BRUCELLOSIS

CHI Formulary Development Project

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Abbreviations

APHIS	Animal & Plant Health Inspection Service
AST	Aspartate Transaminase
BMAT	Brucella Microagglutination Test
BMBL	Biosafety in Microbiological and Biomedical Laboratories
BSC	Biological Safety Cabinet
BSPB	Bacterial Special Pathogens Branch
CADTH	Canadian Agency for Drugs and Technologies in Health
CBC	Complete Blood Count
CDC	Centers for Disease Control and Prevention
CFIA	Canadian Food Inspection Agency
CFT	Complement Fixation Test
CLSI	Clinical and Laboratory Standards Institute
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
CSTE	Council of State and Territorial Epidemiologists
DSAT	Division of Select Agents and Toxins
EDTA	Ethylenediaminetetraacetic Acid
ELISA	Enzyme-Linked Immunosorbent Assay
EOC	Emergency Operations Center
ESR	Erythrocyte Sedimentation Rate
FAO	Food and Agricultural Organization
GLEWS	Global Early Warning System
GoR	Grade of Recommendation
HAS	Haute Autorité de Santé
HSCT	Hematopoietic stem cell transplantation
IQWIG	Institute for Quality and Efficiency in Healthcare
LoE	Level of Evidence
LPS	Lipopolysaccharide

LRN	Laboratory Response Network
MALDI-TOF MS	Matrix-Assisted Laser Desorption/Ionization Time-Of-Flight Mass Spectrometry
MIC	Minimum Inhibitory Concentration
MOH	Ministry of Health
MZCP	Mediterranean Zoonoses Control Programme
NICE	National Institute for Health and Care Excellence
NMFS	National Marine Fisheries Service
OIE	Organization for Animal Health
PBAC	Pharmaceutical Benefits Advisory Committee
PCR	Polymerase Chain Reaction
PEP	Post Exposure Prophylaxis
PPE	Personal Protective Equipment
RT-PCR	Reverse-Transcriptase Polymerase Chain Reaction
SAT	Standard Agglutination Test
SCT	Stem Cell transplant
S-LPS	Smooth Lipopolysaccharide
SoA	Strength of Agreement
SOT	Solid Organ Transplant
SPIDS	Saudi Pediatric Infectious Diseases Society
TMP/SMX	Trimethoprim–Sulfamethoxazole
WHO	World Health Organization
ZSAL	Zoonotic and Select Agent Laboratory

Executive Summary

Brucellosis, also known as **undulant fever** or **Malta fever**, is a zoonotic infectious disease caused by various species of the bacteria Brucella. It primarily affects animals such as cattle, goats, sheep, and swine, but it can also be transmitted to humans. Brucellosis typically occurs through consumption of infected animals' products including infected tissues and fluids like blood, urine and milk and consumption of infected dairy products. Contacts of skin or mucous membranes with animals infected tissues like placenta and miscarriage products and inhalation of infected aerosolized particles of tissues and fluids and fluids are also important routes of transmission.

Human brucellosis is generally caused by 4 Brucella species namely, B. melitensis (isolated from small ruminants such as sheep and goats, as well as camels), B. abortus (isolated from cattle), B. suis (isolated from swine), and B. canis (isolated from dogs). B. melitensis causes most of human brucellosis.

Clinical signs of brucellosis can be diverse and nonspecific, making diagnosis challenging. Common clinical manifestations include intermittent fever, night sweats, fatigue, and joint pain. Additionally, patients may experience flu-like symptoms such as headache, muscle aches, and weight loss.[1]

In chronic cases, brucellosis can affect various organs, leading to complications such as endocarditis, arthritis, or neurological involvement. Given the broad spectrum of symptoms, a thorough patient history, including occupational and travel-related exposures, is crucial.

Diagnosis often relies on a combination of clinical evaluation, serological tests, and microbiological culture. Serological tests, such as the Rose Bengal test, agglutination tests, and enzyme-linked immunosorbent assays (ELISA), are commonly used to detect antibodies against Brucella.[1] Culture of the bacteria from blood, bone marrow, or other tissues remains the definitive diagnostic method, although it may take several weeks for results.

Brucellosis management can be complex and may require a multidisciplinary approach involving infectious disease specialists, clinical pharmacists, and public health officials. The key to successful management is early diagnosis, appropriate antibiotic therapy, and a focus on prevention to reduce the incidence of this zoonotic disease.

Brucellosis is a significant public health concern in regions with close human-animal interaction and can have long-term health effects if not properly treated.

Brucellosis is most prevalent in regions where there is close contact between humans and livestock, including the Mediterranean Basin, the Middle East, parts of Central and South America, Africa, and Central Asia. These areas are considered

endemic for brucellosis, and the disease is a persistent problem. Saudi Arabia serves as one of the endemic countries grappling with the substantial public health and economic ramifications of brucellosis. Over the period from 2004 to 2012, the national registry of the Ministry of Health in Saudi Arabia documented a total of 37,477 reported cases of brucellosis, though there has been a recent decline in the number of cases in more recent years.[2]

Brucellosis is firmly entrenched in Saudi Arabia, as noted in the Ministry of Health's 2011 report, indicating an incidence of 18 cases per 100,000 individuals annually. A comprehensive seroprevalence study revealed an overall rate of 15% among the Saudi population, with a slightly lower seroprevalence of 10% in children aged 0 to 14 years.[3]

Due to its widespread occurrence, the Ministry of Health (MOH) in Saudi Arabia has designated brucellosis as a notifiable disease. Consequently, all health sectors are required to report cases of this disease.

Newer data from the MOH reveals an incidence rate of 6.77 cases per 100,000 population in 2020. This figure marks the lowest reported incidence over the past five years.[4,5]

Brucellosis remains endemic in Saudi Arabia, with its incidence surpassing that of both unindustrialized and industrialized countries. The prevalence of brucellosis in the Kingdom positions it as a significant health concern. Reports suggest that hospitalization is necessary for nearly 15% of patients.

The elevated prevalence of brucellosis in Saudi Arabia can be attributed to several factors. The nomadic way of life, which involves the rearing of animals, particularly sheep and camels, plays a pivotal role in disease transmission. A traditional belief in the perceived health benefits of consuming raw milk, especially from camels, contributes to the spread of the disease. High numbers of animals are being imported from regions in Africa where brucellosis is endemic, coupled with inadequate adherence to national and international guidelines for animal screening and quarantine measures. Practices such as raising different species, such as sheep and cattle, together, facilitate disease transmission.

Brucella spp. are small, gram negative, non-motile, non-spore-forming, rod shaped (coccobacilli) bacterial organisms. It is a zoonotic disease caused by the ingestion of raw unpasteurized milk from infected animals or close contact with their secretions. There are different animal reservoirs for different Brucella spp. that are known to cause human disease:[3]

Table 1. Transmission of Brucellosis

Species	Animal Host	Virulence
Brucella melitensis	Goats, sheep, camels	++++
Brucella abortus	Cows, other Bovidae animals and camels	+++
Brucella canis	Dogs	+
Brucella suis	Pigs	+

Additional species of Brucella, including Brucella ovis, Brucella neotomae, Brucella microti, and marine Brucella species (Brucella pinnipediae and Brucella cetaceae), are recognized; however, it is worth noting that only the marine species have been sporadically linked to human disease. They have the capacity to trigger human brucellosis, with a specific inclination for causing neurobrucellosis disease.

In Saudi Arabia and many neighboring countries, the most prevailing causative agent is B. melitensis, contributing to 70-90% of brucellosis cases. B. abortus ranks as the second most common pathogen responsible for the disease, while the other species are rarely associated with brucellosis.[2]

Transmission of these organisms to humans occurs via the following means:[3]

1. The ingestion of unpasteurized, raw milk or other dairy products, particularly soft cheeses, butter, and cream. It's noteworthy that hard cheeses, sour milk, and yogurt are less likely to transmit the disease due to the effects of propionic and lactic fermentation.
2. Direct contact with the secretions of infected animals or their products, such as placentas or aborted materials.
3. Airborne transmission of aerosolized materials through open wounds or mucous membranes, whether in animal enclosures or in laboratory settings when handling blood and other fluid cultures. It has been observed that direct contact with soil, animal feces, and dust contaminated with Brucella is associated with an elevated risk of infection.
4. Vertical transmission, sexual transmission, and breast milk transmission have been occasionally reported as potential routes of infection.

Moreover, Saudi Arabia, being the epicenter of Islam, attracts millions of pilgrims who converge at its mosques to partake in Hajj rituals and Omrah, potentially exposing them to brucellosis.

These factors collectively contribute to the persistence of brucellosis in Saudi Arabia, making it imperative for public health initiatives to address these challenges to effectively mitigate the disease's impact.

Periodic outbreaks of brucellosis can occur due to various factors, such as inadequate vaccination programs, suboptimal animal health management, and disruptions in healthcare services. These outbreaks may occur in both endemic and non-endemic regions.

Brucellosis is often underreported and underdiagnosed, making it challenging to estimate its global prevalence accurately. However, it remains a significant concern in many parts of the world, particularly in low- and middle-income countries.

People at the highest risk of brucellosis include farmers, ranchers, veterinarians, and laboratory workers who come into close contact with infected animals or their tissues. Occupational exposure is a significant risk factor, and measures to protect these workers are crucial.

Understanding the international prevalence and risk factors associated with brucellosis is essential for designing effective public health interventions and control strategies. These may include vaccination programs for livestock, promoting safe food practices, improving healthcare infrastructure, and raising awareness about the disease in both endemic and non-endemic regions. Public health efforts aim to reduce the burden of brucellosis and minimize its impact on human and animal health.

This report compiles all clinical and economic evidence related to Brucellosis management according to the relevant sources. The ultimate objective of issuing Brucellosis guidelines by the Council of Health Insurance is to update the IDF (CHI Drug Formulary) with **the best available clinical and economic evidence related to drug therapies, ensuring timely and safe access to Brucellosis patients in Saudi Arabia**.

Main recommendations issued by different Health Technology Assessment (HTA) bodies on the use of the current medications in brucellosis were reviewed and summarized under each drug therapy table in Section 2.0. These include the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), the Institute for Quality and Efficiency in Healthcare (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC).

The management of brucellosis involves a **multidisciplinary approach**. **Drug therapy is an integral component for the management of brucellosis.** The primary treatment for brucellosis is a prolonged course of antibiotics. Commonly used antibiotics include doxycycline and rifampin or doxycycline and streptomycin, administered for a duration of 6 weeks to several months. The choice of antibiotics and the duration of treatment may vary based on the patient's age, the severity of the infection, and the specific Brucella species involved.

Symptomatic treatment is essential to manage the various symptoms of brucellosis. This may include pain relievers for joint pain and fever, as well as rest and hydration.

Section 2.0 provides a full description of each pharmacological agent with final statements on the placement of therapy. All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) reflecting specific drug class role in the management of Brucellosis.

Major recommendations for suggested brucellosis treatments are summarized in the table below:

Table 2. SFDA-Registered Drugs for the Management of Brucellosis

Medication	Indication	Line of Therapy	Level of Evidence/ Recommendation	HTA Recommendations
Doxycycline	Acute Brucellosis	**1st**	Grade A	Positive Recommendation from HAS
Gentamicin	Acute brucellosis	**2nd**	Grade B	-
Ciprofloxacin	Acute brucellosis	**2nd**	Grade B	-
Co-trimoxazole	Acute brucellosis for children < 8 years old	**1st**	Grade A	-
Rifampicin	Brucellosis in pregnant women	**1st**	Grade A	Positive Recommendation from HAS
Ceftriaxone	Neurobrucellosis	**Alternative**	Grade A	-

Table 3. Non-SFDA Registered Drugs for the Management of Brucellosis

Medication	Indication	Line of Therapy	Level of Evidence/Recommendation
Streptomycin	Brucellosis	1st	Strong Recommendation

The report concludes with the addition of a key recommendation synthesis section, which emphasizes the utilization of each drug class for specific patient groups.

Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

1.1 KSA Guidelines

1.1.1 Saudi Pediatric Infectious Diseases Society (SPIDS) Clinical Practice Guidelines on the Prevention, Diagnosis, and Management of Brucellosis in Children (2014)

The purpose of these guidelines endorsed by the Saudi Pediatric Infectious Diseases Society (SPIDS) is to increase the awareness of pediatricians and other childcare providers, such as family medicine and general practitioners, about brucellosis, its varied clinical presentations and its impact on child health, to provide insight to the epidemiology of brucellosis in Saudi Arabia, the modes of transmission and preventive measures, and to set a standard scheme for the diagnosis, antimicrobial therapy, management and follow up of childhood brucellosis.[3]

Clinical presentation

Brucellosis manifests as a systemic infection encompassing a wide clinical spectrum, ranging from asymptomatic cases to severe and potentially fatal illnesses. The symptoms of brucellosis are predominantly nonspecific, with the primary clinical presentation being an acute febrile illness, with or without indications of localization. In general, infections caused by B. melitensis tend to be more severe than those induced by B. abortus. Human infections resulting from B. suis are also typically severe, while mild disease is commonly associated with B. canis, a species infrequently encountered in humans. The incubation period typically spans 2–4 weeks but can range from as low as 5 days to several months.

In most cases, children who are infected with brucellosis exhibit an acute to sub-acute clinical presentation, typically lasting for a period of 2 to 4 weeks.

The classic general symptoms associated with brucellosis comprise:

- Headache
- Myalgia or bone pain
- Anorexia and weight loss
- Profuse sweating
- Malodorous perspiration
- Depression or mood disorders

- Fever
- Arthralgia or arthritis

Key clinical signs often are:

- Fever
- Arthritis
- Enlargement of the liver (hepatomegaly)
- Enlargement of the spleen (splenomegaly)
- Stiffness in the neck
- Miscellaneous symptoms like skin rashes, cervical lymph node enlargement, drowsiness, periorbital swelling, and ataxia.

