where tuberculosis poses a problem, the treatment compliance in a disease in which symptoms disappear a few days after initiating treatment, the difficulty of patient follow-up in underdeveloped rural areas and the relapses, which are observed approximately in 10 % of the patients [19].

4. Duration of treatment

Various efforts have been made to evaluate the ideal treatment duration for brucellosis; studies with doxycycline plus an adjunct for a total duration of 30 days have yielded a higher percentage of relapses, and the addition of gentamicin or newer quinolones, or application of triple regimens, has not consistently exhibited an advantage or equality in the efficacy of shorter periods of treatment. In the treatment of brucellosis, the rule is that a longer treatment duration causes fewer relapses, and many cases with residual complaints after regimen completion can be effectively treated with a protracted course of doxycycline alone. Many specialists treat patients for a shorter period, but the lack of data on the geographical distribution of biotypes of *Brucella melitensis* and the virulence of both *B. melitensis* and *B. abortus* and inadequate data on diagnosis and follow-up preclude any permanent conclusions. A total

of 45 days of treatment seems to be the golden equilibrium of acceptable success, compliance and lack of significant side effects [4, 14].

5. Special issues

Treatment protocols for brucellosis may differ in children aged less than 8 years and pregnant women, because of adverse reactions of some medications, including inhibition of bone growth due to tetracycline treatment in children and teratogenic potential of some drugs, such as streptomycin [5].

Patients with localisations such as spondylitis, endocarditis, neurobrucellosis and abscess formations in body organs may require hospitalisation for possible surgery, and triple antibiotics (doxycycline, aminoglycoside and rifampicin) should be used for a longer period of up to 6 months. Urgent valve replacement or drainage of abscesses may also be required with antibiotics (Table 1) [15, 20, 21].

5.1. Paediatric population

Children often have fewer or milder symptoms than adult patients. Doxycycline and tetracycline are not recommended for children younger than 8 years of age because of irreversible staining of permanent teeth. Thus, the use of tetracyclines in children is prohibited, and the suggested combinations for children include rifampicin plus trimethoprim–sulfamethoxazole or rifampicin plus streptomycin or another aminoglycoside. The preferred treatment regimen for brucellosis in children 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 [4, 6, 22].

5.2. Pregnancy

Among pregnant women with clinical evidence of brucellosis, high rates of spontaneous abortion, premature delivery and intrauterine infection with foetal death have been described. Women who received early diagnosis and adequate treatment had successful maternal and foetal outcomes. The use of tetracyclines and streptomycin should be avoided for treatment of human brucellosis during pregnancy. Rifampicin is the mainstay of treatment in pregnancy. Recent reports suggest that, among antibiotic use permitted during pregnancy, there is no superior combination with rifampicin in treatment outcome [4, 6]. 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 [6, 23]. Furthermore, some studies indicated that ceftriaxone/rifampicin treatment can be the most effective treatment for pregnant women with brucellosis [24].

5.3. Treatment of focal diseases

Focal disease in brucellosis includes endocarditis, myocarditis, pericarditis, aortic root abscess and vertebral infection. A prolonged course of 6–52 weeks was traditionally recommended for focal disease such as endocarditis, spondylitis or neurobrucellosis. The occurrence of focal disease in brucellosis was reported to be epididymo-orchitis (7.5 %), meningitis (3.6 %), endocarditis (1.5 %), bone and joint symptoms (55 %) and septic arthritis (5–10 %) [9, 25, 26].

5.3.1. Osteoarticular brucellosis and spondylitis

Osteoarticular complications of brucellosis are the most common and in cases of spondylitis, often the most troublesome. Whereas sacroiliitis and peripheral arthritis rapidly resolve with the administration of antibiotic regimens employed in the treatment of uncomplicated brucellosis, spondylitis often requires protracted antibiotic administration or combined medical and surgical treatment. Patients with focal spinal disease may have higher rates of treatment failure if they are treated with doxycycline plus rifampicin for 6 weeks. Thus, such patients may require a longer course of therapy for more than 5 months [4, 14, 27].

Many patients with spondylitis experience residual complaints and some have been treated with various regimens for protracted periods, sometimes exceeding 12 months. Limited data support the inclusion of an aminoglycoside in the treatment regimen of spondylitis patients. Spondylitis may be the one aspect of brucellosis where quinolones may prove cost-effective; their ability to penetrate and achieve significant concentrations in bone and soft tissues allows their use in brucellar spondylitis for maximising response. An initial report of a combination of doxycycline and ciprofloxacin for a period of 3 months has been encouraging [4, 14, 28].

5.3.2. *Brucella* endocarditis

Brucella endocarditis is another ominous, but fortunately extremely rare, complication (2–5 %). As a rule, brucellar endocarditis is treated surgically, and the duration of postsurgical antibiotic treatment ranges 3–15 months, usually utilising at least three of the active compounds against brucellosis [4, 14].

