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DOI: 10.46903/gjms/16.04.1988

REVIEW ARTICLE

ANTIBIOTICS IN THE MANAGEMENT OF BRUCELLOSIS

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ABSTRACT

Brucellosis is the most common zoonotic bacterial infection in the world. The causative organism is Brucella spp. and the incubation of period is 5 days to 5 months. Although immunological tests are widely used for the diagnosis but cultures of the blood or other clinical specimens is the gold standard for the diagnosis. Outbreaks of brucellosis occur from time to time. It spreads mostly in the communities having close contact with the sheep and cattle, like farmers, cattle grazers, veterinary workers, and butchers. In the urban situation the outbreaks usually occur due to consumption of unpasteurized milk or its products. The clinical features of brucellosis are protean but the major one is a prolonged fever. Infected animals are the reservoirs and the sources of infection. Antibiotics have a major role in the management of brucellosis. Although a single antibiotic may be effective but a combination is preferred to prevent the chances of development of resistance and recurrence of disease. Antibiotics commonly used in the management of brucellosis are doxycycline, rifampicin, streptomycin, fluoroquinolones, cotrimoxazole, and chloramphenicol. Resistance to one or the other antibiotic have been reported from time to time. Dual therapy is commonly prescribed and triple therapy is used in serious conditions like neuro-brucellosis, endocarditis, or recurrence. The objective of this review was to evaluate the effects of various antibiotic regimens in the management of brucellosis. Antibiotic resistance is a problem which can aggravate the situation in future. We suggest that antibiotics' use should be rationalized to prevent future drug resistance. At least dual therapy should be used to prevent the chances of recurrence and triple therapy for complicated cases and in cases of relapse. There should be no compromise on the optimal doses and duration of therapy.

KEY WORDS: Brucellosis; Antimicrobial susceptibility; Antibiotics; Antimicrobials; Brucella mellitensis; Brucella abortus.

This article may be cited as: Hayat Z, Khan H, Ahmad I, Habib H, Hayat K. Antibiotics in the management of brucellosis [Review article]. Gomal J Med Sci 2018 Oct-Dec;16 (4):114-6. https://doi.org/10.46903/gjms/16.04.1988

INTRODUCTION

Transmission of disease from animals or zoonosis is not an uncommon phenomenon. It can occur in both urban and rural settings.[1] Brucellosis is the most common zoonotic bacterial infection in the world.[2] It is also an important infectious cause of fever of unknown origin.[3] There are a reported 500,000 cases of human brucellosis per year worldwide. However, the true incidence is estimated to be 5,000,000 to 12,500,000 cases annually. Countries with the highest incidence of human brucellosis are Syria, Mongolia, and Tajikistan.[4]

The causative organism of brucellosis is Brucella spp. Of the 12 species of Brucella, all of which are infecting mammals, only four are pathogenic for humans: B. melitensis, B. abortus, B. suis and, in very few cases, B. canis.[5] Brucella melitensis is however the most frequently involved species in the human brucellosis.[6] The incubation of period of brucellosis is highly variable, usually 2-4 weeks, but can be 5 days to 5 months.[7] Although immunological tests are widely used for the diagnosis but cultures of the blood or other clinical specimens is the gold standard for the diagnosis.[6,8]

Outbreaks of brucellosis occur from time to time. It spreads mostly in the communities having close contact with the sheep and cattle, like farmers, cattle grazers, veterinary workers, and butchers. However, in the urban situation the outbreaks usually occur due to consumption of unpasteurized milk or its products.[6]

The clinical features of brucellosis are protean but the major one is a prolonged fever. Brucellosis may present with acute or subacute course, with continuous, or intermittent fever, profuse sweating, fatigue, anorexia, weight loss, headache, arthralgia

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and generalized body aches. Brucella endocarditis and neuro-brucellosis are the serious manifestations of brucellosis.[6]

Brucellosis is a notifiable disease in most of the countries. Infected animals (mainly cattle, sheep, goats, pigs and less commonly dogs and other animals) are the reservoirs and the sources of infection.[6]

Antibiotics have a major role in the management of brucellosis. Although a single antibiotic may be effective but usually a combination is used to prevent the chances of development of resistance and recurrence. Antibiotics commonly used in the management of brucellosis are doxycycline, rifampicin, streptomycin, fluoroquinolones, trimethoprim/sulfamethoxazole (cotrimoxazole), and chloramphenicol. Resistance to one or the other antibiotic have been reported from time to time, mostly in the in-vitro studies. Double therapy commonly prescribed is doxycycline + streptomycin, doxycycline + rifampicin, and rifampicin + fluoroquinolone. Triple therapy like doxycycline + rifampicin + cotrimoxazole in used in serious conditions like neuro-brucellosis, endocarditis, or recurrence.[9]

