REVIEW ARTICLE

Update on the treatment of adult cases of human brucellosis

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INTRODUCTION

Brucellosis is a worldwide health concern and still remains endemic in many developing countries including Iran, and hundreds of thousands of new cases of brucellosis are reported annually (1,2). The disease mainly affects animals and produces genitourinary infections that may lead to abortion (3). Transmission of Brucella from infected animals to human occurs either by occupational contact or by consumption of contaminated animal products especially milk, cream, butter, and fresh cheese (4,5).

Human brucellosis has a wide clinical spectrum and presents with various diagnostic difficulties since it mimics many other diseases. It often results in complications like peripheral arthritis, epidydimoorchitis, sacroiliitis, spondylitis, cerebrospinal involvement and endocarditis (4-7). Furthermore, interest on the pathogen has resurfaced due to its inclusion in the potential biological weapon list of most authorities (8). Moreover, brucella remains the commonest cause of laboratory-acquired infections augmented in invigorating scientific interest in an ancient pathogen (9).There is still no optimal therapy for some particular forms of brucellosis. In this paper

we introduce current recommendation in the treatment of adult cases of brucellosis.

Basic parameters of pathophysiology

The most important aspects of brucella interaction with the human hosts were recognized previously and understanding of disease evolution has improved significantly in recent years through advances in molecular biology. The pathogen is able to survive for long time in humans, by residing in brucella containing vacuoles (BCV) that progressively evolve through the pathogen's interaction with macrophage and non-professional phagocytes' organelles (10). Recent advances have focused on the role of other cell types, as dendritic cells as possible reservoirs of brucella in the human body. This may alter our treatment approaches (11). These BCVs serve as a hiding place, allowing Brucella to escape recognition from the immune system and proliferate without affecting cellular viability. Furthermore, acidity of the environment surrounding the bacteria does not allow optimal antibiotic action. Given the fact that the pathogen resides in a relatively antibiotic-resistant environment, it is not surprising that antibiotic combinations were early recognized as obligatory in order to minimize treatment failures, either in the form of relapses or frank absence of response.

History of therapeutic approaches

The efficacy of certain antibiotics in the treatment of brucellosis has changed few in the last 5 decades. Spink in the 1950s recommended that a regimen including tetracycline and streptomycin is more efficient in disease control than various single regimens (12). This regimen has been used in the following years, and even today is considered as one of the two optimal regimens endorsed by the WHO (tetracycline replaced by doxycycline). Rifampicin in combination with doxycycline for treatment of human brucellosis was introduced in 1970s (13). This combination is the second regimen of therapy in WHO guidelines.

Other combinations such as co-trimoxazole plus rifampin were used in special situations such as pregnant women and children, or as a third agent in multiple regimens (14). Other aminoglycosides have been proven efficient, most prominently gentamicin (15). Quinolones have been studied in various combinations, but their efficacies were not superior to traditional regimens (16).

Is there a need for new therapeutic approaches?

The aforementioned efficacy rates refer to uncomplicated brucellosis, or disease with minor complications. Serious complications like spondylitis, endocarditis and neurobrucellosis that are associated with a higher mortality rate can be considered as situations for which traditional antibiotic treatment is often not adequate.

On the other hand, molecular diagnostic studies raise interesting questions about the overall ability of antibiotic regimens to eradicate the pathogen from the human body. Navarro et al (17) have recently shown that a significant number of successfully treated patients who remained clinically healthy for prolonged follow-up periods were still positive for Brucella DNA. This may further lead to discussion about the utility of immune response stimulation in order to achieve an optimal therapeutic result, a notion that has been for long entertained in the setting of the ill-defined chronic brucellosis.

Optimizing antibiotic delivery

An interesting new approach, still in pre-clinical evaluation, is the optimization of antibiotic delivery in the macrophages by the use of antibiotic-containing microparticles. The development of gentamicin-loaded poly (D,L-lactide-co-glycolide) microspheres and studies of their release patterns are promising in this field, since optimisation of encapsulation efficiency and gentamicin loading may lead to prolonged antibiotic release (18).

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 (19-20). This agent promises for a role for tigecycline in this infection. Although the efficacy of both of these agents in hauman brucellosis need to be approved in clinical trial.

