Chapter

# Update of Antibiotic Therapy of Brucellosis

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## Abstract

Currently, the only option for treating brucellosis is antibiotics especially to prevent complications. In this chapter, we want to talk about the drug therapy in brucellosis and the update of these therapies in the last years. Also, we will expose the principal antibiotics in brucellosis such as doxycycline, rifampin, streptomycin, cotrimoxazole (TMP/SMX), and gentamicin by talking about each one of their mechanism of action, pharmacokinetics, administration, risk assessment, adverse effects, and principal drug interactions. Furthermore, we will add the evidence of efficacy therapy in monotherapy or combinate therapy based on the evidence.

**Keywords:** brucellosis, aminoglycoside, doxycycline, rifampin, treatment

## 1. Introduction

Brucellosis is a zoonotic disease that can affect humans around the world, and it can affect any organ system. About the treatment, it is characterized to be prolonged therapy with a concomitant use of at least two or three antibiotics at different administration routes. The antibiotics have some special indications for administration, interactions, and risk assessment to prevent adverse reactions. That is why we will expose the principal antibiotics in brucellosis treatment based on the last evidence.

## 2. Antibiotic treatment

The principal objective of the treatment in brucellosis is to control the disease, prevent complications, relapse, and unfavorable outcomes. In the context of a zoonotic infection, the goal of its management is an appropriate antibiotic therapy with a prolonged duration of treatment, nevertheless the most effective antibiotic and treatment durations are unclear. Also, there are some limitations to choose the best treatment because of the need to choose antibiotics that act intracellularly and to prevent relapses with a prolonged therapy that can lead to increase the adverse effects of the drugs [1].

Furthermore, the monotherapy for brucellosis has been considered inadequate due to unacceptably high relapse rates, now we present possible treatment schemes [2, 3].

Uncomplicated brucellosis: (defined by not having focal disease like spondylitis, neurobrucellosis or endocarditis, and adults or > 30 kg):

- Doxycycline 100 mg orally twice daily for 6 weeks, plus streptomycin 1 g intramuscularly one daily for the first 14–21 days (or gentamicin 5 mg/kg for 5–14 days) [1, 2, 4].

- Doxycycline 100 mg orally twice daily plus rifampin 600–900 mg (15 mg/kg) orally one daily for 6 weeks [1, 3].

- Consider triple therapy with addition of amikacin (intramuscularly twice a day for 7 days) to relief symptoms more rapid.

Alternative agents: (they may be useful in the setting of drug resistance, allergy, antimicrobial toxicity or relapse in combination with doxycycline or rifampin)

- Ciprofloxacin 500 mg twice daily or ofloxacin 200 mg twice daily [5, 6].

- Trimethoprim-sulfamethoxazole (TMP-SMX) one double-strength tablet twice a day.

Focal disease: spondylitis, neurobrucellosis, endocarditis, or localized suppurative lesions (it requires longer courses of therapy at least 12 weeks):

- Spondylitis

  - Doxycycline 100 mg orally twice daily for 12 weeks plus streptomycin 1 g intramuscularly once daily for the first 14–21 days [7].

  - Alternative: doxycycline 100 mg orally twice daily plus rifampin 600–900 mg (15 mg/kg) once daily for 12 weeks.

  - Surgery in the context of spinal instability, persistence or progression of neurological deficit or localizes abscess epidural or paravertebral [8].

- Neurobrucellosis

  - Doxycycline, rifampin, and ceftriaxone or TMP-SMX.

  - Corticosteroids may be appropriate in the setting of neurobrucellosis complicated by iritis, papilledema, myelopathy, polyneuropathy, or cranial nerve palsies.

- Endocarditis

  - Doxycycline plus rifampin 300 mg every 12 h and gentamycin 5 mg/kg each day, the duration of therapy is uncertain usually for 6 weeks to 6 months [9].

  - Surgery: valve replacement.

Pregnant women: [2, 10].

- Limited data.

- Rifampin 900 mg once daily, with or without TMP-SMV (one double-strength tablet twice a day) for 6 weeks or rifampin with ceftriaxone.

Children

- Uncomplicated brucellosis

- (<8 years of age): oral TMP-SMX [10 mg/kg per day TMP (maximum 480 mg/day) and 50 mg/kg per day SMX (maximum 2.4 g/day) by mouth divided into two doses] daily plus rifampin [15–20 mg/kg per day by mouth (maximum 900 mg/day) divided in one or two doses] (or gentamycin 5 mg/kg IV daily for 7 days) for 6 weeks [10–12].

- (>8 years of age): oral doxycycline [2–4 mg/kg per day by mouth (maximum 200 mg/day) divided into two doses] or tetracycline [30–40 mg/kg per day by mouth (maximum 2 g/day) divided into four doses] plus rifampin for 6 weeks [11].

- Osteoarticular disease, neurobrucellosis, or endocarditis

  - <8 years of age: oral TMP-SMX for at least 6 weeks plus parenteral aminoglycoside [gentamicin (5 mg/kg per day parenterally divided into one to three doses) or streptomycin (20–40 mg/kg per day (maximum dose 1 g/day) parenterally divided in two doses)] for the first 14 days of therapy.

  - >8 years of age: oral doxycycline or tetracycline for at least 6 weeks, plus parenteral aminoglycoside (gentamicin or streptomycin) for the first 14 days of therapy.

## 2.1 Doxycycline

### *2.1.1 Mechanism of action*

It belongs to the group of tetracyclines that are a series of derivatives of basic four-ring structure. Doxycycline inhibits bacterial protein synthesis by binding to the 30S bacterial ribosome and blocking the access of aminoacyl tRNA to the A (acceptor) site on the mRNA-ribosome complex and inhibits protein synthesis [13].

### *2.1.2 Antimicrobial activity*

Doxycycline is a bacteriostatic antibiotic with activity against *Streptococcus pneumoniae* and *H. influenzae* and excellent activity against atypical pathogens such as *Mycoplasma* and *Chlamydophila pneumoniae*, methicillin-resistant *Staphylococcus aureus* and methicillin-susceptible *Staphylococcus aureus*, *Bacillus anthracis*, and *Listeria monocytogenes* and most strains of *Brucella* are susceptible. Some species such as *Pseudomonas aeruginosa* are resistant [13, 14].

### *2.1.3 Pharmacokinetics*

See **Table 1**.

### *2.1.4 Administration*

- Oral: administer with meals to decrease gastrointestinal (GI) discomfort. Administer capsules and tablets with a considerable amount of water and have patient sit up for at least 30 minutes to reduce esophageal irritation. Oral administration is preferable unless patient has significant nausea and vomiting [13].