Other rare manifestations include:

- CNS meningitis, encephalitis, meningoencephalitis, brain abscess, and Guillain Barr syndrome
- Lung pneumonia
- Cardiac endocarditis and myocarditis
- Liver transaminasemia and abscess
- Spleen abscess
- Genitourinary epedidemo-orchitis and nephritis
- Eye uveitis
- Thyroid abscess
- Spine epidural abscess
- Hematologic immune thrombocytopenic purpura and hemophagocytic syndrome

Management

Management of brucellosis relies on adherence to the following criteria:

1. Using an antibiotic that has the ability to act intracellularly in an acidic media.
2. Using combined therapy.
3. Using antimicrobials for a prolonged duration according to the system involved.

Table 4. Drugs Used for Brucellosis and Their Dosages (Adapted from the SPIDS 2014 Guidelines)

Drug	Dosage
Rifampicin	20 mg/kg/day in two divided doses (max. 600 mg)
Doxycycline	5 mg/kg/day in two divided doses (max. 200 mg) (only for children more than 8 year of age)
TMP/SMX	10 mg of trimethoprim/kg/day (max. 480 mg)
Gentamicin	5-7.5 mg/kg/day IM or IV either as a single dose or three divided doses
Streptomycin	15 mg/kg IM or IV once daily (max. 1 g/ day) (only for children more than 8 year of age)
Ciprofloxacin	30 mg/kg/day in two divided doses (max. 1.5 g)

Combination regimens have yielded successful results in the management of brucellosis in children. These include:

- Rifampicin and TMP/SMX for children below 8 years of age.
- Doxycycline and TMP/SMX or rifampicin for children older than 8 years of age. This combination has been shown to have the highest success rate and should be used in children over 8 years to avoid the staining of the teeth in younger children.
- In serious infections, such as neurobrucellosis and endocarditis, three to five drugs need to be used for a longer period, usually for three to 12 months (table 5).
- Gentamicin for 7 days or streptomycin for 14 days can be used for patients requiring hospitalization.
- The use of streptomycin has been associated with a lesser degree of relapse but is not significantly superior.

Table 5. Treatments for Different Manifestations of Brucellosis (Adapted from the SPIDS 2014 Guidelines)

Disease	Therapy		Comments and duration of therapy
	Children < 8 years	Children > 8 years	
Common diseases: Acute brucellosis, *brucella* arthritis,	Rifampicin and septra OR rifampicin for 45	Doxycycline and rifampicin OR Doxycycline for 45	Hospitalized patients add

brucella osteomyelitis, *brucella* bacteremia	days and gentamicin for 7 days	days and streptomycin for 14 days OR Doxycycline for 45 days and gentamicin for 7 days	gentamicin for 5-7 days. Duration of therapy 6 weeks.
Serious illness: *Brucella* endocarditis	Rifampicin, septra, and ciprofloxacin	Doxycycline, septra, and rifampicin	Gentamicin for the initial two weeks. Surgical intervention is indicated. Duration of therapy is 3-9 months.
Neurobrucellosis	Rifampicin, septra, and ciprofloxacin	Doxycycline, septra, and rifampicin	Gentamicin for the initial two weeks. Ceftriaxone has shown some efficacy, and it is usually used in the initial therapy for 2-4 weeks. Duration of therapy is 3-6 months up to one year in complicated cases.

Monitoring response to therapy

Clinical response

All patients who are started on therapy for brucellosis should be followed closely in the clinic to monitor the persistence of the response and compliance to therapy. In patients who have CBC laboratory abnormalities, such as a positive blood culture and/or liver enzymes, they should have their tests repeated one week after starting therapy.

If culture yields a positive result, attention needs to be paid to the susceptibility pattern although most *brucella* isolates remain sensitive to the first line antibiotics.

Serology response

Brucella titers decline slowly and may remain moderately high for months. Therefore, there is no need to repeat a titer early during therapy. One serology titer should be repeated by the end of therapy to evaluate the trend and demonstrate a decrease in the titer.

Relapse

Among treated patients, 3e9% will have a relapse or reinfection. Most relapses occur in the first year following therapy. If an affected patient begins to have symptoms, serology and blood culture should be repeated. Sites that may be affected such as the CNS or heart should be examined fully.

Prevention

Public awareness about the endemicity of brucellosis in KSA should be increased. It is important to avoid all risk factors leading to acquiring brucellosis, which means stressing the importance of avoiding raw milk or its products and avoiding contact with sick animals.

Animal owners should be aware that brucellosis is prevalent among animals and thus regular checkups of these animals are required. Mixing different herds of animals together should be avoided as this may facilitate transmission.

Screening the family members of patients with acute brucellosis in endemic areas is strongly recommended to enhance the detection rate, to initiate early treatment and to reduce complications.

1.1.2 Saudi Pediatric Infectious Society (SPIDS) Brucella Infection: A Manual Guide and Atlas (2022)

In this Saudi Pediatric Infectious Disease Society (SPIDS) concise work done by a collaboration of many intrigued and experienced pediatric infectious disease consultants, one finds a complete knowledge of various aspects of pediatric brucellosis starting by a section on epidemiology and moving along microbiology to a detailed clinical presentation and ending by therapy and prevention. It also contains a special chapter dedicated to Brucella infection in neonates and immunocompromised hosts. This book chapter is intended to be an aid to all those who deal with brucellosis in children, pediatricians, pediatric residents, family physicians as well as pediatric infectious disease fellows.[5]

Clinical presentation of acute brucellosis

The onset of acute illness typically manifests with a gradual onset of symptoms, including fever, malaise, myalgia, and arthralgia. Additional manifestations encompass night sweats, characterized by a distinctive moldy odor, along with chills,

rigors, bone aches, low back pain, weight loss, fatigue, headache, dizziness, depression, and/or anorexia.

Fever, often high grade, follows an intermittent pattern and persists for days to weeks. While irregular undulation has been described, it is not a common feature in children. Brucellosis is considered among the differential diagnoses for fever of unknown origin.

Less frequently, patients may present with dyspepsia, mouth ulcerations, jaundice, and abdominal pain. Other reported manifestations include coughing, dyspnea, epistaxis, hemoptysis, lymphadenopathy, testicular pain, and scrotal swelling.

Physical findings are diverse and nonspecific. In confirmed cases of brucellosis in children, key signs include fever in over 90%, arthritis in 70% to 85%, hepatomegaly in 15% to 40%, and splenomegaly in 13% to 30%. Additional physical findings, although infrequent, may involve neurological signs, lymphadenopathy, skin rash, testicular swelling, and/or jaundice.

Brucellosis infection has the potential to affect one or more focal sites, with the likelihood of focal involvement varying widely. Almost any organ can be impacted by brucellosis, with the probability of focal involvement ranging from 6% to 92%.

Osteoarticular brucellosis

Bones and joints constitute the predominant sites of brucellosis, accounting for up to 80% of cases. Various syndromes, including sacroiliitis, spondylitis, peripheral arthritis, osteomyelitis, bursitis, and tenosynovitis, have been documented. Unlike adults, where sacroiliitis and spondylitis are more prevalent, childhood brucellosis commonly affects large peripheral joints like knees, hips, and ankles, although any joint can be involved.

Monoarthritis is a more frequent occurrence, manifesting in 70-90% of patients. Arthritis typically presents alongside fever, malaise, weight loss, and other systemic symptoms. Prominent features include limited joint movement, swelling, and tenderness, resembling other forms of pyogenic arthritis.

Brucella-associated osteomyelitis is infrequent in children, with reported occurrences ranging from 2% to 10%. Typically, it affects long bones and vertebrae. Lumbar vertebrae are more commonly involved than the thoracic and cervical spine. In some cases, it may be accompanied by a paravertebral abscess, although this is less common than spinal brucellosis.

Sacroiliitis is an uncommon manifestation in children, but when it does occur, it is unique to Brucella. Patients typically present with fever and back pain, often radiating down to the legs (sciatica). Children may exhibit reluctance to walk and bear weight on the extremity.

Additionally, a post-infectious spondyloarthropathy affecting multiple joints has been documented. This condition is believed to be induced by circulating immune complexes.

Conventional radiography in osteoarticular brucellosis is generally of limited utility, but ultrasound and MRI prove valuable in revealing involvement of the hip and vertebrae. Vertebral osteomyelitis is visibly evident on radionuclide scans through an increase in tracer uptake in the affected vertebra; however, MRI stands out as a superior diagnostic tool, providing a comprehensive view of the extent of destruction and any associated collections.

Synovial fluid aspiration is seldom necessary unless significant joint effusion is present. The fluid tends to be exudative, with Brucellae isolated in over half of the cases. Reactive arthropathy may emerge shortly after the initiation of antibiotic therapy, potentially indicating a Herxheimer-like reaction.

Most experts concur that the treatment of brucellosis involving the spine should be sustained for a minimum of three months.

Neurological brucellosis

Neurobrucellosis encompasses various neurological complications linked to brucellosis. While symptoms such as headache, mental inattention, and/or depression are common complaints in human brucellosis, true invasion of the nervous system is observed in only 2% to 6% of cases. In B. melitensis infection, direct invasion of the central nervous system occurs in about 5% of cases. Meningitis, meningoencephalitis, and/or seizures represent the most prevalent manifestations of neurobrucellosis. Brucella meningitis can manifest as either acute or chronic and often arises later in the disease course, although it may occasionally be the initial presentation.

Additional neurological complications encompass encephalitis, myelitis, neuritis, radiculopathy, mycotic aneurysms, increased intracranial pressure with papilledema, choreoathetosis, and ventriculoperitoneal shunt infection.

Psychological manifestations like depression can serve as a potential presentation of neurobrucellosis, particularly in adults. Autonomic dysfunction that leads to hypertension has also been reported. When examining cerebrospinal fluid (CSF), typical findings include lymphocytic pleocytosis, elevated protein levels, and often hypoglycorrhachia, which necessitates differentiation from central nervous system tuberculosis or other infections. Occasionally, CSF analysis may yield normal results. Positive cultures for Brucellae in cerebrospinal fluid are found in less than 50% of cases.

Confirmation of neurobrucellosis involves demonstrating Brucella antibodies through agglutination tests or enzyme-linked immunosorbent assays (ELISA). The

polymerase chain reaction (PCR) is considered the most sensitive method, given that other tests may yield negative results.

In pediatric neurobrucellosis, neuroimaging results can range from normal to various abnormalities, encompassing inflammatory and vascular changes, abscesses, and/or hydrocephalus.

Gastrointestinal brucellosis

Brucellosis, particularly when attributed to B. melitensis, is frequently transmitted through food. Systemic symptoms typically take precedence over gastrointestinal symptoms. Some patients may experience nausea, vomiting, and abdominal discomfort. Occasionally, rare cases involving ileitis, colitis, and spontaneous bacterial peritonitis have been documented.

The liver is a common site of involvement in brucellosis. Cases related to B. suis have been associated with hepatic abscesses and chronic suppurative lesions affecting the liver and other organs. In the context of brucellosis, reports include instances of acute and chronic cholecystitis, splenic infarcts, and splenic abscess.

Liver function tests may show normal or mildly elevated results. Histological changes in the liver can vary, but cases attributed to B. abortus may exhibit epithelioid granulomas that closely resemble lesions seen in sarcoidosis.

Cardiovascular brucellosis

Infective endocarditis stands out as the most prevalent cardiovascular manifestation and the leading cause of death resulting from brucellosis. This complication is reported in approximately 2% of cases and can affect both native and prosthetic heart valves. The aortic valve tends to be more frequently involved than the mitral valve. Myocarditis and pericarditis may occur independently or in conjunction with endocarditis.

Aneurysms of the sinus of Valsalva and other vascular structures are observed more commonly in cases where infection is attributed to B. suis. Mycotic aneurysms, typically affecting the middle cerebral artery, can manifest as a neurological complication of infective endocarditis.

Respiratory brucellosis

Cough is a prevalent symptom in cases of brucellosis; nonetheless, respiratory tract lesions are typically observed in fewer than 5% of cases in most reported series. The range of pulmonary involvement is extensive and encompasses pneumonia, pulmonary nodules, and empyema.

Brucellae are seldom detected on stains or grown from expectorated sputum. Therefore, a definitive diagnosis relies on isolating the organism from other anatomical sites.

Cutaneous brucellosis

Patients with brucellosis may exhibit diverse skin lesions, encompassing rashes, nodules, papules, erythema nodosum, petechiae, and purpura. Cutaneous ulcers, abscesses, and suppurative lymphangitis appear to be more prevalent in cases associated with B. suis.

Genitourinary brucellosis

Orchitis or epididymitis is a relatively frequent occurrence in adults with brucellosis but is uncommon in children. When it does manifest, it typically presents as a unilateral condition. Renal involvement in brucellosis is infrequent, and while Brucella can be detected in urine using appropriate techniques, it generally does not impair renal function. Nephritis or glomerulonephritis usually occurs in tandem with endocarditis.

Ophthalmic brucellosis

Direct ocular involvement is infrequent in cases of brucellosis. The most prevalent ocular manifestation is uveitis, which can manifest as chronic iridocyclitis, nummular keratitis, multifocal choroiditis, or optic neuritis. Brucella organisms have not been identified in the structures of the eye in humans. Several of these features are regarded as late complications, potentially mediated by the immune system.

Hematological abnormalities in brucellosis

Mild hematologic abnormalities, including anemia, lymphocytosis, and thrombocytopenia, may arise during the course of brucellosis, but they typically resolve promptly upon the initiation of antimicrobial therapy. In rare instances, more serious complications such as pancytopenia, thrombocytopenic purpura, hemolytic anemia, hemophagocytic lymphohistiocytosis, thrombotic thrombocytopenic purpura, and myelodysplastic syndrome have been reported. Occasionally, severe thrombocytopenia is associated with epistaxis, gingival bleeding, hematuria, and cutaneous purpura.