Immunomodulation

The notion that the outcome of brucellosis is related to equilibrium between host immune response and pathogen virulence is old, and mainly utilized in the setting of chronic brucellosis. New data raise the possibility of a typical tuberculosis-like behaviour of brucellosis, with "clinical cure" equalling immune system control of the pathogen but not eradication (17,21). Thus, brucellosis may actually be a chronic disease, and eradication may actually never be feasible. Immune response then would be crucial in controlling symptomatic disease and antibiotics may only serve in minimizing the microbial burden with which the immune system has to deal. There is few data on the effect of immune response stimulators in the treatment of brucellosis. The most studied agent is levamisole with immunostimulatory potential, in particular regarding cellular immunity, which is the

main component of immune response in brucellosis (21). Certain studies have outlined that the addition of levamisole to classic antibiotic regimens may prove beneficial in patients with "chronic" brucellosis (22,23). Furthermore, one study has shown that levamisole may have a beneficial effect in cellular immunity in patients with acute brucellosis (24). An even better result in a similar patient population was observed with the use of interferon alpha in one study (25). Therefore, more studies are needed to clarify the efficacy of Immunomodulators in the treatment of brucellosis.

Important points which need to be evaluated in the brucellosis management

Optimisation of treatment first needs a better understanding of the molecular pathophysiology of the disease, and fortunately more and more information is gained rapidly on this subject. An important subsequent target would be to raise awareness on the disease and its global impact, which is often neglected due to the minimal mortality of brucellosis. This is particularly important in the endemic regions of brucellosis (26). Increased awareness and global collaboration, would allow for re-evaluating the efficacy of existing treatment options, and for field-testing of newer approaches. A modification of our understanding of the disease, and thus of our treatment approaches should be continued.

Current recommendations in treatment of human brucellosis
General consideration

For selection of any regimen of therapy, we must consider both therapeutic failure and relapse. Therapeutic failure is defined as the persistence of clinical symptoms and signs of the disease with or without bacteremia and or discontinuation of treatment due to serious side effects of one or more drugs.

Relapse is defined as the recurrence of signs and symptoms of the disease with or without recurrent bacteremia after completion of therapy.

We recommend post- treatment follow up periods for 2 years.

Treatment of uncomplicated brucellosis or brucellosis with peripheral arthritis, sacroiliitis or epidydimoorchitis
Regimens of choice

We recommend three following regimens of therapy in these situations: Streptomycin plus doxycycline, gentamicin plus doxycycline or doxycycline plus rifampin.

Streptomycin 15mg/kg daily intramuscularly for 2-3 weeks plus doxycycline 100 mg bid for 45 days. Failure of therapy and relapse with this regimen was reported up to 8% (27-30).

Gentamicin 5mg/kg for 7 days (at most 240 mg/day) plus doxycycline 100 mg bid for 45 days. Failure of therapy and relapse with this regimen was reported between 5 to 12% (30-32) (table 1).

Rifampin 600-900 mg plus doxycycline 100 mg bid for 45 days. Rifampin should be administered one or two hours before lunch for prevention of doxycycline and rifampin interaction. Failure of therapy and relapse with this regimen was reported up to 24% (28,29,33) (table 1).

We recommend that patients younger than 60 years to be treated with combination of streptomycin and doxycycline or gentamicin and doxycycline. Patients older than 60 years should be treated with rifampin and doxycycline due to increased incidence of ototoxiciy or nephrotoxicity of streptomycin or gentamicin in this age group.
Alternative regimens

Ofloxacin 400 mg twice daily plus doxycycline or ciprofloxacin 500 mg twice daily for 6 weeks plus doxycycline 100 mg bid for 45 days are recommended for the treatment of brucellosis (34).

TMP-SMX (800+160 mg) twice daily plus rifampin or doxycycline is another alternative regimen in the treatment of human brucellosis (35). The failure of therapy and relapse for these regimens are shown in table 1.

Treatment of neurobrucellosis

A variety of nervous system complications have been reported in brucellosis, including meningitis, meningoencephalitis, brain abscess, demyelinating syndromes, and meningovascular syndromes.

Treatment of neurobrucellosis poses special problems because of the need to achieve high concentrations of antimicrobial drugs in the CNS. The recommended regimens for treatment of neurobrucellosis are;

● Streptomycin for 2-3 weeks plus doxycycline and rifampin for 8 months (36).