- IV: infuse prolonged over 1–4 hours to prevent thrombophlebitis.

| | |
|---|---|
| Absorption | Oral: almost completely absorbed from the gastrointestinal tract (GI) (90–100%), plasma concentration may be reduced 20% by high-fat meal or milk<br>Time to peak serum: oral: 2–4 hours |
| Distribution | Widely distributed into tissues and fluids including synovial, pleural, prostatic, seminal fluids and bronchial secretions, saliva, aqueous humor<br>Poor cerebrospinal fluid penetration<br>Protein binding: >90%<br>Distribution volume<br>Bioavailability: reduced at high pH |
| Metabolism | Not hepatic, partially inactivated in GI tract by chelate formation |
| Elimination | Half-time elimination: 18–22 hours, end-stage renal disease: 18–25 hours<br>Excretion: feces (30%); urine (23–40%) |

**Table 1.**
*Pharmacokinetics parameters of doxycycline [13].*

### *2.1.5 Risk assessment*

When therapy of doxycycline needs to be used in prolonged therapy, some parameters need to be taken to prevent some of the adverse effects: complete blood count (CBC), renal and liver function tests periodically, during therapy [13].

### *2.1.6 Adverse effects*

- Gastrointestinal: it can produce GI irritation especially after oral administration (epigastric burning, abdominal discomfort, nausea, vomiting and diarrhea). To prevent this, the patient should take oral formulations with a glass full of water, administration on an empty stomach is generally not recommended [14].

- Photosensitivity: it may produce photosensitivity reactions in treated individuals exposed to sunlight. The patient needs to use skin protection and avoid prolonged exposure to sunlight and ultraviolet light [14].

- Hepatotoxicity: rarely occurs during the treatment. If patient became symptomatic, assess liver function tests, and discontinue drug [14].

- Hypersensitivity syndromes: severe skin reactions have been reported. Discontinue therapy for serious hypersensitivity reactions.

- Superinfection: prolonged use may result in fungal or bacterial superinfection like pseudomembranous colitis.

- Tissue hyperpigmentation: may induce hyperpigmentation in many organs: nails, bone, skin, eyes, thyroid, oral cavity (permanent brown discoloration of the teeth in children <8 years or in children from pregnant women in their last half of pregnancy), and sclerae, most dependently of time and chronic use [15].

### *2.1.7 Principal drug interactions*

See **Table 2**.

| Drug | Risk rating | Interaction | Mechanism | Management |
|---|---|---|---|---|
| Antacids (aluminum hydroxide, calcium carbonate, magnesium carbonate, sodium bicarbonate) | Consider therapy modification | Antacids may decrease the absorption of doxycycline | Formation of chelates between antibiotic and antacids that reduces absorption from the GI tract [16] | Separate administration of both by a few hours when possible Monitor for decreased therapeutic effects of antibiotic [17] |
| Barbiturates | Consider therapy modification | Barbiturates may decrease the serum concentration of doxycycline | Uncertain. Induction of doxycycline metabolism or excretion by the barbiturates [18] | Monitor decreased therapeutic effects of antibiotic if used concurrently with a barbiturate |
| Aspirin | Monitor therapy | Aspirin may decrease the serum concentration of doxycycline | Buffered aspirin contains antacids that alkaline environment may also reduce absorption [19] | Administer doxycycline at least 2 hours before or 6 hours after aspirin ingestion |
| Rifampin | Monitor therapy | Rifampin may decrease the serum concentration of doxycycline | Unknown. Rifampin induction of doxycycline metabolism and/or excretion [20] | Monitor closely for reduced doxycycline response in patients receiving rifampin |

**Table 2.**
*Principal drug interactions of doxycycline.*

### *2.1.8 Important*

- Tetracyclines are inexpensive, widely available, and poor associated with side effects, and also it have proven safe in all age groups [21].
- The doxycycline-streptomycin regimen is considered the first line and has been proven to be more effective than doxycycline-rifampin in some studies [4, 22].
- Do not administer to children <8 years of age due to permanent discoloration of teeth, retardation of skeletal development, and bone growth; more common with long-term use, but may be observed with repeated, short courses [12, 23].

## 2.2 Streptomycin

### *2.2.1 Mechanism of action*

It is an aminoglycoside antibiotic bactericidal. Aminoglycosides diffuse through aqueous channels formed by porin proteins in the outer membrane of Gram-negative bacteria to enter to the periplasmic space, and its transport across the cytoplasmic membrane depends on an electrical gradient coupled to electron transport to drive permeation of these antibiotics. That is why they are not used in anaerobic environments of abscess. Once streptomycin is inside the cell, it binds to the 30S ribosomal subunit and interferes with protein synthesis by causing misreading and

premature termination of mRNA translation, and the resulting aberrant proteins may be inserted into the cell membrane altering permeability [24–26].

### *2.2.2 Antimicrobial activity*

It is less active than other members of the class against aerobic Gram-negative, and it is used for the treatment of unusual infections and in combination with other antimicrobial agents. The inhibitory activity of aminoglycosides persists after the serum concentration has fallen below de minimum inhibitory concentration (MIC), and it is known as the post antibiotic effect and it improves the efficacy of high-dose extended-interval dosing regimens for aminoglycoside. It is used for the treatment of tuberculosis, tularemia, severe *M. avium* complex, brucellosis, and enterococcal endocarditis in combination with other drugs [24, 27].

### *2.2.3 Pharmacokinetics*

See **Table 3**.

| | |
|---|---|
| Absorption | Oral: poorly absorbed, IM: well absorbed<br>Time to peak IM: 1–2 hours |
| Distribution | Into most body tissues and fluids except the brain and adipose tissue (because of their polar nature)<br>Protein binding: 34%<br>Volume of distribution (Vd): 260 mL/kg |
| Metabolism | None known |
| Excretion | Half-time elimination: adults: 2–4, 7 hours, prolonged with renal impairment<br>Urine: 29–89% as unchanged drug<br>Bile, saliva, sweat and tears: (1%) |

**Table 3.**
*Pharmacokinetic parameters of streptomycin [24, 28].*

### *2.2.4 Administration*

Streptomycin may be administered by deep intramuscular injection into large muscle mass, rotate injection sites (it may be painful with a hot tender mass developing at the site injection) or intravenously (after dilution in admixture, infuse over 30–60 minutes). High-dose, extended-interval administration is the preferred administration of aminoglycosides because of less toxic effect than divided doses [24, 27].

### *2.2.5 Risk assessment*

It is important to monitor hearing tests (baseline and periodic audiograms), BUN, creatinine, and serum drug concentrations should be monitored in all patients:

- Therapeutic peak: 20–30 mcg/mL [25].

### *2.2.6 Adverse effects*

- Ototoxicity: aminoglycoside induces ototoxicity irreversible, bilateral, high-frequency hearing loss or vestibular hypofunction. It has been seen degeneration of hair cells and neurons in the cochlea and accumulation in the perilymph and endolymph at high antibiotic concentration in plasma. The initial symptoms such

as high-pitched tinnitus, nausea, vomiting, and difficulty in equilibrium may be reversible, so it should be monitored carefully for ototoxicity [24].