Clinical presentation of chronic brucellosis

Given the lack of a specific definition for chronic brucellosis by the United States Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO), clinicians commonly categorize patients with clinical manifestations persisting for more than one year after the diagnosis of brucellosis as having chronic brucellosis.

Laboratory findings and diagnosis of human brucellosis

The diagnosis of a patient suspected of having brucellosis necessitates a multifaceted approach, encompassing elements such as medical history, clinical examination, radiological investigation, and routine laboratory testing.

Accurate diagnosis of brucellosis is crucial for initiating timely and effective treatment. Moreover, it holds significant public health implications, signaling exposure to infected animals, consumption of contaminated food (meat and/or dairy products), and potential lapses in adhering to laboratory safety procedures.

A comprehensive evaluation should be conducted for all individuals suspected of having brucellosis. This includes a complete blood count (CBC), typically revealing normal results, although some patients may exhibit anemia, leukopenia, or pancytopenia. Inflammatory markers such as the erythrocyte sedimentation rate (ESR) are usually elevated, with values ranging modestly from 20 to 80 mm/h.

Liver function tests may indicate mild to moderate elevation of liver enzyme levels, particularly aspartate transaminase (AST), while high levels of bilirubin are infrequent but possible. Renal function tests typically yield normal results, although in rare cases, glomerulonephritis may occur, accompanied by variable elevations in creatinine and blood urea nitrogen.

Brucellosis specific tests

The laboratory diagnosis of brucellosis involves a combination of methods:

1. Direct diagnostic tests that rely on bacterial isolation and identification, as well as molecular techniques such as polymerase chain reaction (PCR)
2. Indirect methods, or immunological tests designed to detect the immune response to Brucella antigens.

Table 6. Diagnostic Modalities (Adapted from the SPIDS 2022 Brucella Book)

Diagnostic approach	Diagnostic test	Principle	Recommended use	Sample types
Direct	Culture	Isolation of organism from different specimen directly	To be cultivated in the new BACTEC or BacT/Alert bottles	Blood, synovial fluid, or other tissue that has focal infection
	NAAT usually PCR	Serum is the sample of choice for NAAT-based	Can be used for the diagnosis of brucellosis with focal	

		diagnosis of human brucellosis	complications such as neurobrucellosis	
Indirect (serology)	Tube standard agglutination test (SAT) or microplate agglutination	Detection of antibodies to smooth lipopolysaccharide	Widely used especially in acute cases	Serum
	2-mercaptoethanol test	Chemical inactivation of agglutinating capabilities of the IgM pentamer by 2-mercaptoethanol	Monitoring of the response to antimicrobial agent in already diagnosed patients; early detection of treatment failure by quantitating IgG level	
	Enzymatic-linked immunosorbent assay (ELISA)	Plates are usually sensitized with cytosolic protein antigens. It can be also applied for the detection of S-LPS.	Test of choice for complicated, focal, and chronic cases. Monitoring of the response to antimicrobial agent in already diagnosed patients; early detection of treatment failure by quantitating IgG level.	

Direct *Brucella* testing (isolation of *Brucella*)

Culture detection of Brucella species

Blood culture stands as a pivotal tool in diagnosing bloodstream infections. Historically, conventional blood culture methods faced challenges in detecting Brucella organisms from peripheral blood samples. Presently, automated blood

culture systems offer enhanced specificity and sensitivity in the detection of Brucella organisms. Isolation of Brucella from blood cultures has been reported in approximately 40-60%, reaching almost 92% in acute infections presenting within two weeks of illness.

Beyond blood, Brucella species can also be isolated from various biological specimens, including bone marrow, bone, tissues, pus, and sterile body fluids like cerebrospinal, synovial, and/or pleural fluids, attributable to the hematogenous spread of Brucella and bacterial seeding in distant organs.

The gold standard for diagnosing Brucella species involves isolating them from samples, and this approach is favored for several reasons:

1. The isolation of Brucella species from blood culture serves as a confirmation of the disease's presence in its early stages, especially when serological test results are negative, or antibody titers are low or borderline.
2. Culture is crucial for conducting identification and drug susceptibility testing when indicated.
3. The noteworthy advantage of isolating Brucella lies in establishing a robust diagnosis for patients with clinical presentations not initially suspected of brucellosis. This is particularly pertinent when the organism is detected from blood culture as part of the routine workup for non-specific febrile illness.

Factors affecting the yield of the cultures include:

1. Slow growth rate of the organism.
2. Low bacterial load in the blood.
3. Reduced CO2 emission.
4. Laboratory safety risks requiring level 3 biosafety facilities.
5. Need for well-trained technical personnel to ensure safety while dealing with live bacteria for identification and antimicrobial susceptibility testing.
6. Influence of the disease stage (acute, sub-acute, or chronic) and the presence of focal infection; sensitivity decreases in prolonged disease and with focal infections. Persons with chronic brucellosis are less likely to have positive Brucella cultures. For instance, culture yield is higher in the first 2 weeks of illness but decreases in longer-lasting illness. It can reach 90% in the early days of the infection when patients exhibit fever and chills, yet it falls to 30% in long-term disease.
7. Factors such as Brucella titer levels, culture technique, and prior antimicrobial therapy also significantly influence culture positivity rates.

Specimen collection

The dependability of test results is crucial for making precise diagnostic and treatment decisions. The accuracy of test findings relies on appropriate patient preparation, specimen collection, and specimen processing. The precision of test results is influenced by the integrity of the specimens.

Blood samples

For blood samples in adults, it is advisable to collect two sets of blood samples with a 20-minute interval. However, for infants and younger children, a 3 mL blood sample is adequate for culturing into a pediatric vial due to the significantly higher intensity of bacteremia in children for physiological reasons.

Inoculated vials must be transported to the laboratory and maintained at room temperature until they are introduced into the automated blood culture system (e.g., BACTEC 9240, BacT/Alert, and Vital systems). These vials should undergo incubation for up to 5 days. Nevertheless, in cases with a high index of suspension where a negative blood culture persists after 5 days, an extension of the incubation period up to three weeks is recommended.

Bone marrow

Collected bone marrow should be promptly sent to the laboratory, and inoculation of culture media should be carried out within 1 to 2 hours of obtaining the specimens. In instances of prolonged transport times, specimens should be kept moist and cooled to temperatures between 2 and 8 °C.

Cerebrospinal fluid (CSF)

More than 1 mL of cerebrospinal fluid (CSF) is drawn under aseptic conditions into a sterile, leak-proof container. It should be transported rapidly to the laboratory as soon as it is collected for bacterial culture or PCR testing.

Tissues, sterile body fluids, and abscess

Specimens, including tissues, sterile body fluids, and abscess fluid, need to be collected under aseptic conditions into a sterile container. In the case of tissues, the container should have several drops of sterile saline solution added to preserve moisture. It is imperative to submit these specimens to the laboratory within 1 to 2 hours of their collection.

Culturing methods and processing

Conventional methods

Brucella species thrive on standard solid culture media commonly employed in the everyday operations of clinical microbiology laboratories. To cultivate these bacteria successfully, the plate should undergo aerobic incubation for a period of up to 14 days at 35 °C within an atmosphere enriched with 5% to 10% CO2. It is crucial to

emphasize that all procedures must be meticulously executed within a class II biological safety cabinet.

Automated culture systems

The advanced and more contemporary automated culture systems are progressively supplanting traditional methods. Presently, the diagnosis of brucellosis often involves the utilization of third-generation continuous monitoring blood culture systems, exemplified by BACTEC 9240 and BacT/Alert. These systems embody safe and rapid technological advancements and are predominantly integrated into the infrastructure of most clinical microbiology laboratories.

Table 7. Culturing Systems for Brucellosis (Adapted from the SPIDS 2022 Brucella Book)

Conventional	Automated
Different agar plates (Selective supplement agar) with broth (enrichment) media	Liquid media (Blood culture bottle)
Incubated at 37°C with 5-10% CO_2, up to 14 days	Incubated for 5-7 days
Manual monitoring	Continuous monitoring by the instrument
Labor-intensive, skilled employee	Less labor work
Lack of sensitivity	More sensitive
Risk of laboratory acquired infection	Prevent laboratory-acquired infection

Brucella species identification

Brucellae can be discerned through a variety of both conventional and innovative techniques, encompassing phenotypic identification approaches like phage typing, cultures, biochemical tests, serological traits, and molecular methodologies.

Traditional phenotypic identification

- Colony Morphology: Brucella spp. typically exhibit growth on blood agar or chocolate agar after 48 to 72 hours of incubation. Colonies are characterized by their small size (0.5–1 mm in diameter), round shape, and variations in smooth or rough textures during bacterial growth. These colonies possess smooth margins, are nonhemolytic, convex, and translucent, presenting a distinctive pearly appearance.

  Brucella spp. are slow-growing, facultative, and capnophilic, signifying their dependence on CO2 for optimal growth.

- Microscopic Examination: Microscopically, Brucellae species manifest as short, slender, pleomorphic gram-negative coccobacilli.
- Phenotypic and Biochemical Characteristics: Brucella bacteria exhibit non-motility, non-toxigenicity, and non-sporulation. Positive reactions for oxidase, catalase, and urease, coupled with the absence of sugar fermentation, contribute to the phenotypic characterization. Despite these traits, the phenotypic diagnosis of brucellosis faces limitations due to the extended turnaround time and the potential exposure of laboratory staff to highly contagious bacteria.

Modern techniques in identification of Brucella species

- Molecular Techniques (Polymerase Chain Reaction (PCR)-Based Diagnosis)

  The polymerase chain reaction (PCR) technique has emerged as a recent and valuable tool in the diagnosis of brucellosis. It is employed for the direct detection of Brucella spp. in clinical samples or for identifying culture growth at subspecies levels.

  Various PCR methods are under development, contributing significantly to brucellosis diagnosis. Examples include single-plex and multiplex PCR, reverse-transcriptase polymerase chain reaction (RT-PCR), and the multiple-locus variable number of tandem repeats (MLVA)-based genotyping technique.

  Compared to traditional diagnostic methods for brucellosis, PCR-based tests offer advantages in terms of speed and sensitivity. RT-PCR, in particular, exhibits high sensitivity (93.5%) and specificity (97.7%) in diagnosing active brucellosis. Early diagnosis and the ability to predict clinical outcomes contribute to improved patient management.

  In situations where blood cultures prove impractical, such as chronic cases, PCR is valuable for diagnosing asymptomatic but highly exposed individuals, as well as relapsed cases regardless of the disease's duration or type. Contrasting with serological tests alone, the combination of PCR and enzyme-linked immunosorbent assay (PCR/ELISA) enables the direct quantification of PCR products by detecting nucleic acids instead of proteins. This combined approach is not only more specific and sensitive than PCR alone but is also easily performed, yields relatively quick results, and carries a lower risk of contamination. In recent years, it has gained widespread acceptance in the molecular diagnostics of brucellosis, especially in immunocompromised hosts.

- MALDI-TOF Technique

  Matrix-Assisted Laser Desorption/Ionization Time-Of-Flight mass spectrometry (MALDI-TOF MS) is a valuable tool for the identification of Brucellae spp. It can be applied directly to colonies of Brucella on solid media or from positive blood culture broth.

  The utilization of MALDI-TOF in Brucella identification is characterized by its rapidity, accuracy, and cost-effectiveness. This method is capable of identifying Brucella isolates at the sub-species level. However, it entails a certain level of risk, as it involves working with potentially live bacteria, potentially resulting in laboratory-acquired brucellosis. On rare occasions, there may be instances where this procedure mistakenly identifies Brucella as Ochrobactrum. Therefore, in areas where brucellosis is endemic, if Ochrobactrum is identified in the laboratory, confirmation through conventional and/or molecular methods should be sought.

- Antibiotic Susceptibility Testing

  Performing susceptibility testing for Brucella spp. is not recommended due to the absence of acquired antibiotic resistance against therapeutically effective drugs and to mitigate the risk of laboratory-acquired brucellosis. This type of testing should specifically be conducted in laboratories equipped with biocontainment level 3 biosafety cabinets.

  Various methods, including broth microdilution, agar dilution, and E-test strips, are employed for susceptibility testing. Given the slow growth and fastidious nature of Brucella, the minimum inhibitory concentration threshold is extrapolated from Clinical and Laboratory Standards Institute (CLSI) data for slow-growing bacteria such as Haemophilus spp. (Table 8).

Table 8. Clinical and Laboratory Standards Institute (CLSI) Breakpoints for MIC Testing of Brucella spp. (Adapted from the SPIDS 2022 Brucella Book)

Antimicrobial agent	S	R
Doxycycline	≤ 4	≥ 16
Rifampin	≤ 1	≥ 4
Gentamicin	≤ 4	
TMP-SMX	≤ 0.5	≥ 4
Ciprofloxacin and moxifloxacin	≤ 1	

It is essential to note that different methods may yield different results, emphasizing the need for caution and precision in susceptibility testing for Brucella.

Indirect testing of brucellosis

Serological diagnosis of brucellosis

Serological tests play a crucial role in addressing challenges associated with brucellosis diagnosis, such as the limited yield of culture, the requirement for biosafety level 3, and the need for highly skilled technicians to handle high-risk organisms.

The serological diagnosis of brucellosis relies on the reactivity of antibodies against the smooth lipopolysaccharide (S-LPS). The immunodominant S-LPS is a shared feature among all Brucella spp. pathogenic to humans, with the exception of B. canis and B. ovis (rough Brucella species), which naturally lack the O-chain component of S-LPS. Various immunological diagnostic tests, including enzyme-linked immunosorbent assay (ELISA), standard agglutination test (SAT), Rose Bengal test (RBT), complement fixation test (CFT), and/or indirect Coombs test, are employed for the detection of Brucella antibodies. Immunochromatographic lateral flow and indirect fluorescent antibodies are also utilized for this purpose.