Cases of isolated conservative treatment of brucellar endocarditis exist, and conservative treatment can be considered an option in the absence of prosthetic valves, the absence of congestive heart failure and the presence of only mild extravalvular heart involvement and assuming that antibiotic administration starts immediately after diagnosis [4, 14]. Most patients with brucellar endocarditis are usually treated with the use of a combination of tetracycline and doxycycline, rifampin and an aminoglycoside or TMP–SMX for a mean duration of 3 months. Surgical interventions are more likely to be required for treatment of patients with heart failure, valvular destruction and abscesses [9, 14].

5.4. Chronic brucellosis

There is no consensus on the definition of chronic brucellosis, and thus, there is no background for establishing guidelines for treatment. Protracted courses of the usual regimens should be

advocated, but treatment options are largely subject to specialist preferences and individualised patient parameters. One important aspect of the so-called chronic brucellosis is the possibility of an underlying immune-mediated mechanism in its pathogenesis: numerous anecdotal reports of the use of corticosteroids in patients with 'chronic' brucellosis exist but cannot be substantiated. Others suggest that the clinical entity that is characterised as chronic brucellosis is in fact a result of impaired cellular immunity; thus, the use of interferon has been advocated, but this approach cannot be substantiated either [4, 6].

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, 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, paraspinal 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 14–21 days	Consider TMP–SMZ, ciprofloxacin 750 mg PO twice daily or ofloxacin 400 mg PO twice daily as a substitute for doxycycline or rifampicin

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

^aThe 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.

^bPatients 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.

Table 1. Recommended treatment for brucellosis according to patient group^a

6. Future targets

6.1. Re-evaluating current alternatives

Because the current officially endorsed regimens are not ideal, other approaches using currently existing antibiotics should be further validated. Gentamicin has been recently validated in a large sample with excellent results, yet its parenteral administration does not service the requested convenience, and the agent should be further evaluated only for seriously complicated, hospitalisation-requiring cases. On the other hand, co-trimoxazole-containing regimens can be considered as convenient (all-oral) regimens that may be of significantly lower cost than traditional combinations in certain developing countries. The emergence of community-acquired resistance should be studied for rifampicin; its potential overuse/abuse may reflect on increasing rifampicin resistance in *Mycobacterium tuberculosis* because both brucellosis and tuberculosis can simultaneously be endemic/exist in the same countries in many parts of the world [4, 7].

6.2. Optimising antibiotic delivery

An interesting new approach, still in preclinical evaluation, is the optimisation of antibiotic delivery in the macrophages by using antibiotic-containing microparticles. The development of gentamicin-loaded poly-(D,L-lactide-co-glycolide) (PLGA) microspheres and studies of their release patterns are promising in this field because optimisation of encapsulation efficiency and gentamicin loading may lead to prolonged antibiotic release. Gentamicin-containing PLGA microspheres can be successfully phagocytosed by infected THP-1 human monocytes, and the antibiotic reaches *Brucella*-specific compartments and reduces the intracellular *Brucella* infection [7, 14].

6.3. Novel compounds

Following development, many agents have generated hope as a possible monotherapeutic treatment of human brucellosis with most of these hopes proving to be futile in clinical practice. Most of these new agents are costly, intravenously administered antibiotics that would be neither practical nor cost-effective for the disease. There is one new agent that is unique enough to generate theoretical interest of its possible future role in brucellosis treatment. Tigecycline is a novel glycylcycline antibiotic, a 9-t-butylglycylamido minocycline, which inhibits bacterial protein synthesis with 3- and 20-fold greater potency than that of minocycline and tetracycline, respectively, partly attributed to its binding to additional ribosomal subunit targets. Tetracyclines are the mainstay of most antibiotic regimens for brucellosis, and replacing doxycycline with a more potent analogue might not only increase efficacy but might offer further advantages by possibly reducing treatment duration [7, 14].

7. Conclusion

Brucellosis, the most common bacterial zoonosis in the world, is still endemic in many developing countries. The optimal duration of antibiotic treatment in patients with brucellosis

is unclear, even for the most common clinical presentation of acute, uncomplicated brucellosis without focal disease [4, 6].

Most cases with uncomplicated brucellosis in adults can be readily treated with the combination of doxycycline and rifampicin (in a dose adjusted to body weight) for 45 days. The use of doxycycline for 45 days in combination with streptomycin for 14 days (or gentamicin for 5–7 days) is a reasonable alternative approach. For patients with treatment failure or repeated relapses, an array of second-line agents, such as quinolones, or trimethoprim-sulfamethoxazole can be utilised [4, 14].

For patients with complicated disease, therapeutic intervention demands a careful evaluation of the patient and a thorough therapeutic plan. Patients with spondylitis should possibly receive a quinolone in the initial regimen, for a protracted period [4, 14].

Attempts at monotherapy should be reserved for therapeutic trials or cases where traditional therapeutic regimens have failed. Chronic brucellosis should be ideally classified as a clinical entity and treated for a protracted period with one of the accepted regimens [4, 6].

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