- Nephrotoxicity: it is because the accumulation and retention of aminoglycoside in the proximal tubular cells and the initial manifestations of damage at this site are mild proteinuria and hyaline and granular casts, and also the glomerular filtration rate is reduced after several additional days [24].

*2.2.7 Principal drug interactions*

See **Table 4**.

| Drug | Risk rating | Interaction | Mechanism | Management |
|---|---|---|---|---|
| Colistimethate | Consider therapy modification | Aminoglycosides may enhance the nephrotoxic and neuromuscular-blocking effect of colistimethate | Additive nephrotoxic effects<br>Alteration in membrane permeability that leads to cellular lysis by colistimethate [29, 30] | This combination should be avoided, if they must be used together to monitor patients' renal and neuromuscular function |
| Penicillins | Consider therapy modification | Penicillins may decrease the serum concentration of aminoglycosides | Inactivation of aminoglycosides by extended spectrum penicillins, especially in renal dysfunction [31, 32] | Monitor serum aminoglycoside concentration, and do not administer dose together through the same IV line |

**Table 4.**
*Principal drug interactions of streptomycin.*

*2.2.8 Important*

- Streptomycin is not available always in some regions and it is administered only intramuscularly or intravenously, so it is a disadvantage [2].

- Gentamicin has replaced streptomycin for some indications because the toxicity of gentamicin is renal and mostly reversible although streptomycin is most vestibular compromise and irreversible [24].

## 2.3 Gentamicin

*2.3.1 Mechanism of action*

Gentamicin is a bactericidal aminoglycoside. It binds to the 30S ribosomal subunit and interferes with initiation of protein synthesis causing misreading of mRNA, premature termination of translation, and incomplete synthesized protein, creating nonfunctional proteins [24, 33].

*2.3.2 Antimicrobial activity*

Gram-negative bacteria such as *Pseudomonas aeruginosa*, *Proteus* species, *Escherichia coli*, *Klebsiella* species, *Enterobacter* species, *Serratia*, *Citrobacter*, and *Staphylococcus* species [24].

### *2.3.3 Pharmacokinetics*

See **Table 5**.

| | |
|---|---|
| Absorption | Intramuscular: rapid and complete<br>Oral: poorly absorbed<br>Time to peak: IM 30–90 minutes; IV: 30 minutes after 30-minute infusion |
| Distribution | Primarily into extracellular fluid, renal cortex. Poor penetration in cerebrospinal fluid (CSF) and ocular tissues<br>Vd: children: 0.35 L/kg; adults: 0.2–0.3 L/kg<br>Protein binding: <30% |
| Metabolism | Minimal metabolism |
| Excretion | Half-life elimination: adults 2 hours, renal failure: 41–24 hours<br>Urine: >70% as unchanged drug<br>Clearance is decreased in renal impairment |

**Table 5.**
*Pharmacokinetic parameters of gentamicin [24, 34, 35].*

### *2.3.4 Administration*

- IM: it should be administered by deep IM route.
- IV: infuse over 30–120 minutes [27].

### *2.3.5 Risk assessment*

During therapy with gentamicin, you should monitor parameters like: urinalysis, urine output, BUN, serum creatinine, plasma gentamicin levels (before and after the third dose), hearing tests before, during and after treatment especially in prolonged therapy [36, 37].

- Therapeutic peak: 5 and 12 μg/mL [36, 37].

### *2.3.6 Adverse effects*

- Nephrotoxicity: usual risk factors include preexisting renal impairment, concomitant nephrotoxicity drugs, advanced age, and dehydration. If nephrotoxicity occurs, it is better to discontinue therapy because the renal damage is usually reversible [24, 38].
- Ototoxicity: use with caution in patients with preexisting vertigo, tinnitus or hearing loss [24, 38].
- Neuromuscular blockade: aminoglycosides may inhibit prejunctional release of acetylcholine reducing postsynaptic sensitivity to the transmitter, and this reaction can follow intravenous, intramuscular or even oral administration of this antibiotics, especially with concomitant use of anesthesia and other neuromuscular blocking agents. It can be reversed by intravenous administration of calcium salt [24].

### *2.3.7 Principal drug interactions*

See **Table 6**.

| Drug | Risk rating | Interaction | Mechanism | Management |
|---|---|---|---|---|
| Amphotericin B | Monitor therapy | Amphotericin B may enhance the nephrotoxic effect of aminoglycosides | Unknown. Probably synergism [39] | Monitor renal function |
| Bisphosphonate derivatives | Monitor therapy | Aminoglycosides may enhance the hypocalcemic effect of bisphosphonate derivates [40] | Association of aminoglycosides with hypocalcemia, probably inhibition of the activity of the parathyroid glands reducing parathyroid hormone production [40, 41] | Monitor serum calcium, serum magnesium and serum creatinine and renal function during concomitant use |
| Furosemide, bumetanide, torsemide (loop diuretics) | Monitor therapy | Diuretics may enhance nephrotoxicity and ototoxicity of aminoglycosides | Uncertain. Damage in proximal tubular cells and decrease glomerular filtration rate. [42, 43] | Monitor toxic effects or avoid concomitant use except in life-threatening situations |

**Table 6.**
*Principal drug interactions of gentamicin.*

## 2.4 Rifampin

### *2.4.1 Mechanism of action*

Rifampin is a bactericidal drug that kills cell growing and it binds to the beta subunit of DNA-dependent RNA polymerase (rpoB) to form a drug-enzyme complex blocking the chain formation in RNA transcription [44].

### *2.4.2 Antimicrobial activity*

It inhibits most Gram-positive bacteria and Gram-negative microorganisms such as *Escherichia coli*, *Pseudomonas*, *Proteus*, and *Klebsiella*, and also it is active again *Neisseria meningitidis*, *Haemophilus influenzae*, and *Mycobacterium tuberculosis* [44].

### *2.4.3 Pharmacokinetics*

See **Table 7**.

| | |
|---|---|
| Absorption | Oral: well absorbed (bioavailability 68%). Food may delay or reduce peak by one-third. It should be taken on an empty stomach<br>Time to peak serum: oral: 2–4 hours |
| Distribution | Good penetration into many tissues and crosses CSF<br>Vd: 53 L/kg<br>Protein binding: 80% |
| Metabolism | Microsomal B-esterases and cholinesterases. Also, 85% liver metabolism (potently induction CYP 1A2, 2C9, 2C19 and 3A4) and enterohepatic recirculation |
| Excretion | Half-life elimination: 3–4 hours, prolonged with hepatic impairment feces (60%) and urine (30%) as unchanged drug |

**Table 7.**
*Pharmacokinetic parameters of rifampin [34, 44–46].*

*2.4.4 Administration*

- IV: administer IV preparation by slow infusion rate IV over 30 minutes to 3 hours, monitor administration to prevent extravasation.
- Do not administer IM or SC.
- Oral: administer on an empty stomach with a glass of water to increase absorption [44].