Presently, SAT and ELISA stand out as the most widely employed serodiagnostic methods for human brucellosis in clinical laboratories.

Specimen collection

A volume exceeding 1 mL of whole blood should be gathered using ethylenediaminetetraacetic acid (EDTA) lavender tubes or serum (red-top) tubes and forwarded to the laboratory for brucellosis diagnostic testing.

Standard Agglutination Test (SAT)

- SAT is the prevailing method for diagnosing human brucellosis caused by B. abortus, B. melitensis, and B. suis species. This assay is effective in detecting antibodies to brucellar smooth lipopolysaccharide (S-LPS) and is particularly suitable for acute brucellosis. However, it cannot diagnose brucellosis caused by B. canis species as these bacteria lack S-LPS.
- The SAT assay involves measuring the agglutination titer of various serum dilutions against a standard concentration of a whole Brucella cell suspension. The test employs serum dilutions in the range of 1:20 through 1:20,480, with a positive diagnostic titer considered to be 1:160 when correlated with a positive clinical presentation. In endemic areas, a proposed cut-off of 1:320 enhances the specificity of SAT for the serodiagnosis of human brucellosis. A substantial majority of children with acute brucellosis (92%) exhibit titers of 1:320 or higher.
- **False-negative** results may occur due to the prevalence of non-agglutinating antibodies or the prozone phenomenon. In cases of suspected false negatives

based on clinical and/or epidemiological reasons, SAT should be repeated at least 2-3 weeks apart.

- **False positives** can result from cross-reactive IgM of other bacteria or the persistence of IgM antibodies in cured patients despite an adequate response to antimicrobial therapy. Consequently, the interpretation of SAT tests for brucellosis is impacted by limited specificity.
- Combining SAT with the 2-mercaptoethanol agglutination test to degrade IgM antibodies, leaving the IgG isotype, proves useful for distinguishing acute from chronic brucellosis. Elevated antibody titers may indicate disease reactivation, while declining IgG titers signify an adequate response to treatment.
- **Limitations of SAT** for brucellosis include its inability to detect B. canis, false-negative results in the early stages of the disease, or the presence of blocking antibodies. False positives, stemming from cross-reactivity with IgM of other bacteria, and the lack of seroconversion due to the prozone phenomenon can be addressed by using serum dilutions above 1:1280.

Enzyme-Linked Immunosorbent Assay (ELISA)

- The ELISA assay stands out as one of the most extensively employed serodiagnostic tests for human brucellosis. This test is conducted in 96-well microtiter plates pre-coated with a standardized Brucella antigen, typically purified LPS.
- ELISA assays are versatile, capable of measuring various reactive antibodies, including IgM, IgG, and IgA. Consequently, ELISA is the preferred method for distinguishing between acute and relapsing infections and evaluating the response to therapy. It is also recommended for patients with complicated, focal, and chronic infections, as well as for detecting antibodies in cerebrospinal fluid (CSF) specimens in the serodiagnosis of neurobrucellosis. Epidemiological surveys widely adopt ELISA due to its effectiveness in identifying specific immunoglobulin isotypes.
- False-negative results for IgM may occur due to an excess of IgG, while false-positive results for IgM may be attributed to the presence of rheumatoid factor. The sensitivities and specificities of ELISAs exhibit variable ranges depending on study circumstances, but the combined sensitivity and specificity of ELISA for IgG and ELISA for IgM are comparable to the SAT assay.
- The ELISA technique is the recommended test for diagnosing brucellosis relapse due to its ability to differentiate IgG, IgM, and IgA and to detect relapse infection or assess the response to therapy.

Other indirect tests for diagnosis of brucellosis

In recent times, alternative assays have been developed as rapid, point-of-care tests designed for bedside use, providing immediate results. Examples include:

- Dipstick Assay:

  A strip of nitrocellulose featuring S-LPS derived from B. abortus antigen is applied in a distinct line.

- Lateral Flow Assay (LFA):

  A modified version of an ELISA contained in a suitable plastic device, capable of detecting anti-human IgM and anti-human IgG.

- Monospecific Antisera:

  Commercial kits comprising standardized, attenuated, stained, smooth, and specific antigen suspensions of Brucella. These kits exhibit specific reactivity toward antibodies to B. abortus and B. melitensis. The recent introduction of synthetic antigens holds promise for enhancing the sensitivities and specificities of future tests.

  Rapid, point-of-care assays for brucellosis are characterized by their high sensitivity, rapidity, and the ability to provide results within a few minutes. These assays are employed for screening suspected brucellosis patients, but it is essential to confirm the results through SAT or other serological tests.

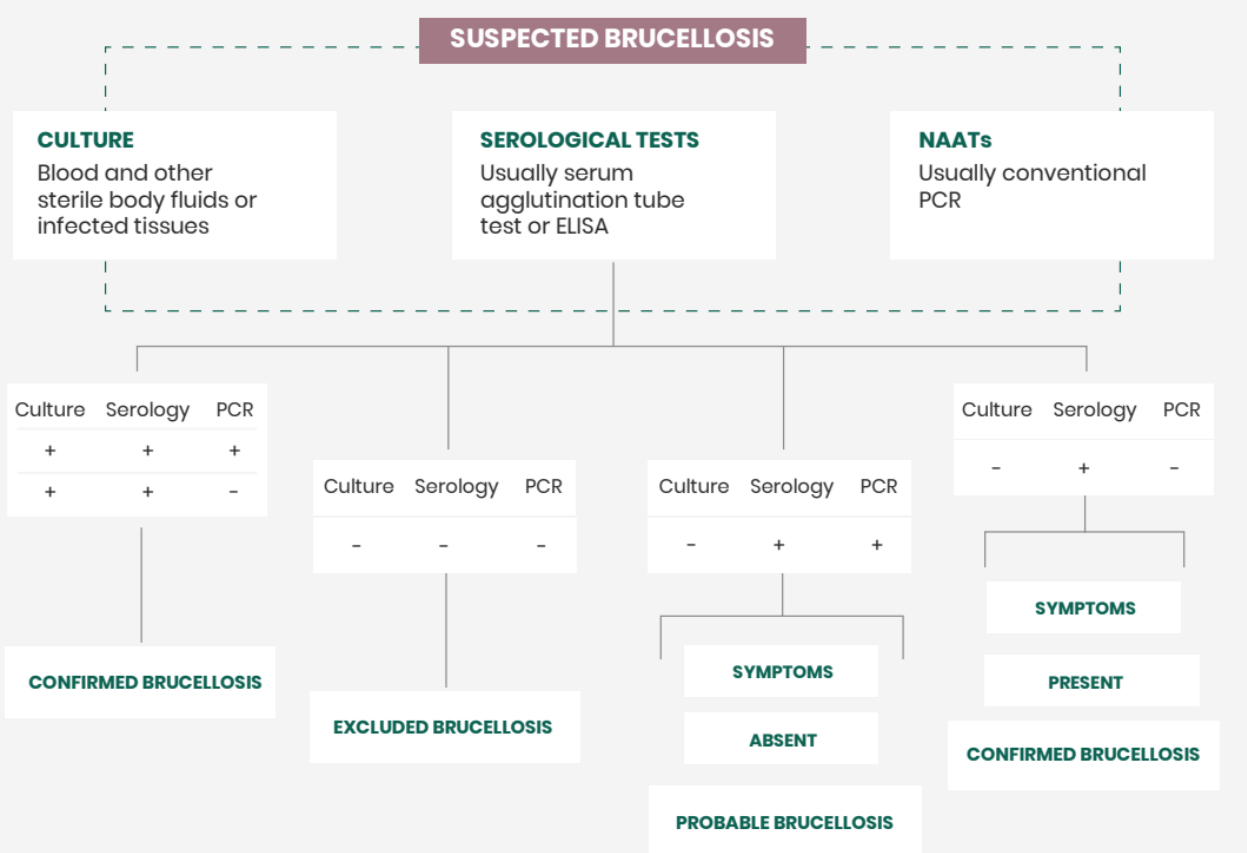

Figure 1. *Diagnostic algorithm for human brucellosis (retrieved from the SPIDS 2022 Brucella book)*

Treatment of human brucellosis

Upon confirming the diagnosis of brucellosis, a crucial decision must be made regarding whether the patient should receive outpatient or inpatient management. Hospitalization should be considered in the following situations:

1. For sick or visibly unwell patients
2. For patients unable to tolerate oral medications,
3. In cases of complicated brucellosis, such as neurobrucellosis, endocarditis, osteomyelitis, and/or arthritis with joint effusion that necessitates joint aspiration or surgical intervention. In the absence of these indications, outpatient treatment is generally deemed appropriate.

The treatment of Brucella infections is limited to a select number of antibiotics; however, the success rate of treatment is typically high and approaches 90%–95%.

To effectively treat human brucellosis, antibiotics capable of penetrating macrophages and functioning in the acidic intracellular environment are essential. Recommended antibiotics for this purpose include doxycycline, rifampicin,

trimethoprim–sulfamethoxazole (TMP/SMX or Bactrim), streptomycin, gentamicin, and fluoroquinolones.

For **children**, successful outcomes have been observed with specific combinations, such as **rifampicin** and **TMP/SMX** for those below 8 years of age, and either doxycycline and TMP/SMX or rifampicin for children older than 8 years of age. These combinations have demonstrated high success rates in various studies, including randomized control trials and meta-analyses.

In uncomplicated cases, evidence suggests that combination therapy should be maintained for a minimum of 6 weeks. However, for severe infections like neurobrucellosis and endocarditis, a combination of 3-5 drugs is typically required for an extended period, often ranging from 3 to 12 months.

For hospitalized patients, gentamicin for 7 days or streptomycin for 14 days may be utilized. These recommendations are based on multiple studies and are supported by randomized control trials and meta-analyses.

Table 9. Treatment of Brucellosis (Adapted from the SPIDS 2022 Brucella Book)

System	Antimicrobial of choice	Alternative regimens	Duration of therapy	Comments
Non-severe disease Acute brucellosis with non-localized disease or Brucella bacteremia	≥ 8 years: Doxycycline + TMP/SMX Or Doxycycline + rifampicin < 8 years: TMP/SMX + rifampicin	Ciprofloxacin + rifampicin Or ≥ 8 years: Doxycycline + TMP/SMX	6 weeks	Consider Gentamicin for 5-7 days for hospitalized patients with bacteremia. Fluoroquinolones combinations are associated with higher relapse rates compared to other regimens.
Brucella arthritis/ spondylitis/ sacroiliitis	≥ 8 years: Doxycycline + TMP/SMX + gentamicin Or Doxycycline + rifampicin + gentamicin < 8 years: TMP/SMX + rifampicin + gentamicin	Ciprofloxacin + rifampicin	12 weeks	Consider Gentamicin for 7 days.
Severe or complicated disease				
Brucella osteomyelitis	≥ 8 years:		4 – 6 months	Consider Gentamicin or Streptomycin for 2

	Doxycycline + TMP/SMX + rifampicin + gentamicin < 8 years: TMP/SMX + rifampicin + ciprofloxacin + gentamicin			weeks. Surgical intervention in cases of abscess formation.
Brucella endocarditis	≥ 8 years: Doxycycline + TMP/SMX + gentamicin Or Doxycycline + rifampicin + gentamicin < 8 years: TMP/SMX + rifampicin + gentamicin		3 – 9 months	Gentamicin in the first 2 weeks. Surgical intervention is associated with significant reduction in mortality. It is indicated in endocarditis and mycotic endovascular infections.
Neurobrucellosis	≥ 8 years: Doxycycline + TMP/SMX + rifampicin + gentamicin < 8 years:	Ceftriaxone in place of gentamicin	3-6 months (up to one year in complicated cases). 6 weeks to 6 months (for Brucella shunt infection).	3 to 4 drug regimens are advised. Gentamicin in the first 2 weeks. Ceftriaxone showed some efficacy, used in the first for 2-4 weeks. Duration: Guided by CSF

	TMP/SMX + rifampicin + ciprofloxacin + gentamicin			clearance and clinical response. Brucella shunt infection: Shunt removal. Duration: Based on the clinical and microbiological response
Pulmonary brucellosis	≥ 8 years: Doxycycline + rifampicin < 8 years: TMP/SMX + rifampicin	Ciprofloxacin + rifampicin	6 weeks	Consider Gentamicin for 7 days. Pleural effusion and surgical resection of pulmonary nodules to be considered.

Other therapeutic considerations

In certain situations, surgical intervention may be deemed necessary to expedite the response to medical therapy and avert complications. This intervention is warranted in cases of abscesses that significantly impact physiological function or do not respond to medical treatment, such as spinal abscesses or paraspinal collections leading to neurological deficits. Surgical involvement is also essential in instances of endocarditis with substantial vegetation, as seen in many cases of brucellosis endocarditis. Conditions involving valvular dysfunction, annular abscess, mycotic aneurysm, and septic emboli also necessitate surgical interventions. Studies in adults indicate that early surgical intervention correlates with a notable reduction in mortality.

Corticosteroids may serve as a beneficial adjunct to antibiotics in children with confirmed Brucella meningitis, myelitis, radiculopathy, cranial nerve palsy, optic neuritis, uveitis, and certain autoimmune diseases like hemolytic anemia, thrombocytopenia, and pancytopenia.

The use of immunomodulator therapy, including Levamisole and interferon alpha, in adults has yielded mixed results, and therefore, their utilization is not recommended.

Follow up of patients with brucellosis

Overview

Despite significant advancements in scientific and medical technology, the clinical diagnosis, rapid laboratory detection, therapy, and follow-up of human brucellosis continue to pose challenges. The disease tends to persist and relapse, contributing to ongoing medical concerns. Various factors, such as a broad spectrum of clinical manifestations, antimicrobial resistance, variable pathogenicity among different strains, and the absence of standardized and efficient laboratory testing, as well as a reliance on mono-therapeutic approaches, have been implicated in inadequate treatment, prolonged follow-up, and a high relapse rate in clinically healthy brucellosis cases.