Apart from antibiotics, some herbal products have also been tested in the management of brucellosis at least in the animal studies. A study on mice showed that the Caryopteris mongolica root extract may be useful in the treatment of brucellosis patients, when given in combination with doxycycline or other antibiotics, to reduce the toxicity of high-dosage of antibiotics, and to prevent the development of antibiotic resistance.[10]

For prevention of brucellosis the public awareness to avoid consuming unpasteurized milk and derivatives and animals screening and vaccination are the most important steps.[6]

DISCUSSION

Antibiotics have the basic role in the management of brucellosis. Judicial use of antibiotics in optimal doses and duration is mandatory to prevent the resistance. Studies from different geographical areas have revealed variable results of sensitivity to various antibiotics. Several meta-analyses of randomized controlled trials and systematic reviews on the treatment of brucellosis are published in the recent past. The choice and duration of therapy are related to the patient characteristics like age, and the presence of focal disease. Double therapy is commonly recommended, but a triple regimen including an aminoglycoside is advised for patients with endocarditis or meningitis.[9,11] Even with adequate treatment, relapses of disease may occur during the following year. Complications and relapse can be successfully treated with a triple-drug regimen.[12] Experience suggests that streptomycin may be substituted with gentamicin in double or triple therapy regimen for 7-10 days, but no study directly comparing the two aminoglycosides is currently available.[6]

In a study by Liu et al[13], from China it was observed that B. melitensis isolates were susceptible to the majority of tested antibiotics. Minocycline and sparfloxacin showed very good bactericidal effects. But an unusual finding in this study was that rifampin and cotrimoxazole resistant isolates were observed for the first time at least in China.

In a study by Somily et al[14] from Saudi Arabia described 163 brucellosis patients treated with antimicrobial therapy consisting of doxycycline, rifampicin, streptomycin, tetracycline and cotrimoxazole in varying combinations. They reported a relapse rate of 3.6% and treatment failure rate of 2.1%. Doxycycline-rifampicin and doxycycline-streptomycin were the most commonly prescribed drug regimens for adults and children older than 8 years, and rifampin - cotrimoxazole for children younger than 8 years. All treatment failures and relapses occurred among children <10 years of age or adults >45 years.

Strains resistant to rifampicin are reported from various regions from time to time. A study by Shevtsov et al[15] from Kazakhstan conducted between 2008-2014, on 329 clinical isolates of Brucella melitensis in humans showed that almost half (48%) of the isolates were resistant to rifampicin. All these isolates were however susceptible to other commonly used antibiotics like streptomycin, tetracycline, doxycycline, and even gentamycin. Also in the study from Ulanqab, Inner Mongolia, China by Liu et al[13] on 85 Brucella isolates from blood collected between 2011 and 2015, rifampin and cotrimoxazole resistant isolates were observed. A meta-analysis with 1383 patients with brucellosis from 14 trials by Meng et al[16] found that patients who received rifampicin therapy had a higher risk of overall failure and relapse compared with streptomycin.

A study from Turkey by Kesli et al[17] with a total of 106 brucella strains isolated from blood cultures between January 2011 and June 2013, the in vitro antibacterial susceptibilities showed no evidence of resistance to any of the commonly used antibiotics. Similarly, in another study also from Turkey by Baykam et al[18] exploring the in vitro susceptibility of Brucella species with 42 blood isolates, 37 identified as B. melitensis and five as B. Abortus, showed that doxycycline had the lowest and rifampicin the highest MIC50 values. Four strains were non-susceptible to rifampicin, and one strain was resistant to cotrimoxazole. There was no significantly important resistance problem for antibiotics targeted against Brucella species in Turkey.

CONCLUSION

We described in this review the main features of brucellosis and discussed the various options of antibiotic in its management. Antibiotic resistance is a problem which can aggravate the situation in future.

We suggest that antibiotics' use should be rationalized to prevent future drug resistance. At least dual therapy should be used to prevent the chances of recurrence and triple therapy for complicated cases and in cases of relapse. There should be no compromise on the optimal doses and duration of therapy.

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

GRANT SUPPORT AND FINANCIAL DISCLOSURE

None declared.

AUTHORS' CONTRIBUTION

The following authors have made substantial contributions to the manuscript as under:

Conception or Design:	ZH, HK
Acquisition, Analysis or Interpretation of Data:	ZH, HK, IA, HH, KH
Manuscript Writing & Approval:	ZH, HK, IA, HH, KH

All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.