*2.4.5 Risk assessment*

During the therapy with rifampin, it should be monitored with periodical liver function test, CBC, and therapeutic drug monitoring of rifampin [47].

*2.4.6 Adverse effects*

- Hypersensitivity reactions: cases of severe cutaneous adverse reactions like Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug reaction with eosinophilia. It is mediated by hypersensitivity type I (IgE). It requires discontinue of therapy and management of the symptoms [48].
- Flu-like syndrome: symptoms of fever, chills, headache related with the use of oral rifampin. It is related with regimens of >600 mg once or twice weekly, and it resolves spontaneously. Flu-like syndrome is mediated by hypersensitivity type III (antibodies against rifampicin IgM that produce immunocomplex) [48, 49].
- Hematologic effects: it may cause thrombocytopenia, leukopenia, or anemia. The platelets are damaged by complement activation following the formation of drug-antibody complex [48, 50].
- Hepatotoxicity: it may cause hepatic dysfunction especially if it is used with other hepatotoxic agents [44].

*2.4.7 Principal drug interactions*

Most of the interactions of rifampin are because it is a strong inducer of CYP3A4 and CYP2C19, moderate inducer of CYP2C8 and CYP2C9, and P-glycoprotein inducer (**Table 8**) [51].

*2.4.8 Important*

- In children, pregnant or lactating women rifampin should not be used except where tetracyclines are contraindicated or when there are limitations on the use of streptomycin or gentamicin and it should not be used alone [1, 6, 9].
- It can be an alternative treatment for doxycycline or aminoglycosides, but the use of rifampin should be restricted in endemic areas of tuberculosis because monotherapy with rifampin can lead to the selection of resistant *Mycobacterium tuberculosis* strains [1, 3, 6, 9].

| Drug | Risk rating | Interaction | Mechanism | Management |
|---|---|---|---|---|
| Apixaban | Avoid combination | Rifampin is a strong inducer CYP3A4 and may decrease the serum concentration of apixaban | Induction of the CYP3A4-mediated metabolism of apixaban [52] | Avoid concurrent use |
| Esomeprazole | Avoid combination | Rifampin may decrease the serum concentration of esomeprazole | Rifampin induction of CYP3A4- and CYP2C19-mediated esomeprazole metabolism [53] | Avoid concomitant use |
| Risperidone | Consider therapy modification | Rifampin is a CYP3A4 inducer that may decrease the serum concentration of risperidone [46] | Unknown. Enzyme-inducing drugs may decrease risperidone [54] | Consider increasing the dose of oral risperidone (no more than double the original dose) if a CYP3A4 inducer is initiated |

**Table 8.**
*Principal drug interactions of rifampin [55].*

## 2.5 Ciprofloxacin

### *2.5.1 Mechanism of action*

The fluoroquinolones inhibit two bacterial enzymes: DNA gyrase (in many Gram-negative bacteria) and topoisomerase IV (in many Gram-positive bacteria) blocking the DNA bacterial replication. This action results in damage of bacterial DNA and cell death being bactericidal agents [56, 57].

### *2.5.2 Antimicrobial activity*

It is a bactericidal agent against *Proteus*, *E. coli*, *Klebsiella*, *Salmonella*, *Shigella*, *Enterobacter*, and *Campylobacter* [56].

### *2.5.3 Pharmacokinetics*

See **Table 9**.

| | |
|---|---|
| Absorption | Oral: well absorbed<br>Bioavailability: 70%. Avoid taking with most antacids and milk |
| Distribution | Widely distributed in kidneys, gallbladder, liver, lungs, gynecological tissue, and prostatic tissue<br>Protein binding: 20–40%<br>Vd: 2.1–2.7 L/kg |
| Metabolism | Poor hepatic metabolism and forms 4 metabolites, inhibitor of CYP1A2 |
| Excretion | Half-life elimination: children: 4–5 hours and adults: 3–5 hours, prolonged in older adults and in renal impairment<br>Urine 50% as unchanged drug), feces (15%) |

**Table 9.**
*Pharmacokinetic parameters of ciprofloxacin [55, 56].*

*2.5.4 Administration*

- Oral: administer with food to minimize GI symptoms, avoid antacid use, milk, yogurt or calcium-fortified juices alone.

- IV: administer by slow IV infusion over 60 minutes [56].

*2.5.5 Risk assessment*

During the treatment with ciprofloxacin parameters like: CBC, renal and hepatic function, signs and symptoms of tendonitis should be monitored [56].

*2.5.6 Adverse effects*

- Gastrointestinal: nausea, vomiting, and abdominal discomfort [56].

- Neurologic: headache and dizziness, peripheral neuropathy, it can occur at any time during treatment and can last for months to years after finishing the treatment [58].

- Musculoskeletal: tendon rupture or tendinitis usually of the Achilles tendon, arthralgias, and join pain are reported, especially in ancient people and patients taking corticosteroids [59, 60].

- QT interval prolongation and arrhythmia: it may be produced by inhibition of potassium channels encoded by the KCNH2 gene (HERG gene). Ciprofloxacin use should be avoided in patients with a history of QT prolongation, torsade de pointes, uncorrected hypokalemia, cardiac disease or concomitant use of other medications that prolong the QT interval [56, 61].

*2.5.7 Principal drug interactions*

See **Table 10**.

| Drug | Risk rating | Interaction | Mechanism | Management |
|---|---|---|---|---|
| Antacids, multivitamins and minerals like folate and iron | Consider therapy modification | Antacids may decrease the absorption of quinolones | The carbonyl functional groups on the antibiotic forms a chelate with the cations of the antacid resulting in inactive antimicrobials [62, 63] | Avoid concurrent administration of quinolones and antacids or quinolones should be administered at least 2 hours before or 2 hours after antacids or 6 hours after multivitamins |
| Theophylline | Consider therapy modification | Quinolones may decrease the metabolism of theophylline | Quinolone inhibition of CYP1A2 and CYP3A4 isoenzymes limiting the metabolism of theophylline [64, 65] | Consider a reduction in the dosage of theophylline (25–50%) during the concurrent use to minimize the theophylline toxicity |

**Table 10.**
*Principal drug interactions of ciprofloxacin.*

### *2.5.8 Important*

- It may be useful in the setting of drug resistance, antimicrobial toxicity, and some cases of relapse.

## 2.6 Trimethoprim-sulfamethoxazole (TMP/SMX)

### *2.6.1 Mechanism of action*

The combination of trimethoprim with sulfamethoxazole enhances the effectivity and synergist antimicrobial activity. TMP inhibits bacterial dihydrofolate reductase preventing the formation of tetrahydrofolic acid, and SMX is a structural analog of the para-aminobenzoic acid (PABA), and it binds to the dihydropteroate synthetase and competes with PABA to inhibit the synthesis of dihydrofolic acid [56, 66].