The overarching objective of medical therapy for brucellosis is to manage the illness effectively, preventing complications, relapse-related sequelae, and mortality.

Typically, post-treatment follow-up for brucellosis patients involves a comprehensive approach. This includes a thorough patient history, clinical examination, blood cultures, serological tests, and nucleic acid amplification assays to ensure a comprehensive evaluation of the patient's condition.

Clinical response of patients with brucellosis

Patients typically exhibit a prompt response to therapy for Brucella infection. Acute brucellosis, when devoid of neurobrucellosis or Brucella endocarditis, is more

prevalent and can often be effectively managed on an outpatient basis, even in individuals with bacteremia. Improvement is commonly observed within 3-7 days of initiating therapy. The majority of patients with brucellosis tend to achieve complete recovery over a few weeks to months following appropriate treatment. Close monitoring and follow-up are strongly recommended to ensure the sustained therapeutic response and adherence to brucellosis therapy. It is crucial to pay special attention to medication side effects, as these can potentially lead to premature discontinuation of therapy.

Over time, abnormalities in the CBC typically normalize. In cases where a culture yields positive results, careful consideration should be given to the susceptibility pattern, even though the majority of Brucella isolates generally remain sensitive to first-line antibiotics.

Short- and long-term follow-up for patients with brucellosis

The follow-up course is typically tailored to the particular manifestation of brucellosis.

For patients presenting with febrile illness without focalization or with simple focalization, such as arthritis, short-term follow-up is usually recommended.

On the other hand, patients with neurobrucellosis, endocarditis, hepatosplenic brucellosis, osteomyelitis, spondylitis, or those requiring combined follow-up with other specialties generally necessitate long-term follow-up. (Table 10)

Diagnostic tests during follow-up of patients with brucellosis

- **Culture**: In cases where the blood culture yields an initial positive result, it should be repeated within 3-5 days of therapy initiation to confirm the achievement of sterile conditions. If the culture remains positive, hospitalization is recommended for intravenous therapy and a comprehensive assessment for any focal infection. Additionally, antibiotic susceptibility should be assessed, and the administration of appropriate antibiotics should be initiated.
- **Serology**: Follow-up serological testing is typically conducted 4-6 weeks after the commencement of appropriate therapy. While a decrease in serological markers is usually observed, the extent of reduction may not be highly significant. Monitoring the therapeutic response is more accurately achieved by observing the decline in IgG levels, given that IgM may persist for 1-2 years. Consequently, in cases where titers persistently remain elevated, differentiation of the immunoglobulin response should be performed. This can be accomplished either by employing ELISA, which separately detects IgG, or by introducing 2-mercaptoethanol into the SAT test for IgG quantitation. If IgG levels persistently remain elevated but the patient is

clinically well, a preferred follow-up interval is every 3 months, with serological testing conducted for one year to ensure the absence of relapse.

- **Molecular testing (PCR):** PCR is generally considered inadequate for routine follow-up due to the potential persistence of Brucella genetic material for extended periods, even after the patient is deemed cured. This persistence is attributed to the organism's hidden intracellular nature and very low metabolic growth. However, PCR may be considered for patients who remain symptomatic with low titers or those with undiagnosed persistent febrile illness.

Table 10. Follow-Up Summary (Adapted from the SPIDS 2022 Brucella Book)

Condition	Hospitalization	Outpatient
• Febrile illness without focalization • Bacteremia without focalization • Simple focalization like arthritis	Patient can be treated as an outpatient. Except if indication for admission is present.	• Start therapy • Follow up in one week to assure compliance and response • Repeat blood culture if initially positive • If a good response is obtained, recheck in 6 weeks for serology and to ensure a decrease in titer • If titer remains persistently high with good clinical response, keep checking every 3 months for a period of one year
Neurobrucellosis	Hospitalization for 4 to 6 weeks with complete clinical response and improvement in diagnostic tests (negative blood and cerebrospinal (CSF) cultures and decrease in serum and CSF titers and erythrocyte sedimentation rates (ES)	Usually need therapy for 3 to 12 months with monthly serology, CBC, and ESR

Endocarditis	Hospitalization for 4 to 6 weeks with complete clinical response and improvement in diagnostic tests (negative blood culture, decrease in serum titer and ESR)	Usually for 6 to 12 months with monthly serology, CBC, and ESR

Brucellosis and different treatment outcomes

Despite receiving appropriate treatment, some patients may persist with symptoms. To effectively address brucellosis, the treating physician should be cognizant of various treatment outcomes, including treatment failure, relapse, and/or reinfection.

Failure of therapy is characterized by the persistence of clinical symptoms post-treatment, signifying a therapeutic failure. While rare, it raises concerns about potential resistance patterns in brucellosis. There is currently no consensus on the duration after starting treatment that persistent symptoms should be considered indicative of treatment failure. According to some experts, failure is defined as the presence of signs and symptoms after 4 weeks of treatment.

Relapse involves the recurrence of Brucella signs and symptoms along with the re-isolation of Brucellae from the blood. Among treated patients, 3%-9% may experience a relapse or reinfection, with most relapses occurring within the first year following therapy.

In a multivariate model aimed at predicting relapse, independent predictors encompassed factors such as a temperature of ≥38.3 °C, a duration of symptoms <10 days before treatment, and positive blood cultures at baseline.

The primary causes of therapy failure or relapse involve several factors:

- **Compliance Issues**: This may result from patient negligence or adverse drug effects. Some drugs used for Brucella treatment, particularly doxycycline, can induce unwanted reactions, such as photosensitivity. Patients should be cautioned about potential adverse skin effects and advised to contact a physician if such events occur.
- **Short Treatment Duration (<6 weeks)**: Most studies indicate a lower rate of relapse when the therapy duration is 6 weeks or longer.
- **Single Therapy Effectiveness**: The use of a single therapy has been demonstrated to be ineffective in treating brucellosis.
- **Exposure to Infectious Source**: Frequent exposure to an infectious source is a notable factor.

- **Presence of Localized Foci/Disease**: The existence of localized foci or disease contributes to therapy failure or relapse.
- **Drug Resistance**: Although very rare, drug resistance should be considered.

Reinfection is a potential concern in areas with ongoing exposure. Distinguishing between relapse and reinfection can be challenging, particularly in certain regions.

Management of relapse, failure of therapy, and reinfection

In the event of relapse or reinfection, it is advisable to refer the patient to a pediatric infectious disease clinic for confirmation of diagnosis and further management.

Examination of potentially infected sites, particularly those affecting the Central Nervous System (CNS) or the heart, should be thorough. It is recommended to repeat serological tests and blood cultures, with an anticipated increase in titers. However, for optimal assessment, obtaining separate estimates of IgG and IgM levels is preferred. This can be achieved through ELISA or SAT with 2-mercaptoethanol (2-ME), and in cases of relapse, there is typically a significant increase in IgG levels.

Utilizing scanning techniques such as scintigraphy with technetium-99m or gallium-67, computed tomography, or magnetic resonance imaging can be valuable in localizing an occult focus of infection.

Antimicrobial resistance in brucellosis

Common brucellosis antibiotics and resistance

While the majority of the antimicrobial regimens recommended for brucellosis remain effective, there is an observed increase in antimicrobial resistance among Brucella spp., particularly in Middle Eastern countries where the disease is notably endemic (table 11).

- **Doxycycline**: Numerous studies on minimum inhibitory concentration (MIC) conducted in Middle Eastern countries with endemic brucellosis have consistently shown that Brucella spp. isolates remain susceptible to doxycycline.
- **Streptomycin and gentamicin**: Brucella isolates from the Middle East consistently exhibit susceptibility to streptomycin and gentamicin. Netilmicin, a newer aminoglycoside, was previously employed in the treatment of active brucellosis and demonstrated no reported nephrotoxicity or ototoxicity.
- **Trimethoprim-sulfamethoxazole (TMP-SMZ):** Multiple reports on human isolates indicate decreased susceptibility to TMP-SMZ. Saudi Arabia, in particular, reported a higher rate of TMP-SMZ resistance ranging from 5% to 60%. However, combining TMP-SMZ with rifampicin, with or without streptomycin, resulted in no observed relapses.

- **Rifampicin**: Resistance to rifampicin appears to be emerging with varying rates in different countries, ranging from 0 to 70%. This resistance is attributed to the frequency of rifampicin use, especially in regions where tuberculosis is endemic.
- **Fluoroquinolones**: In monotherapy against active brucellosis, fluoroquinolones prove ineffective, leading to unacceptable therapeutic failures, relapses, resistance development, and an inability to achieve in-vitro synergy with other antibiotics. Consequently, fluoroquinolones should not be the first-line therapy for individuals with active brucellosis.
- **Cephalosporins**: Third-generation cephalosporins, known for their broad antibacterial activities against gram-negative organisms, have shown some success in combination therapy, particularly ceftriaxone. However, as a single agent, ceftriaxone is not effective. While local studies report the efficacy of ceftriaxone in treating complicated brucellosis conditions like neurobrucellosis and orchitis, further research is needed before considering ceftriaxone as a first-line therapy for human brucellosis.

Table 11. Comparative Data of Studies on Antibiotic Therapeutic Regimes Using Brucella Spp. of Human Origin in Saudi Arabia (Adapted from the SPIDS 2022 Brucella Book)

Brucella spp. (No.)	Susceptible strains (% or No.)	Non-susceptible strains (% or No.)	Method
B. melitensis (704) 1997–2012	TGC (100%). MIC was 0.190-2.0 µg/ml in 36.93%, and ≤0.125 µg/ml in 63.07%	ND	E-test
B. melitensis (26) *B. abortus* (1) 1984–1995	TET (100%), STR (100%)	COT (8), RIF (3)	E-test
B. melitensis (63) *B. abortus* (5) 1983–1995	None	COT (40), RIF (5), STR (1), TET (1)	Broth dilution
B. melitensis (116)	AZI, GEN, TET, T/S, RIF, CIP, NOR, SPR, TEM (99%–100%)	None	
B. melitensis (105)	GEN, RIF, TET, T/S (100%)	Fluoroquinolones (1)	Broth dilution

B. melitensis (47)	OFL, DIF, CIP (90%)	None	Broth dilution

AZI, azithromycin; CIP, ciprofloxacin; COT, co-trimoxazole; DIF, difloxacin; GEN, gentamicin; MIC, minimum inhibitory concentration; NOR, norfloxacin; OFL, ofloxacin; RIF, rifampin; STR, streptomycin; T/S, trimethoprim/sulfamethoxazole; TET, tetracycline; TEM, temafloxacin; TGC, tigecycline.

Prevention of human brucellosis and future consideration

Brucellosis, a prevalent zoonotic disease worldwide, exerts a significant impact on human health, the animal industry, and public health. It is a notifiable disease in most countries, and currently, no vaccines are available for preventing brucellosis in humans. Therefore, comprehending the pathogenesis of the disease and its diverse modes of transmission is crucial. The prevention of brucellosis primarily relies on surveillance, the elimination of risk factors, and disease control in livestock. Individuals with elevated risk for brucellosis infection include those who work closely with animals or have contact with their infected tissues or body fluids, such as veterinarians, dairy farmers, ranchers, slaughterhouse workers, hunters, and microbiologists.

The Ministry of Health (MOH) of Saudi Arabia has implemented several strategies to prevent infection:

- Ensure the pasteurization of milk and dairy products, including cheese, to eradicate bacteria and prevent the transmission of infection from animals to humans.
- Ensure thorough cooking of meat at temperatures ranging from 63°C to 74°C.
- Notify laboratory personnel when handling specimens suspected of brucellosis, advising them to work within at least a class II biological safety cabinet (BSC) equipped with proper personal protective equipment and employing primary and secondary barriers.
- Instruct individuals working with animals to safeguard themselves by donning gowns, rubber gloves, and goggles.
- Discourage skin or mucous membrane contact with infected animal tissues (such as placenta and miscarriage products) or fluids (such as blood, urine, or milk).
- Prevent the mixing of different herds and eliminate infected ones to curb disease transmission among animals.
- Implement protective measures in slaughterhouses, including segregating the killing floor from other processing areas, designating spaces for known infected animals, employing protective clothing and disinfectants, and controlling air circulation.

- Ensure routine check-ups for domestic livestock, vaccinate all seronegative animals, and cull diseased ones.
- Counsel lactating mothers diagnosed with active brucellosis to discontinue breastfeeding until completion of treatment and closely monitor infants for signs of infection.
- Conduct serological testing for blood and organ donors.
- Administer post-exposure antimicrobial prophylaxis for individuals with high-risk exposure to Brucella isolates, using the recommended regimen of doxycycline plus TMP/SMX for 21 days with follow-ups for six months from the last exposure. Note that inadvertent exposure to live-attenuated animal vaccines may lead to human infection with Brucella, requiring careful follow-up and serological monitoring.
- Obtain a thorough family history, as some family members may have been exposed to the same source, exhibiting subtle symptoms such as malaise, headache, and/or fatigue. Contacts with high serology should undergo testing and, if positive, receive treatment. A study by Alsubaie et al found that 23% of brucellosis family members displayed various symptoms confirmed by positive Brucella titers.
- Develop health education initiatives aimed at the general public to enhance community awareness of this severe infection, mitigate its transmission, and prevent potential complications. An essential approach, as advocated by the Saudi Pediatric Infectious Diseases Society (SPIDS), emphasizes the significance of collaboration between relevant governmental sectors, including the Ministry of Health, Ministry of Agriculture, Custom Department, and Municipal Department, to establish an effective Brucella control program.

