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# 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 combine 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 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 Poor cerebrospinal fluid penetration Protein binding: >90% Distribution volume 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 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 the 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 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) Protein binding: 34% Volume of distribution (Vd): 260 mL/kg
Metabolism	None known
Excretion	Half-time elimination: adults: 2–4, 7 hours, prolonged with renal impairment Urine: 29–89% as unchanged drug 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 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 Oral: poorly absorbed 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 Vd: children: 0.35 L/kg; adults: 0.2–0.3 L/kg Protein binding: <30%
Metabolism	Minimal metabolism
Excretion	Half-life elimination: adults 2 hours, renal failure: 41–24 hours Urine: >70% as unchanged drug 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 derivatives [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 Time to peak serum: oral: 2–4 hours
Distribution	Good penetration into many tissues and crosses CSF Vd: 53 L/kg 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 discontinuation 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 Bioavailability: 70%. Avoid taking with most antacids and milk
Distribution	Widely distributed in kidneys, gallbladder, liver, lungs, gynecological tissue, and prostatic tissue Protein binding: 20–40% 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 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 joint 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 Vd: adults: 1.3 L/kg 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 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 glycylicycline 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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