### *2.6.2 Antimicrobial activity*

The antibacterial spectrum is most *S. pneumoniae*, *S. aureus*, and *Staphylococcus epidermidis*, some *E. coli* according to the geographic region, *Proteus mirabilis*, *Klebsiella*, *Enterobacter*, also *Brucella abortus* [56].

### *2.6.3 Pharmacokinetics*

See **Table 11**.

| | |
|---|---|
| Absorption | Oral: rapid 90–100%, TMP is absorbed more rapidly than sulfamethoxazole, bioavailability of 85% |
| Distribution | Good penetration in middle ear fluid, sputum, vaginal fluid, and bronchial secretions<br>Vd: adults: 1.3 L/kg<br>Protein binding: SMX 70%, TMP 44% |
| Metabolism | Hepatic, SMX via CYP2C9 and also conjugated with glucuronide; TMP to oxide and hydroxy derivatives |
| Excretion | Half time elimination: TMP: children 3.7–5.5 hours and adults: 6–11 hours. SMX 9–12 hours<br>Both excreted in urine as metabolites and unchanged drug |

**Table 11.**
*Pharmacokinetic parameters of TMP/SMX [56].*

### *2.6.4 Administration*

- Oral: administer without regard to meals and a lot of water.

- IV: infuse over 60–90 minutes, and it is not administered by IM injection [56].

### *2.6.5 Risk assessment*

Some monitoring parameters during the treatment are CBC, serum potassium, creatinine, and BUN [56].

### *2.6.6 Adverse effects*

- Blood dyscrasias: agranulocytosis, aplastic anemia, leukopenia, or thrombocytopenia because of the margin between toxicity for bacteria and humans related with folate deficient [67].

- Neurologic effects: it is associated with adverse neurologic events like aseptic meningitis, tremor, delirium because TMP/SMX crosses the blood-brain barrier [67].

- Dermatologic reactions: severe reactions including Stevens-Johnson syndrome produced by immune-mediated idiosyncratic reactions associated with reactive metabolite leading to drug-specific antibodies [67].

- Hyperkalemia: it is produced because of the TMP similar structure to potassium-sparing diuretics. Potential risk factors include renal impairment, older age, and concomitant use of medications causing or exacerbating hyperkalemia [56].

### *2.6.7 Principal drug interactions*

See **Table 12**.

| Drug | Risk rating | Interaction | Mechanism | Management |
|---|---|---|---|---|
| Phenytoin | Consider therapy modification | TMP/SMX may increase the serum concentration of phenytoin | TMP inhibition of CYP2C8 and CYP2C9-mediated phenytoin metabolism [68] | Consider alternatives to this combination when possible |
| Warfarin | Consider therapy modification | TMP/SMX may enhance the anticoagulant effect of vitamin K antagonists | Multifactorial. Sulfonamide displacement of warfarin from protein binding sites, reductions in GI flora responsible for production of vitamin K [69, 70] | Monitor toxic effects of warfarin. Consider reducing warfarin dose by 10–20% prior starting the sulfonamide antibiotic and monitoring INR closely [71] |

**Table 12.**
*Principal drug interactions of TMP/SMX.*

### *2.6.8 Important*

- TMP-SMX may be used as an additional agent in complex cases of focal brucellosis, relapse, or refractory disease [2].

- 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 [21].

- It has been a popular choice and it is included in combination regimens around the world, due to its lower cost compared to other antimicrobials being the most cost-effective drug against brucellosis in developing countries [2].

- No alternative anti-brucellosis therapy for children under 8 years old has been reported, but there is a case that had a 2.5 years old patient with brucellosis

with TMP-SMX allergy, they use as an alternative for treatment ciprofloxacin having a good result of the treatment and continue follow up visits, but there are no evidence enough for this treatment, so it is necessary to search for alternative treatment for this patient population [12].

## 3. Other considerations about treatment

- Doxycycline is the drug of choice in the treatment of brucellosis, but antibiotic susceptibility patterns of *Brucella* appears to vary geographically, that is why tigecycline can be an option for treatment in brucellosis. Tigecycline is a glycylcycline derivate from tetracycline and minocycline. It has demonstrated activity against *Enterobacteriaceae*, Gram-positives, atypical, and anaerobes. It has the lowest minimal inhibitory concentration on in vitro efficacy models, and also it provided the better synergistic activity compared to doxycycline. Tigecycline can be a therapeutic alternative for brucellosis especially in patients in whom conventional antibiotics is contraindicated or limited because of the presence of severe comorbidities or drug-drug interactions, but it should be supported with more clinical studies [72].

- There are some regional experience and some different treatments that differs according the regional experiences but here are some considerations:

  - The World Health Organization (WHO) recommends the use of doxycycline for 6 weeks combined with rifampicin for 6 weeks, or streptomycin for 2–3 weeks, but this regimen has not been universally used in clinical practice. Even this fact it remains unclear what is the best regimen to be used and more clinical studies are needed in this regard [2].

  - From the comparison of regimens that can be established in randomized clinical trials are: doxycycline and streptomycin vs. doxycycline and rifampicin that favors the first combination in terms of relapse (OR 3.52; CI 95% = 2.14–5.81; $p < 0.001$); doxycycline and streptomycin vs. doxycycline and gentamicin is not statistically significant as regards either relapses (OR = 1.65; CI 95% = 0.53–5.15; $p = 0.386$); doxycycline and rifampicin vs. doxycycline and quinolone favors the first one (OR 3.92; CI 95% = 1.35–11.42; $p = 0.01$) [73].

  - The most effective regimen is combined doxycycline for 45 days with streptomycin for 14 days, in endemic areas where many patients have a mild form of the disease and diagnosis and prescription can be made in the urgency room the used to use gentamycin for the first 5–7 days [4, 73].

  - About the comparison of the efficacy of gentamicin for 5 days plus doxycycline for 8 weeks vs. streptomycin for 2 weeks plus doxycycline for 45 days in human brucellosis, there is a clinical trial that compare the efficacy showing that this treatment is not superior to the standard treatment regimen [74].

  - There are a few studies using doxycycline, rifampicin, and aminoglycosides vs. other regimens in uncomplicated brucellosis with no conclusions on the value of this triple therapy, also some studies were performed only in patients with osteoarticular complications. Another option for triple therapy is doxycycline,

rifampin, and amikacin (intramuscularly twice a day for 7 days) that have higher efficacy and more rapid action in terms of relief of symptoms, but it has no significant difference in drug side-effects and disease relapse, thus adding amikacin to the standard treatment regimen seems beneficial [6, 75].

## 4. Conclusion

In conclusion, there are some antibiotic therapies that are approved for the treatment of brucellosis, and some of them are in prolonged therapy that could affect the adherence of the patient and some of the antibiotics have important recommendations and need to be used in some conditions. Also, they have some parameters that may be monitorable to prevent adverse effects and to improve the outcome of the treatment in all the patients.