Brucellosis and future considerations

While industrialized nations have largely eliminated the disease, brucellosis continues to be a prevalent zoonotic ailment in developing countries. Classified as a bioterrorism organism, Brucella is notable for its low infectious doses (10–100 bacteria), ability to endure in the environment, swift transmission through various routes, including aerosols, and the challenge in determining an optimal antibiotic treatment course. Concerns about the resurgence of brucellosis in the near future have arisen, driven by the discovery of new atypical Brucella species with unique genetic properties and recent reports of disease transmission. There is an urgent need for the development of novel concepts and strategies for disease control.

Brucellosis in Special Hosts

Congenital brucellosis

- Cases of congenital (neonatal) brucellosis have been infrequently reported in endemic regions, encompassing The Mediterranean, Middle East, Arabian Peninsula, Central and South America, Asia, and Africa. A recent systematic review identified 44 instances of congenital brucellosis in the literature search, with eight cases documented in Saudi Arabia.
- Nearly half of the documented cases involved premature births. Brucellosis during pregnancy is recognized to contribute to fetal death, miscarriages, preterm deliveries, and low birth weights. The majority of affected neonates typically exhibit nonspecific clinical symptoms, including fever, respiratory distress, lethargy, irritability, hypoglycemia, seizures, jaundice, and hepatosplenomegaly, resembling symptoms of non-specific bacterial infections in infants. Some patients may experience failure to thrive and prolonged, intermittent fever. Bone marrow suppression, evidenced by petechial rash from thrombocytopenia and/or anemia, can occur. In rare instances, an infant may be asymptomatic, and the infection may only be detected through a positive blood culture. Uncommon complications, such as myocarditis and hydrocephalus, have been reported. Most neonates with brucellosis survive, although a small number succumb to sepsis-related complications.
- Mothers of affected infants typically have a history of brucellosis, contact with animals, or consumption of unpasteurized dairy products. The primary method for laboratory diagnosis relies on positive blood cultures, with advancements in blood culture techniques, such as BACTEC or BACT/Alert, significantly enhancing Brucella detection rates. In a systematic review covering 44 cases of congenital brucellosis, 36 cases yielded positive blood cultures. Neonatal serology exhibits limited sensitivity and specificity, with negative results possibly stemming from immature immune responses, especially in premature infants. Positive results may be attributed to the passive transfer of maternal antibodies. However, when ELISA tests are employed to detect IgM separately, a positive IgM indicates acute infection in infants. The SAT can identify total immunoglobulins (IgG and IgM), and chelating IgM with 2-mercaptoethanol helps differentiate the immunoglobulin classes. Although PCR is highly sensitive, its availability is limited.
- Combination therapy is essential, involving gentamicin for 7 days, rifampicin for 6 weeks, and TMP/SMX for 6 weeks. In case of TMP/SMX side effects, such as elevated bilirubin levels or a rash, ciprofloxacin may be a suitable alternative. Beta-lactams may be considered in the presence of

neurobrucellosis, although their efficacy is suboptimal and cannot be considered a primary therapeutic option.

Brucellosis in immunocompromised patients

While brucellosis is commonly acknowledged in immunocompetent individuals, there is a growing recognition of its impact on immunocompromised patients residing in endemic regions. The disease can manifest either as an acute febrile illness or a chronic medical condition, and its clinical presentations can be deceptive, often resembling other systemic diseases.

Diagnosing and presenting brucellosis in an immunocompromised population pose significant challenges. Additionally, relapses and the progression of acute infections to chronic conditions are not uncommon in these individuals. Therefore, in endemic regions, swift diagnosis and treatment of brucellosis are crucial to prevent undesirable complications and enhance outcomes. Immunocompromised individuals, including those with human immunodeficiency virus (HIV) infection, are more prone to developing aggressive forms of brucellosis.

The epidemiology of brucellosis has undergone significant changes since the mid-1980s. Official statistics in some Brucella-endemic countries may not accurately reflect the true burden of the disease due to inadequate health systems. However, recent advancements in diagnostics, increased survival rates for immunocompromised patients, insufficient infection control measures, and unregulated animal transportation across borders have contributed to a recent rise in brucellosis incidence in these populations globally.

Brucella species can be contracted through the consumption of raw milk and unpasteurized dairy products, inhalation of aerosolized particles, and direct contact with animals and their products. In immunocompromised patients, additional risk factors are acknowledged, including organ donation, bone marrow transfusions in recipients of hematopoietic stem cell transplantation (HSCT), and blood product transfusions.

Recipients of bone marrow and/or solid organ transplants often receive blood or blood-related products, increasing their susceptibility to infections, including brucellosis, which is recognized as a bloodborne pathogen. However, there have been very few reported cases of blood transfusion-related brucellosis in countries where brucellosis is endemic. In a study involving 632 participants, four donors exhibited positive serology for brucellosis, and Brucella species were detected by RT-PCR in two donors. Although bloodborne transmission is reported to be rare, the data may underestimate the actual number due to inadequate reporting systems. Therefore, screening donated blood for Brucella should be considered in endemic areas. Additionally, careful monitoring of exposure histories is crucial for identifying patients at a high risk of contracting the disease.

Immunocompromised individuals may exhibit clinical manifestations of brucellosis similar to those in immunocompetent individuals. However, the diagnosis may be delayed due to the overlap between the clinical features of brucellosis and those of the underlying disease. Moreover, the interaction between anti-Brucella medications and chemotherapeutic agents, along with immunosuppressive drugs, could impede the response to therapy. Consequently, complications are more likely to arise, making the treatment of brucellosis in these populations particularly challenging.

Individuals undergoing chemotherapy and using immunosuppressive drugs, including immunomodulatory agents, and those with malignancies, especially lymphoma, face an elevated risk of brucellosis recurrence. In regions with continuous exposure, distinguishing between relapse and reinfection can be challenging.

Donor-derived infections and pre-transplant screening in solid organ transplant (SOT)

The success of a solid organ transplant (SOT) hinges on thorough pre-transplant screening of donors and recipients. Detecting and addressing infectious complications in SOT recipients depends on various factors, such as culturing the organism from a different site through culture or histology, positive serological tests indicating exposure to pathogens or active disease, and risk stratification for those with resistant organisms for both prevention and therapeutic measures in case of reactivation. Given the substantial demand for organ transplantation and the limited availability of organs, it is crucial to minimize organ rejection from donors with specific infectious etiologies by carefully assessing the benefit and risk. Evaluating the risk of infection transmission through an allograft for a specific donated organ can be challenging, as knowledge of infection transmission is often limited.

To eliminate the risk of disease transmission during solid organ transplantation, Screening strategies for organ donors should encompass an understanding of the regional epidemiology of infections, especially endemic ones like brucellosis. Additionally, the incorporation of rapid molecular diagnostics, such as PCR, becomes particularly relevant in populations where serology interpretation might pose challenges.

Brucellosis is solid organ transplantation (SOT)

- In recent years, instances of brucellosis following SOT have been relatively infrequent, primarily associated with renal, liver, and less commonly cardiac transplantation. The estimated risk of Brucella transmission from transplanted organs is less than 1%, but the actual incidence is likely underestimated due to inadequate reporting and prior screening practices. Factors such as exposure to animals or their products in endemic regions and the degree of immunosuppression significantly contribute to the heightened risk of

brucellosis. The timeframe for the development of brucellosis post-transplantation varies, ranging from as early as 2 months to as late as 20 years; however, the mean duration from transplant to infection is approximately 5 years. Transplant recipients face multiple risk factors, including donor-derived infections, blood transfusions, reactivation of previous infections, and new infections, resulting in a spectrum of manifestations from acute to chronic, subclinical, asymptomatic, and severe systemic infections.

Prevention of infections in solid organ transplants

- Enhancing donor screening protocols, thoroughly assessing the exposure history of both donors and recipients, and incorporating molecular diagnostic testing can contribute to mitigating the risk of donor-derived infections. Implementing structured education programs tailored for transplant recipients and their household contacts, particularly in the initial six months post-transplantation, regarding transmission risks, can significantly reduce the likelihood of brucellosis in these immunocompromised individuals.

Brucellosis in recipients of hematopoietic stem cell transplant (HSCT)

- In regions where brucellosis is prevalent, such as Saudi Arabia, it poses a significant infectious risk for individuals undergoing hematopoietic stem cell transplantation (HSCT). Brucellosis in HSCT recipients can arise either from allografts obtained from donors with the infection or after successful engraftment post-transplant. The pre-donation phase, preceding donor clearance, necessitates a thorough medical history, encompassing potential Brucella infection risk factors like animal exposure and prior infection. Serological testing for Brucella typically occurs during donor evaluation at least 30 days before stem cell donation. In cases where serology is inconclusive or of limited value, RT-PCR can serve as a screening tool. Donors with brucellosis undergoing HSCT should undergo treatment for the infection and must refrain from donating stem cells until fully recovered for a minimum of 2 years. However, decisions regarding the use of stem cells from donors with active or suspected infections should consider the recipient's transplantation urgency, the availability of alternative donors, and the informed consent of the recipient. Thorough assessment of all available data about the donor's infection, including susceptibility testing, antimicrobial treatment, and clinical response, is imperative in this regard.

Brucellosis in patients with HIV infection

- HIV infections can induce significant immune suppression, leading to heightened B-cell activity and hypergammaglobulinemia. This condition of hypergammaglobulinemia might lead to false-positive results for Brucella in immunoassays.

- Moreover, HIV infection results in impaired B-cell memory and compromised antibody production. Individuals infected with HIV, particularly those with diminished memory B-lymphocytes, demonstrate defective humoral immunity and generate abnormal IgG levels, contributing to a decline in memory B-lymphocytes. This immune dysfunction increases susceptibility to brucellosis and other bacterial infections.
- The typical clinical presentation includes elevated fever, sweating, arthralgia, myalgia, lower back pain, and acute abdominal pain. Leukopenia, a common manifestation of both HIV infection and brucellosis, is observed with significantly lower white blood cell counts in HIV-positive and brucellosis-infected patients compared to uninfected individuals. Recent research indicates that lymphopenia and immune suppression elevate the risk of brucellosis relapse in these populations.

Diagnosis of brucellosis in immunosuppressed patients

Various serological tests are employed in clinical settings for diagnosing brucellosis. However, their interpretation in immunocompromised patients presents challenges, as results can vary significantly based on the degree and type of immunosuppression. In cases where brucellosis is strongly suspected, obtaining cultures and molecular testing is crucial. Over the past few years, molecular diagnostics for brucellosis have gained widespread use, particularly in immunocompromised hosts.

Treatment

When dealing with an immunocompromised patient suspected of having brucellosis, it is highly advisable to seek consultation with an infectious disease specialist. The diagnostic and therapeutic approaches in such cases can be more challenging compared to immunocompetent individuals. Maintaining a high index of suspicion, ensuring prompt diagnosis, and initiating appropriate treatment in the early stages of infection are crucial for achieving a cure, preventing chronic morbidity, and optimizing time management in addressing the infection.

Emphasizing the significance of antimicrobial therapy guided by antibiotic susceptibility testing is vital in curbing drug resistance development and reducing complications. The treatment regimen for brucellosis in immunocompromised patients aligns with that for individuals with a normal immune system. However, consideration must be given to potential interactions between antibiotic regimens, particularly rifampin, and immunosuppressive therapy. In certain situations, alternative regimens may need to be selected. When a patient has Brucella bacteremia or a complex Brucella infection, initiating antimicrobial therapy at least two weeks before chemotherapy or immunosuppressive treatment is recommended.

1.2 North American Guidelines

1.2.1 Centers for Disease Control and Prevention (CDC) Brucellosis Reference Guide (2017)

In February 2017, the National Center for Emerging and Zoonotic Infectious Diseases of the CDC published a brucellosis reference guide on exposures, testing and prevention of the infection[6].

Clinical Presentation

Definition by the Council of State and Territorial Epidemiologists (CSTE) - 2010 Case Description

This illness is characterized by the abrupt or gradual onset of fever accompanied by one or more of the following: night sweats, arthralgia, headache, fatigue, anorexia, myalgia, weight loss, arthritis/spondylitis, meningitis, or focal organ involvement (such as endocarditis, orchitis/epididymitis, hepatomegaly, or splenomegaly).

Incubation Period

- Highly variable (ranging from 5 days to 6 months)
- Average onset occurs between 2 to 4 weeks after exposure

Symptoms/Signs

Acute phase:

- Non-specific symptoms: Fever, chills, sweats, headache, myalgia, arthralgia, anorexia, fatigue, weight loss
- Common sub-clinical infections
- Presence of lymphadenopathy (10–20%) and splenomegaly (20–30%)

Chronic phase:

- Recurrent fever
- Arthritis and spondylitis
- Possible focal organ involvement (as indicated in the case definition)

Case Classification

Probable—An illness clinically compatible with at least one of the following:

- Epidemiological connection to a confirmed human or animal brucellosis case
- Presumptive laboratory evidence, lacking definitive confirmation, of Brucella infection

Confirmed—An illness clinically compatible with definitive laboratory evidence of Brucella infection.

Human pathogens and select agent reporting

Select agents and toxins constitute a specific category of biological agents and toxins known for their potential to pose a significant threat to public health. Brucella species, including B. suis, B. melitensis, and B. abortus, fall under this category due to their ease of aerosolization, low infectious dose (ranging from 10 to 100 microorganisms), prolonged incubation period, and the diverse clinical manifestations they can induce, all of which present challenges in achieving timely diagnoses. As a consequence of these factors, these Brucella species have been designated as select agents.

Entities, including clinical or diagnostic laboratories, that identify B. suis, B. melitensis, or B. abortus are obligated to promptly (within 24 hours) notify the Division of Select Agents and Toxins (DSAT) at the Centers for Disease Control and Prevention (CDC).