● Doxycycline plus rifampin plus cotrimoxazole for 8 months (37,38).

There is no consensus on the optimum duration of therapy, but most authorities agree that therapy needs to be prolonged. Duration of therapy with either regimen is for 6-8 months (39-41).

Clinical and serologic responses and improvements in CSF parameters are used to monitor the course of treatment

Treatment of brucellar endocarditis

Infective endocarditis presents a special problem because of the need for bactericidal concentrations of drug within the vegetations. Although there are reports of successful treatment of brucella endocarditis with antibiotics alone (42), most patients have required drug therapy combined with valve replacement surgery (43,44). In patients who were cured with antibiotics alone, combinations of doxycycline plus streptomycin and rifampin or combination of gentamicin plus doxycycline and rifampin for up to 9 months were used (45). In patients who underwent valve replacement, doxycycline and streptomycin combined with other drugs, such as TMP/SMZ or rifampin, were given postoperatively for periods as short as two weeks and as long as 13 months. Consequently, the optimal therapy for brucella endocarditis remains to be determined. Nevertheless, combination therapy with doxycycline plus an aminoglycoside (streptomycin or gentamicin) and another drug, such as cotrimoxazole or rifampin, usually with valve replacement, offers a reasonable chance for cure. The optimal duration of therapy for endocarditis is also unknown, but prolonged treatment (at least 4-6 months) is generally recommended (44).

Spondylitis

Most patients with spondylitis respond to antimicrobial therapy alone, however some authorities recommend that patients with brucellar spondylitis receive therapy for at least three months. Surgical intervention may also be required when spinal instability threatens serious neurologic injury. Combination of two drugs is recommended (46-49).

Treatment of brucellosis in HIV positive individuals

Brucellosis does not appear to be an opportunistic infection and it does not pose special problems in treatment. So far, 12 cases of brucellosis in HIV positive cases were reported. The course of infection in HIV positive patients did not differ from that of HIV negative individuals, including favorable responses to the usual regimens of antimicrobial drugs (50).

Conclusion

Uuncomplicated brucellosis cases or brucellosis with peripheral arthritis, epidydimoorchitis or sacroiliitis patients need to be treated with streptomycin and doxycycline or gentamicin plus doxycycline or doxycycline plus rifampin as discussed above. Duration of therapy in neurobrucellosis and spondylitis is relatively high (4-9 months). Most patients with brucellar endocarditis require drug therapy combined with valve replacement. Duration of medical therapy is more than 6 months. Treatment of brucellosis in HIV positive cases is similar with HIV negative cases.

Table 1. Failure of therapy and relapse with different common regimens in the treatment of human brucellosis

Regimen of therapy and duration (days)	No. of treated cases	No. of failed/ relapsed cases (%)	Ref
Dox. (45 d) plus Strep. (15 d)	51	3 (5.8)	27
Dox. (45 d) plus Strep. (14 d)	40	3 (7.5)	28
Dox. (45 d) plus Strep. (21 d)	44	1 (2.3)	28
Dox. (45 d) plus Strep. (14 d)	94	7 (7.4)	29
Dox. (45 d) plus Strep. (14 d)	94	7 (7.4)	30
Dox. (45 d) plus Gent. (7 d)	97	5 (5.2)	30
Dox. (45 d) plus Gent. (7 d)	17	1 (5.9)	31
Dox. (45 d) plus Gent. (7 d)	73	9 (12.3)	32
Dox. (45 d) plus Rif. (45 d)	52	7 (13.5)	33
Dox. (45 d) plus Rif. (45 d)	100	24 (24)	29
Dox. (45 d) plus Rif. (45 d)	46	6 (13)	28
Ofl. (45 d) plus Rif. (45 d)	31	2 (6.5)	34
Cotri. (60 d) plus Dox. (60 d)	140	37(26.4)	35
Cotri. (60 d) plus Rif. (60 d)	140	22(15.7)	35

Dox.: Doxycycline, **Strep.**: Streptomycin, **Gent.**: Gentamicin, **Rif.**: Rifampin, **Cotri.**: Cotrimoxazole, **Ref**.: Reference.

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