## Conflict of interest

The authors declare no conflict of interest.

## Notes/thanks/other declarations

None.

## Appendices and nomenclature

| | |
|---|---|
| CBC | complete blood count |
| GI | gastrointestinal |
| h | hours |
| IM | intramuscular |
| IV | intravenous |
| kg | kilograms |
| mg | milligrams |
| MIC | minimum Inhibitory concentration |
| TMP/SMX | trimethoprim-sulfamethoxazole |
| Vd | volume of distribution |

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## References

[1] Yousefi-Nooraie R, Mortaz-Hejri S, Mehrani M, Sadeghipour P. Antibiotics for treating human brucellosis. Cochrane Database of Systematic Reviews. 2012;**10**:CD007179. DOI: 10.1002/14651858.CD007179.pub2

[2] Ariza J, Bosilkovski M, Cascio A, Colmenero JD, Corbel MJ, Falagas ME, et al. Perspectives for the treatment of brucellosis in the 21st century: The ioannina recommendations. PLoS Medicine. 2007;**4**(12):e317. DOI: 10.1371/journal.pmed.0040317

[3] Tuon FF, Cerchiari N, Cequinel JC, Droppa EEH, Moreira SDR, Costa TP, et al. Guidelines for the management of human brucellosis in the state of Paraná, Brazil. Revista da Sociedade Brasileira de Medicina Tropical. 2017;**50**(4):458-464. DOI: 10.1590/0037-8682-0319-2016

[4] Skalsky K, Yahav D, Bishara J, Pitlik S, Leibovici L, Paul M. Treatment of human brucellosis: Systematic review and meta-analysis of randomised controlled trials. The British Medical Journal. 2008;**336**(7646):701-704. DOI: 10.1136/bmj.39497.500903.25

[5] Falagas ME, Bliziotis IA. Quinolones for treatment of human brucellosis: Critical review of the evidence from microbiological and clinical studies. Antimicrobial Agents and Chemotherapy. 2006;**50**(1):22-33. DOI: 10.1128/AAC.50.1.22-33.2006

[6] Alavi SM, Alavi L. Treatment of brucellosis: A systematic review of studies in recent twenty years. Caspian Journal of Internal Medicine. 2013;**4**(2):636-641

[7] Alp E, Doganay M. Current therapeutic strategy in spinal brucellosis. International Journal of Infectious Diseases. 2008;**12**(6):573-577. DOI: 10.1016/j.ijid.2008.03.014

[8] Alp E, Koc RK, Durak AC, Yildiz O, Aygen B, Sumerkan B, et al. Doxycycline plus streptomycin versus ciprofloxacin plus rifampicin in spinal brucellosis [ISRCTN31053647]. BMC Infectious Diseases. 2006;**6**(1):72. DOI: 10.1186/1471-2334-6-72

[9] Mani SR, Gunasekaran K, Iyyadurai R, Prakash JJ, Veeraraghavan B, Mishra A, et al. Clinical spectrum, susceptibility profile, treatment and outcome of culture-confirmed brucellosis from South India. Indian Journal of Medical Microbiology. 2018;**36**(2):289. DOI: 10.4103/ijmm.IJMM_18_236

[10] Castaño MJ, Navarro E, Solera J. Brucellosis, International Encyclopedia of Public Health. 2nd ed. Academic Press; 2017. pp. 281-295. ISBN: 9780128037089. https://doi.org/10.1016/B978-0-12-803678-5.00041-2

[11] Vollmar P, Zange S, Zöller L, Erkel J, Robert Thoma B. Brucellose. Deutsche Medizinische Wochenschrift. 2016;**141**(14):1014-1018. DOI: 10.1055/s-0042-101723

[12] Teker D, Tanir G, Ozmen S, Teke TA, Keles S, Bostancı I. Treatment of brucellosis in a young child with trimethoprim/sulfamethoxazole anaphylaxis. Journal of Infection and Public Health. 2014;**7**(6):553-556. DOI: 10.1016/J.JIPH.2014.07.004

[13] MacDougal C. Protein synthesis inhibitors and miscellaneous antibacterial agents. In: Shanahan JF, Lebowitz H, editors. Goodman & Gilman's: The Pharmacological Basis of Therapeutics. 13th ed. United States of America: Access Medicine, McGraw-Hill Medical; 2018

[14] Joshi N, Miller DQ. Doxycycline revisited. Archives of Internal Medicine. 1997;**157**(13):1421-1428

[15] Diseases C on I, Pediatrics of AA. 2015 Report of the Committee on Infectious Diseases Red Book®. 30th ed. 2015

[16] Ogawa R, Echizen H. Clinically significant drug interactions with antacids. Drugs. 2011;**71**(14):1839-1864. DOI: 10.2165/11593990-000000000-00000

[17] Nguyen VX, Nix DE, Gillikin S, Schentag JJ. Effect of oral antacid administration on the pharmacokinetics of intravenous doxycycline. Antimicrobial Agents and Chemotherapy. 1989;**33**(4):434-436

[18] Neuvonen PJ, Penttilä O. Interaction between doxycycline and barbiturates. British Medical Journal. 1974;**1**(5907):535-536

[19] Jaffe JM, Colaizzi JL, Poust RI, McDonald RH. Effect of altered urinarypH on tetracycline and doxycycline excretion in humans. Journal of Pharmacokinetics and Biopharmaceutics. 1973;**1**(4):267-282. DOI: 10.1007/BF01060035

[20] Colmenero JD, Fernández-Gallardo LC, Agúndez JA, Sedeño J, Benítez J, Valverde E. Possible implications of doxycycline-rifampin interaction for treatment of brucellosis. Antimicrobial Agents and Chemotherapy. 1994;**38**(12):2798-2802

[21] Solera J. Update on brucellosis: Therapeutic challenges. International Journal of Antimicrobial Agents. 2010;**36**:S18-S20. DOI: 10.1016/J.IJANTIMICAG.2010.06.015

[22] Solera J, Martínez-Alfaro E, Sáez L. Meta-analysis of the efficacy of the combination of +rifampicin and doxycycline in the treatment of human brucellosis. Medicina Clínica (Barcelona). 1994;**102**(19):731-738

[23] Bukhari EE. Pediatric brucellosis. An update review for the new millennium. Saudi Medical Journal. 2018;**39**(4):336-341. DOI: 10.15537/smj.2018.4.21896

[24] MacDougall C. Aminoglycosides. In: Brunton LL, Hilal-Dandan R, Knollmann BC, editors. Goodman & Gilman's: The Pharmacological Basis of Therapeutics. 13th ed. New York, NY: McGraw-Hill Education; 2017