Furthermore, facilities involved in the utilization or transfer of B. suis, B. melitensis, or B. abortus must immediately (within 24 hours) inform DSAT via phone, fax, or email in the event of theft, loss, or release of these select agents. The initial report should provide comprehensive details about the incident, covering aspects such as the nature of the incident, date and time, type and quantity of agent, and a summary of events (including incident location, potential exposure of individuals, response actions taken, etc.). In cases of theft or loss, appropriate local, state, or federal law enforcement agencies should be notified, and in the event of a release, relevant local, state, and federal health agencies should be informed.

Select agents in their natural environment are not subject to regulation and may encompass animals naturally infected with a select agent or toxin (e.g., milk samples containing B. abortus). However, a select agent or toxin intentionally introduced (e.g., animals experimentally infected with B. suis, B. melitensis, or B. abortus) or otherwise extracted from its natural source (e.g., blood from a culture bottle plated onto agar and growing B. suis) is subject to select agent regulation.

Attenuated vaccine strains of B. abortus, Strain 19 live vaccine, and B. abortus, Strain RB51, are excluded from select agent reporting requirements, unless there is any reintroduction of factors associated with virulence.

Laboratory Response Network (LRN)

The LRN constitutes a nationwide network comprising local, state, federal, military, and international public health, food testing, veterinary diagnostic, and environmental testing laboratories. It serves as a crucial infrastructure, enhancing

the collective capacity to address biological and chemical public health emergencies.

Upon obtaining results indicating high confidence in presumptive or confirmatory Brucella spp., LRN laboratories are mandated to adhere to notification and messaging protocols.

Notification: LRN Laboratory Directors or their designees must, within 2 hours of securing high-confidence presumptive or confirmatory results, notify:

- The State Public Health Laboratory Director
- The State Epidemiologist
- The Health Officer for the State Public Health Department
- The CDC Emergency Operations Center (EOC)
- The FBI Weapons of Mass Destruction (WMD) Point of Contact (POC)

Messaging: LRN laboratories are required to submit data for all samples, encompassing both positive and negative results related to the event, within 12 hours of obtaining each result, irrespective of whether the situation is an emergency or non-emergency.

Brucellosis holds a reportable status across all 57 states and territories, necessitating those instances of the disease be reported to state and territorial jurisdictions upon identification by a health provider, hospital, or laboratory. Reporting criteria may vary across jurisdictions.

Additionally, brucellosis is classified as a nationally notifiable condition. While the notification of brucellosis cases to the CDC by state and territorial jurisdictions is voluntary and excludes direct personal identifiers, it contributes to nationwide data aggregation and monitoring of disease trends. The case definition for confirmed and probable brucellosis is available on page 3 under the Case Classification section.

- Immediate, Urgent Notification Status: In the case of multiple confirmed and probable cases that are temporally or spatially clustered, an immediate notification to the Emergency Operations Center (EOC) within 24 hours of meeting the notification criteria is imperative. Subsequently, an electronic case notification should be submitted in the next regularly scheduled electronic transmission.
- Standard: For confirmed and probable cases not exhibiting temporal or spatial clustering, electronic case notification should be submitted within the next reporting cycle

Case report form

Health departments and providers are strongly recommended to utilize the approved case report form for reporting brucellosis cases to the Bacterial Special Pathogens Branch. This approach ensures the enhanced collection of standardized data, essential for evaluating risk factors and trends associated with brucellosis. This, in turn, facilitates the implementation of targeted preventive strategies.

Diagnostic testing

CDC/CSTE Laboratory Criteria for Diagnosis:

Definitive:

- Culture and identification of Brucella spp. from clinical specimens.
- Evidence of a four-fold or greater rise in Brucella antibody titer between acute and convalescent phase serum specimens obtained greater than or equal to 2 weeks apart.

Presumptive:

- Brucella total antibody titer of greater than or equal to 1:160 by standard tube agglutination test (SAT) or Brucella microagglutination test (BMAT) in one or more serum specimens obtained after the onset of symptoms.
- Detection of Brucella DNA in a clinical specimen by PCR assay.

The Zoonotic and Select Agent Laboratory (ZSAL) at CDC conducts CLIA-approved diagnostic testing for Brucella spp. on both human and animal samples.

Table 12. Diagnostic Testing Provided by ZSAL (Adapted from the CDC 2017 Guidelines)

Test	Samples accepted	Pros	Cons
Culture	Tissue, whole blood, sera, plasma	Gold standard; allows for genotyping-molecular epidemiology	Requires BSL-3
LRN PCR (for suspect BT and response use)	Environmental samples, swabs, powders, whole blood, sera, tissue	Rapid detection; can be used on isolates and clinical specimens	Requires technical expertise to perform assay; reagents and equipment can be costly; optimal

			specimen type not clear
MAT (serology) *Not available for B. canis or RB51*	Sera	Cheap, assay of choice in acute noncomplicated cases; only equipment needed is reading apparatus	May not diagnose chronic or complicated cases; subjective

Results and notification process

- BMAT results typically require 2 to 3 weeks for processing, contingent upon the time of sample reception at CDC's Zoonotic and Select Agent Laboratory (ZSAL) within the Bacterial Special Pathogens Branch (BSPB). While our laboratory endeavors to analyze your sample within 1 week, the reporting of results may extend beyond this timeframe. The final results will be transmitted to your State Laboratory.
- PCR results from primary specimens are typically available within a swift timeframe of 24 hours.

Diagnostic challenges

- While culture remains the benchmark, the growth characteristics of Brucella spp. pose challenges due to their fastidious and slow-growing nature. Culturing from primary specimens may necessitate up to 21 days of incubation. Notably, bone marrow culture surpasses blood culture in sensitivity, although the invasiveness of the procedure warrants careful consideration. Chronic infections, however, reduce the likelihood of a positive culture.
- The confirmatory serological test for diagnosing brucellosis is agglutination. The standard tube agglutination test (SAT) serves as the reference method, with the BMAT being a modified version.
- Brucella-specific agglutination tests entail the direct agglutination of bacterial antigens by specific antibodies. These tests can detect antibodies of IgM, IgG, and IgA classes.
- IgM antibodies are prevalent during acute infections but diminish within weeks. Relapses are characterized by transient elevations in IgG and IgA antibodies, though IgM levels do not exhibit a similar pattern.
- Sensitivities in detecting IgM using alternative EIA formats have been documented in the range of 67% to 100%, albeit with limited specificity data.

These tests, being qualitative in nature, pose challenges in their interpretation within a clinical context. Moreover, their performance characteristics and utility may vary, particularly in regions with a low prevalence of the disease, such as the United States. It is imperative to confirm the results of EIA tests through a quantitative reference method, such as BMAT.

- Challenges arise in Brucella antibody tests, particularly with IgM, as they may lead to cross-reactions and yield false-positive results. The principal immunodeterminant and virulence factor for Brucella species, smooth lipopolysaccharide (S-LPS) on the outer cell membrane, shares antigenic similarities with the lipopolysaccharide of other gram-negative rods. This similarity can result in false-positive Brucella test outcomes, driven by the cross-reactivity of antibodies to Escherichia coli O157, Francisella tularensis, Moraxella phenylpyruvica, Yersinia enterocolitica, certain Salmonella serotypes, and individuals vaccinated against Vibrio cholerae.
- BMAT, while effective in diagnosing acute cases, exhibits limitations in its performance for chronic cases, especially neurobrucellosis. It tends to be less informative in suspected chronic cases, where an IgG ELISA would provide more insightful results.

Treatment

Table 13 offers a concise overview of the treatment recommendations.

Table 13. Brucellosis Treatment Options (Adapted from the CDC 2017 Guidelines)

Subject	Summary
Adults **Children > 8 years**	Combination therapy to decrease the incidence of relapse: • Oral doxycycline (2–4 mg/kg per day, maximum 200 mg/day, in 2 divided doses) or oral tetracycline (30–40 mg/kg per day, maximum 2 g/day, in 4 divided doses) **-and-** • Rifampin (15–20 mg/kg per day, maximum 600–900 mg/day, in 1 or 2 divided doses). • Recommended for a **minimum** of 6 weeks. Combination therapy with trimethoprim-sulfamethoxazole (TMP-SMZ) can be used if tetracyclines are contraindicated.
Children < 8 years	• Oral TMP-SMZ (trimethoprim, 10 mg/kg per day, maximum 480 mg/day; and sulfamethoxazole, 50

	mg/kg per day, maximum 2.4 g/day) divided in 2 doses for 4 to 6 weeks. Combination therapy: consider adding rifampin. Consult physician for dosing or if rifampin is contraindicated. Tetracyclines (such as doxycycline) should be avoided in children less than 8 years of age.
Pregnancy	Tetracyclines are contraindicated for pregnant patients. Consult obstetrician regarding specific antimicrobial therapy instructions.
Complicated Cases (endocarditis, meningitis, osteomyelitis, etc.)	• Streptomycin* or gentamicin for the first 14 days of therapy in addition to a tetracycline for 6 weeks (or TMP-SMZ if tetracyclines are contraindicated). • Rifampin can be used in combination with this regimen to decrease the rate of relapse. • For life-threatening complications, such as meningitis or endocarditis, duration of therapy often is extended for 4 to 6 months. • Case-fatality rate is < 1%. • Surgical intervention should be considered in patients with complications such as deep tissue abscesses. **May not be readily available in the U.S.*

Exposures in laboratory, surgical, and clinical settings

Exposures in laboratory settings

Upon identifying a potential exposure, the initial step involves determining the specific activities that might have given rise to the exposure. Subsequently, it is crucial to:

- Identify individuals present in the laboratory during the suspected time(s) of exposure.
- Determine their location in relation to the exposure incident.
- Assess the actions taken with the isolates.
- The individuals identified should undergo an evaluation of their exposure risk, guided by the criteria outlined in table 14.

Table 14. Laboratory Risk Assessment and Post-Exposure Prophylaxis (PEP): Minimal (but not zero) Risk (Adapted from the CDC 2017 Guidelines)

Specimen handling	Exposure scenario	PEP	Follow-up/monitoring
Routine clinical specimen (e.g., blood, serum, cerebrospinal fluid)	Person who manipulates a routine clinical specimen (e.g., blood, serum, cerebrospinal fluid) in a certified Class II biosafety cabinet, with appropriate personal protective equipment (i.e., gloves, gown, eye protection).	None	May consider symptom watch for following scenarios: • Person who manipulates a routine clinical specimen (e.g., blood, serum, cerebrospinal fluid) on an open bench with or without appropriate personal protective equipment (i.e., gloves, gown, eye protection), or in a certified Class II biosafety cabinet without appropriate personal protective equipment. • Person present in the lab while someone manipulates a routine clinical specimen (e.g., blood, serum, cerebrospinal fluid) on an open bench, resulting in occurrence of aerosol-generating events (e.g., centrifuging without sealed carriers, vortexing, sonicating, spillage/splashes).
	Person present in the lab while someone manipulates a routine clinical specimen (e.g., blood, serum, cerebrospinal fluid) in a certified Class II biosafety cabinet, or on an open bench where manipulation did not involve occurrence of aerosol-generating events (e.g., centrifuging without sealed carriers, vortexing, sonicating, spillage/splashes).		
Enriched material (e.g., a Brucella isolate, positive blood bottle) or reproductive clinical specimen (e.g.,	Person who manipulates enriched material (e.g., a Brucella isolate, positive blood bottle) or reproductive clinical specimen (e.g., amniotic fluid, placental products) in a certified Class II biosafety cabinet, with appropriate		

amniotic fluid, placental products)	personal protective equipment (i.e., gloves, gown, eye protection).		
	Person present in the lab while someone manipulates enriched material (e.g., a Brucella isolate, positive blood bottle) or reproductive clinical specimen (e.g., amniotic fluid, placental products) in a certified Class II biosafety cabinet.		

Table 15. Laboratory Risk Assessment and Post-Exposure Prophylaxis (PEP): Low Risk (Adapted from the CDC 2017 Guidelines)

Specimen handling	Exposure scenario	PEP	Follow-up/ monitoring
Enriched material (e.g., a Brucella isolate, positive blood bottle) or reproductive clinical specimen (e.g., amniotic fluid, placental products)	Person present in the lab at a distance of greater than 5 feet from someone manipulating enriched material (e.g., a Brucella isolate, positive blood bottle) or reproductive clinical specimen (e.g., amniotic fluid, placental products), on an open bench, with no occurrence of aerosol-generating events (e.g., centrifuging without sealed carriers, vortexing, sonicating, spillage/splashes).	May consider if immunocompromised or pregnant. Discuss with health care provider (HCP). Note: RB51 is resistant to rifampin in vitro, and therefore this drug should not be used for PEP or treatment courses.	Regular symptom watch (e.g., weekly) and daily self-fever checks through 24 weeks postexposure, after last known exposure. Sequential serological monitoring at 0 (baseline), 6, 12, 18, and 24 weeks postexposure, after last known exposure. Note: no serological monitoring currently available for RB51 and B. canis exposures in humans.