[25] Kotra LP, Haddad J, Mobashery S. Aminoglycosides: Perspectives on mechanisms of action and resistance and strategies to counter resistance. Antimicrobial Agents and Chemotherapy. 2000;**44**(12):3249-3256

[26] Busse HJ, Wostmann C, Barker EP. The bactericidal action of streptomycin: Membrane permeabilization caused by the insertion of mistranslated proteins into the cytoplasmic membrane of Escherichia coli and subsequent caging of the antibiotic inside the cells due to degradation of these proteins. Journal of General Microbiology. 1992;**138**(3):551-561. DOI: 10.1099/00221287-138-3-551

[27] Edson RS, Terrell CL. The aminoglycosides. Mayo Clinic Proceedings. 1999;**74**(5):519-528. DOI: 10.4065/74.5.519

[28] Scholar E. Streptomycin. xPharm Compr Pharmacol Ref2007. pp. 1-6. DOI: 10.1016/B978-008055232-3.62678-9

[29] Falagas M, Kasiakou S. Toxicity of polymyxins: A systematic review of the evidence from old and recent studies. Critical Care. 2006;**10**(1):R27. DOI: 10.1186/cc3995

[30] Zhou Y-F, Tao M-T, Feng Y, Yang R-S, Liao X-P, Liu Y-H, et al. Increased activity of colistin in combination with amikacin against Escherichia coli co-producing NDM-5 and MCR-1. The

Journal of Antimicrobial Chemotherapy. 2017;**72**(6):1723-1730. DOI: 10.1093/jac/dkx038

[31] Henderson JL, Polk RE, Kline BJ. In vitro inactivation of gentamicin, tobramycin, and netilmicin by carbenicillin, azlocillin, or mezlocillin. American Journal of Hospital Pharmacy. 1981;**38**(8):1167-1170

[32] Holt HA, Broughall JM, McCarthy M, Reeves DS. Interactions between aminoglycoside antibiotics and carbenicillin or ticarillin. Infection. 1976;**4**(2):107-109

[33] Tangy F, Moukkadem M, Vindimian E, Capmau M-L, Le Goffic F. Mechanism of action of gentamicin components characteristics of their binding to *Eschevichiu coli* ribosomes. European Journal of Biochemistry. 1985;**147**:381-386

[34] Leggett JE. Aminoglycosides. In: Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 8th ed. US: Elsevier Health Bookshop; 2015. ISBN 9781455748013

[35] Pacifici GM. Clinical pharmacology of gentamicin in neonates: Regimen, toxicology and pharmacokinetics. MedicalExpress. 2015;**2**(5):1-9. DOI: 10.5935/MedicalExpress.2015.05.01

[36] Arup Laboratoties. Gentamicin, Random Level [Internet]. 2013. Available from: http://ltd.aruplab.com/tests/pub/0090130

[37] Medscape. Gentamicin Level: Reference Range, Collection and Panels, Background [Internet]. 2014. Available from: https://emedicine.medscape.com/article/2090086-overview

[38] Prayle A, Watson A, Fortnum H, Smyth A. Side effects of aminoglycosides on the kidney, ear and balance in cystic fibrosis. Thorax. 2010;**65**(7):654-658. DOI: 0.1136/thx.2009.131532

[39] Churchill DN, Seely J. Nephrotoxicity associated with combined gentamicin—Amphotericin B therapy. Nephron. 1977;**19**(3):176-181. DOI: 10.1159/000180883

[40] Mayordomo JI, Rivera F. Severe hypocalcaemia after treatment with oral clodronate and aminoglycoside. Annals of Oncology, the journal of the European Society for Medical Oncology. 1993;**4**(5):432-433

[41] Miller PD, Jamal SA, Evenepoel P, Eastell R, Boonen S. Renal safety in patients treated with bisphosphonates for osteoporosis: A review. Journal of Bone and Mineral Research. 2013;**28**(10):2049-2059. DOI: 10.1002/jbmr.2058

[42] Lawson DH, Tilstone WJ, Gray JM, Srivastava PK. Effect of furosemide on the pharmacokinetics of gentamicin in patients. Journal of Clinical Pharmacology. 1982;**22**(5-6):254-258

[43] Nakahama H, Fukuhara Y, Orita Y, Yamauchi A, Takama T, Kamada T. Furosemide accelerates gentamicin accumulation in cultured renal cells (LLC-PK1 cells). Nephron. 1989;**53**(2):138-141. DOI: 10.1159/000185726

[44] Gumbo T. Chemotherapy of tuberculosis, mycobacterium avium complex disease, and leprosy. In: Brunton LL, Hilal-Dandan R, Knollmann BC, editors. Goodman & Gilman's: The Pharmacological Basis of Therapeutics. 13th ed. New York, NY: McGraw-Hill Education; 2017

[45] Wilkins JJ, Savic RM, Karlsson MO, Langdon G, McIlleron H, Pillai G, et al. Population pharmacokinetics of rifampin in pulmonary tuberculosis patients, including a semimechanistic model to describe variable absorption. Antimicrobial Agents and Chemotherapy. 2008;**52**(6):2138-2148. DOI: 10.1128/AAC.00461-07

[46] Mahatthanatrakul W, Nontaput T, Ridtitid W, Wongnawa M, Sunbhanich M. Rifampin, a cytochrome P450 3A inducer, decreases plasma concentrations of antipsychotic risperidone in healthy volunteers. Journal of Clinical Pharmacy and Therapeutics. 2007;**32**(2):161-167. DOI: 10.1111/j.1365-2710.2007.00811.x

[47] Chawla PK, Udwadia ZF, Soman R, Mahashur AA, Amale RA, Dherai AJ, et al. Importance of therapeutic drug monitoring of rifampicin. The Journal of the Association of Physicians of India. 2016;**64**(8):68-72

[48] Martínez E, Collazos J, Mayo J. Hypersensitivity reactions to rifampin. Pathogenetic mechanisms, clinical manifestations, management strategies, and review of the anaphylactic-like reactions. Medicine. 1999;**78**(6):361-369

[49] Machado-Alba JE, Erazo-Bravo NJ, Gaviria-Mendoza A, Medina-Morales DA. Síndrome seudogripal en un paciente con terapia antituberculosa. Infection. 2016;**20**(3):176-179. DOI: 10.1016/j.infect.2015.11.002

[50] Verma AK, Singh A, Chandra A, Kumar S, Gupta RK. Rifampicin-induced thrombocytopenia. Indian Journal of Pharmacology. 2010;**42**(4):240-242. DOI: 10.4103/0253-7613.68432

[51] Chen J, Raymond K. Roles of rifampicin in drug-drug interactions: Underlying molecular mechanisms involving the nuclear pregnane X receptor. Annals of Clinical Microbiology and Antimicrobials. 2006;**5**:3. DOI: 10.1186/1476-0711-5-3

[52] Chang S-H, Chou I-J, Yeh Y-H, Chiou M-J, Wen M-S, Kuo C-T, et al. Association between use of non-vitamin K Oral anticoagulants with and without concurrent medications and risk of major bleeding in nonvalvular atrial fibrillation. Journal of the American Medical Association. 2017;**318**(13):1250. DOI: 10.1001/jama.2017.13883

[53] Park G, Bae SH, Park W-S, Han S, Park M-H, Shin S-H, et al. Drug-drug interaction of microdose and regular-dose omeprazole with a CYP2C19 inhibitor and inducer. Drug Design, Development and Therapy. 2017;**11**:1043-1053. DOI: 10.2147/DDDT.S131797

[54] Kim K-A, Park P-W, Liu K-H, Kim K-B, Lee H-J, Shin J-G, et al. Effect of rifampin, an inducer of CYP3A and P-glycoprotein, on the pharmacokinetics of risperidone. Journal of Clinical Pharmacology. 2008;**48**(1):66-72. DOI: 10.1177/0091270007309888

[55] Bolhuis MS, Panday PN, Pranger AD, Kosterink JGW, Alffenaar J-WC. Pharmacokinetic drug interactions of antimicrobial drugs: A systematic review on oxazolidinones, rifamycines, macrolides, fluoroquinolones, and beta-lactams. Pharmaceutics. 2011;**3**(4):865-913. DOI: 10.3390/pharmaceutics3040865

[56] MacDougall C. Sulfonamides, trimethoprim-sulfamethoxazole, quinolones, and agents for urinary tract infections. In: Brunton LL, Hilal-Dandan R, Knollmann BC, editors. Goodman & Gilman's: The Pharmacological Basis of Therapeutics. 13th ed. New York, NY: McGraw-Hill Education; 2017

[57] Drlica K, Zhao X. DNA gyrase, topoisomerase IV, and the 4-quinolones. Microbiology and Molecular Biology Reviews. 1997;**61**(3):377-392

[58] Etminan M, Brophy JM, Samii A. Oral fluoroquinolone use and risk of peripheral neuropathy: A pharmacoepidemiologic study. Neurology. 2014;**83**(14):1261-1263. DOI: 10.1212/WNL.0000000000000846

[59] Van der Linden PD, Sturkenboom MCJM, Herings RMC, Leufkens HMG, Rowlands S, Stricker BHC. Increased risk of achilles tendon rupture with quinolone antibacterial use, especially in elderly patients taking oral corticosteroids. Archives of Internal Medicine. 2003;**163**(15):1801-1807. DOI: 10.1001/archinte.163.15.1801

[60] Zabraniecki L, Negrier I, Vergne P, Arnaud M, Bonnet C, Bertin P, et al. Fluoroquinolone induced tendinopathy: Report of 6 cases. The Journal of Rheumatology. 1996;**23**(3):516-520

[61] Kang J, Wang L, Chen XL, Triggle DJ, Rampe D. Interactions of a series of fluoroquinolone antibacterial drugs with the human cardiac K+ channel HERG. Molecular Pharmacology. 2001;**59**(1):122-126

[62] Höffken G, Borner K, Glatzel PD, Koeppe P, Lode H. Reduced enteral absorption of ciprofloxacin in the presence of antacids. European Journal of Clinical Microbiology. 1985;**4**(3):345

[63] Shiba K, Sakai O, Shimada J, Okazaki O, Aoki H, Hakusui H. Effects of antacids, ferrous sulfate, and ranitidine on absorption of DR-3355 in humans. Antimicrobial Agents and Chemotherapy. 1992;**36**(10):2270-2274

[64] Prince RA, Casabar E, Adair CG, Wexler DB, Lettieri J, Kasik JE. Effect of quinolone antimicrobials on theophylline pharmacokinetics. Journal of Clinical Pharmacology. 1989;**29**(7):650-654. DOI: 10.1002/j.1552-4604.1989.tb03394.x

[65] Grasela TH, Dreis MW. An evaluation of the quinolone-theophylline interaction using the Food and Drug Administration spontaneous reporting system. Archives of Internal Medicine. 1992;**152**(3):617. DOI: 1001/archinte.1992.00400150127023

[66] Kalkut G. Sulfonamides and trimethoprim. Cancer Investigation. 1998;**16**(8):612-615

[67] Ho JM-W, Juurlink DN. Considerations when prescribing trimethoprim-sulfamethoxazole. Canadian Medical Association Journal. 2011;**183**(16):1851. DOI: 10.1503/CMAJ.111152

[68] Antoniou T, Gomes T, Mamdani MM, Juurlink DN. Trimethoprim/sulfamethoxazole-induced phenytoin toxicity in the elderly: A population-based study. British Journal of Clinical Pharmacology. 2011;**71**(4):544-549. DOI: 10.1111/j.1365-2125.2010.03866.x

[69] Schelleman H, Bilker W, Brensinger C, Han X, Kimmel S, Hennessy S. Warfarin with fluoroquinolones, sulfonamides, or azole antifungals: Interactions and the risk of hospitalization for gastrointestinal bleeding. Clinical Pharmacology and Therapeutics. 2008;**84**(5):581-588. DOI: 10.1038/clpt.2008.150

[70] Lane MA, Zeringue A, McDonald JR. Serious bleeding events due to warfarin and antibiotic co-prescription in a cohort of veterans. The American Journal of Medicine. 2014;**127**(7):657-663.e2. DOI: 10.1016/j.amjmed.2014.01.044

[71] Ahmed A, Stephens JC, Kaus CA, Fay WP. Impact of preemptive warfarin dose reduction on anticoagulation after initiation of trimethoprim-sulfamethoxazole or levofloxacin. Journal of Thrombosis and Thrombolysis. 2008;**26**(1):44-48. DOI: 10.1007/s11239-007-0164-z

[72] Dizbay M, Kilic S, Hizel K, Arman D. Tigecycline: Its potential for treatment of brucellosis. Scandinavian Journal of Infectious Diseases. 2007;**39**(5):432-434

[73] Solís García del Pozo J, Solera J. Systematic review and meta-analysis of randomized clinical trials in the treatment of human brucellosis. PLoS One. 2012;**7**(2):e32090

[74] Roushan MRH, Amiri MJS, Janmohammadi N, Hadad MS, Javanian M, Baiani M, et al. Comparison of the efficacy of gentamicin for 5 days plus doxycycline for 8 weeks versus streptomycin for 2 weeks plus doxycycline for 45 days in the treatment of human brucellosis: A randomized clinical trial. The Journal of Antimicrobial Chemotherapy. 2010;**65**(5):1028-1035

[75] Ranjbar M, Keramat F, Mamani M, Kia AR, Khalilian FO-S, Hashemi SH, et al. Comparison between doxycycline-rifampin-amikacin and doxycycline-rifampin regimens in the treatment of brucellosis. International Journal of Infectious Diseases. 2007;**11**(2):152-156