Table 16. Laboratory Risk Assessment and Post-Exposure Prophylaxis: High Risk (Adapted from the CDC 2017 Guidelines)

Specimen handling	Exposure scenario	PEP	Follow-up/ monitoring
Routine clinical specimen (e.g., blood, serum, cerebrospinal fluid)	Person who manipulates a routine clinical specimen (e.g., blood, serum, cerebrospinal	Doxycycline 100mg twice daily, and rifampin 600 mg once daily, for three weeks. For patients with	Regular symptom watch (e.g., weekly) and daily self-fever checks through 24 weeks postexposure, after

	fluid), resulting in contact with broken skin or mucous membranes, regardless of working in a certified Class II biosafety cabinet, with or without appropriate personal protective equipment (i.e., gloves, gown, eye protection).	contraindications to doxycycline or rifampin: TMPSMZ, in addition to another appropriate antimicrobial, should be considered. Two antimicrobials effective against Brucella should be given. Pregnant women should consult their obstetrician. <u>Note</u>: RB51 is resistant to rifampin in vitro, and therefore this drug should not be used for PEP or treatment courses.	last known exposure. Sequential serological monitoring at 0 (baseline), 6, 12, 18, and 24 weeks post-exposure, after last known exposure. <u>Note</u>: no serological monitoring currently available for RB51 and B. canis exposures in humans.
Enriched material (e.g., a Brucella isolate, positive blood bottle) or reproductive clinical specimen (e.g., amniotic fluid, placental products)	Person who manipulates (or is ≤ 5 feet from someone manipulating) enriched material (e.g., a Brucella isolate, positive blood bottle) or reproductive clinical specimen (e.g., amniotic fluid, placental products), outside of a certified Class II biosafety cabinet.		
	Person who manipulates enriched material (e.g., a Brucella isolate, positive blood bottle) or reproductive clinical specimen		

	(e.g., amniotic fluid, placental products), within a certified Class II biosafety cabinet, without appropriate personal protective equipment (i.e., gloves, gown, eye protection).		
	All persons present during the occurrence of aerosol-generating events (e.g., centrifuging without sealed carriers, vortexing, sonicating, spillage/splashes) with manipulation of enriched material (e.g., a *Brucella* isolate, positive blood bottle) or reproductive clinical specimen (e.g., amniotic fluid, placental products) on an open bench.		

Common aerosol-generating procedures encompass a range of activities, including but not limited to centrifugation without sealed carriers, vortexing, sonication, and incidents leading to spillage or splashes (e.g., breakage of a specimen-containing tube). Additional manipulations, such as automated pipetting of an organism-containing suspension, specimen grinding, blending, shaking, or procedures involving suspension in liquid for standardized concentration in identification, may

necessitate more in-depth examination. This could involve the inclusion of steps deemed as major aerosol-generating activities.

Antimicrobial post-exposure prophylaxis (PEP)

Individuals with high-risk exposures are advised to commence antimicrobial post-exposure prophylaxis at the earliest opportunity, with initiation possible up to 24 weeks after exposure. PEP is generally not recommended for low-risk exposures, though consideration may be given on a case-by-case basis. PEP courses typically involve oral administration of doxycycline (100 mg) twice daily and rifampin (600 mg) once daily for a minimum duration of 21 days. In cases where doxycycline or rifampin is contraindicated, trimethoprim-sulfamethoxazole (TMP-SMZ) or another antimicrobial agent effective against Brucella should be selected for a minimum of 21 days. All decisions regarding PEP regimen and dosing should be made in consultation with the healthcare provider of the affected individual. If clinical symptoms manifest at any point during PEP, and brucellosis infection is confirmed by culture and isolation or serology, PEP is no longer appropriate, and treatment along with monitoring becomes imperative.

Individuals who are pregnant, less than 8 years old, or have contraindications to the specified antimicrobial agents should consult their healthcare provider for alternative PEP. Suitable combinations of agents may be chosen from the treatment references provided earlier.

- Exposure to B. abortus RB51: In the event of exposure to the rifampin-resistant B. abortus RB51 vaccine, PEP should consist of doxycycline combined with another appropriate antimicrobial (such as TMP-SMX) for a duration of 21 days.16 The details regarding the PEP regimen and dosage should be determined in collaboration with the individual's healthcare provider, particularly if there are contraindications to the aforementioned medications.

Symptom surveillance

An occupational health provider should coordinate regular monitoring (at least weekly) for febrile illness or symptoms consistent with brucellosis for all individuals exposed. Additionally, a protocol of daily self-administered temperature checks is recommended for a duration of 24 weeks post-exposure, starting from the last known date of exposure. Exposed individuals should be educated about typical brucellosis symptoms and encouraged to promptly seek medical attention if any illness develops within six months of the exposure, irrespective of whether they have undergone PEP. Workers should notify their healthcare provider of recent Brucella exposure to ensure that diagnostic laboratories are informed and can take appropriate precautions. Individuals with risk factors for brucellosis relapse may necessitate follow-up beyond the initial 24-week period.

- B. canis and B. abortus RB51: Vigilant symptom monitoring is crucial after exposures to Brucella canis and Brucella abortus RB51 vaccine since there is a scarcity of serological tests for identifying seroconversion. These resources can be disseminated to occupational health staff.

Serological monitoring

For all individuals exposed, it is imperative to undergo quantitative serological testing to detect an immune response to Brucella spp. Evidence suggests that seroconversion may occur shortly before the manifestation of symptoms, making it a potential early indicator of infection. To facilitate comprehensive monitoring, it is advised that sera be collected and submitted to the same laboratory at 0 (baseline), 6, 12, 18, and 24 weeks following the exposure event.

The ZSAL at the CDC offers the service of performing serial serological monitoring at no cost. In cases where monitoring is conducted by other laboratories, it is recommended that an agglutination assay be employed to quantitatively assess seroconversion.

B. canis and B. abortus RB51: Presently, there is a lack of serological testing availability for Brucella canis and Brucella abortus RB51 vaccine. Consequently, serological monitoring subsequent to exposure to these strains is not advised, with the exception of obtaining a baseline serum sample to eliminate the possibility of infection with other Brucella spp.

<u>Clinical exposure</u>

It is imperative to adhere to universal precautions and utilize personal protective equipment (PPE) when dealing with body fluids or tissues from a patient with brucellosis. When standard precautions are diligently followed, the majority of clinical procedures are categorized as low-risk activities. Activities posing a higher risk may involve the handling of tissues with potentially elevated concentrations of Brucella organisms (e.g., placental tissues), direct contact with infected blood and body fluids via breaks in the skin, or mucosal exposure to aerosolized Brucella organisms following an aerosol-generating procedure.

Aerosol-Generating Procedures: Aerosols are defined as particles with a diameter less than 10 µm suspended in the air. Aerosol-generating procedures are those that generate aerosols due to mechanical disturbance of the blood or another body fluid18. Such procedures may encompass, but are not confined to, activities like cardiopulmonary resuscitation, disturbance of fluids from an abscess, the use of saws or other electrical devices, and high-pressure irrigation. Further details regarding the application of electrical and irrigation devices can be found in the Surgical Exposure section below.

To the best of our knowledge, seven cases of occupationally acquired brucellosis have been reported in the English literature among healthcare workers since 1990. This includes four infections acquired during obstetrical delivery and three infections through the provision of medical care to brucellosis patients. In each instance, it is likely that healthcare workers were exposed through the high-risk routes of transmission previously mentioned (handling of placental tissues, direct contact with infected blood/tissues, and mucosal exposure to aerosolized Brucella).

Surgical exposure

If a Brucella exposure occurs during a surgical procedure, it is imperative to assess the potential risk for all personnel involved in the surgical unit. Evaluations should consider the extent of compliance with PPE requirements, the types of surgical devices employed, the risk of aerosolization, and the duration of the surgical procedure. The subsequent paragraph, coupled with Table 5, can serve as a reference for conducting a comprehensive risk assessment.

Risk Assessment: Previous definitions of high-risk exposures in surgical settings encompass being present in an operating room during an aerosol-generating event and participating in the cleaning of the operating room after such a procedure. Aerosol-generating procedures may involve, among others, the use of saws or other electrical devices, cardiopulmonary resuscitation, disturbance of fluids from an abscess, and high-pressure irrigation. The assessment of the risk of aerosolization following irrigation should consider the water pressure from the irrigation tool used. High-pressure washes and pulsed lavages are generally categorized as high-pressure irrigation, and their use should be treated as an aerosol-generating event. While hand bulbs are typically considered low-pressure irrigation devices, additional factors, such as surgical technique, should be taken into account before conclusively ruling out this mechanism as an aerosol-generating procedure.

Pre-operative recommendations for surgery on a brucellosis patient include:

- Initiate antibiotic therapy for the patient to reduce the bacterial load in the surrounding tissues.
- Precautions for medical staff before and during the operation:
    - Minimize the use of aerosol-generating procedures throughout the surgical process.
    - Limit the presence in the operating room to essential personnel only.
    - All staff in the operating room should don appropriate PPE, including:
        - Gloves, masks, and eyewear

        - Respiratory protection (e.g., N95) if there is a potential for aerosol-generating procedures.

Post-operative recommendations for surgery on a brucellosis patient include:

- Examination of staff following potential exposure to Brucella organisms should encompass:
    - A comprehensive review of the adequacy of PPE and potential breaches in PPE protocol during the surgical procedure, involving:
        - Symptom and serological monitoring (as applicable) for all personnel identified with a breach in PPE.
        - Deliberation on PEP for all personnel present during or after a potential aerosol-generating procedure.
- Serological monitoring (as applicable) and consideration of PEP for staff members who are pregnant or immunocompromised.
    - Workers are advised to seek medical consultation with their healthcare provider.

Veterinary exposures

Exposure to vaccines

Incidental exposures to live, attenuated vaccine strains of Brucella spp. among veterinarians have been documented, occurring through needle stick injuries and exposure to conjunctiva and open wounds via spray. Individuals administering RB51, S19, and Rev-1 vaccinations are advised to utilize appropriate PPE, incorporating gloves and eye protection. Proper animal restraint is essential to minimize the risk of needle sticks or conjunctival splashes.

Brucella abortus RB51 vaccine

The Brucella abortus RB51 vaccine stands as the exclusive vaccine employed in the United States to prevent brucellosis in cattle herds. While RB51 was designed to be less pathogenic and abortifacient in animals compared to the S19 strain, it does retain pathogenicity in humans. Local adverse events have been reported within 24 hours of exposure, and systemic reactions may manifest 1 to 15 days post-exposure.

- Risk Assessment: Given that vaccine exposures typically occur through direct contact, all individuals exposed to RB51 should be regarded as having a high-risk exposure.
- Symptom Monitoring: Emphasis on symptom monitoring is crucial following exposures to the RB51 vaccine due to the absence of serological tests for identifying seroconversion.

- Antimicrobial PEP: Antibiotic post-exposure prophylaxis is recommended for individuals accidentally exposed to the B. abortus RB51 vaccine. Consult Tables 9,10,11 for PEP guidance. Rifampin, being ineffective due to the strain's resistance, should not be used for PEP. The strain also exhibits resistance to penicillin.
- Serological Monitoring: The RB51 vaccine, being a modified live culture vaccine, currently lacks available serological assays to detect an antibody response to RB51.

Brucella abortus S19 vaccine and Brucella melitensis Rev-1 vaccine

The B. abortus S19 and the B. melitensis Rev-1 vaccines, employed for animal brucellosis outside the U.S., have been associated with inducing systemic disease in humans. Given the extensive human travel and animal trading, instances may occur in the U.S. where individuals are exposed to the vaccine or animals previously vaccinated.

- Risk Assessment: Considering that vaccine exposures usually result from direct contact, all individuals exposed to S19 or Rev-1 strains should be regarded as having a high-risk exposure.
- Antimicrobial PEP: CDC recommends a concurrent prophylaxis regimen of doxycycline and rifampin for three weeks following exposure to the S19 and Rev-1 vaccine strains. Consult Tables 9,10,11 for PEP guidance. Rev-1 displays resistance to streptomycin; hence, this drug should not be employed for PEP or treatment courses.
- Serological Monitoring: For exposures to S19 and Rev-1, serological monitoring is an available option. It is advisable to prioritize quantitative serological monitoring to identify B. abortus S19 infections among veterinary workers, given that patients may exhibit mild clinical symptoms or remain asymptomatic.

<u>Clinical exposure</u>

Veterinarians and breeders face an elevated risk of contracting brucellosis due to their close and direct interaction with infected animals. This heightened risk is compounded by inconsistencies in adhering to standard precautions within veterinary practice.

The greatest risk of exposure occurs when veterinarians handle animals experiencing abortion or parturition. However, high-risk activities also encompass specimen draws during clinical examinations, surgical procedures, and the disinfection and cleaning of contaminated environments. Common routes of exposure during these high-risk procedures include the inhalation of aerosolized Brucella organisms and the contamination of the conjunctiva or broken skin.

Exposure to Brucella canis

Dogs, while susceptible to various Brucella spp., primarily serve as the host for Brucella canis. B. canis is generally considered less virulent than other strains of Brucella species, and the documentation of human cases has been limited, possibly influenced by diagnostic challenges and underreporting.

- Symptom Monitoring: It is crucial to emphasize symptom monitoring following exposure to dogs infected with brucellosis due to the absence of serological tests for identifying seroconversion.
- Serological Monitoring: Although serological monitoring is not available for B. canis exposures, it is recommended to draw baseline serum for serological testing to rule out titers to other Brucella spp., given that veterinary personnel may encounter a variety of species.
- Antimicrobial PEP: A prophylaxis regimen should be considered for all personnel with high-risk exposures. Refer to tables 14, 15, and 16 for PEP guidance.

Marine mammal exposure

Since 2010, numerous marine mammals stranded along the Gulf of Mexico, Atlantic, and Pacific coasts have exhibited laboratory evidence of brucellosis infection. While cases of marine-associated brucellosis in humans have not been recorded in the U.S., four instances have been documented globally. One individual was exposed in a laboratory while handling samples from an infected dolphin, and three individuals fell ill after consuming raw fish or shellfish. Those who come into contact with marine mammals, especially those stranded or visibly unwell, face potential infection risks from B. ceti or B. pinnipedialis.

- Risk Assessment: Engaging in activities with infected marine mammals that involve aerosol-generating procedures (such as the use of saws) or cleaning facilities with high-pressure equipment during and after a necropsy presents a higher risk. Failure to utilize personal PPE, including appropriate respiratory protection, during these activities increases the likelihood of occupational exposure to Brucella spp.
- Symptom Monitoring: Individuals exhibiting signs and symptoms up to 24 weeks after exposure to infected marine mammals are advised to promptly consult their local healthcare provider for diagnosis. It is crucial to inform the doctor that there may have been exposure to an infectious zoonotic disease, such as Brucella.
- Serological Monitoring: Serologic testing for B. ceti and B. pinnipedialis can be conducted using the BMAT. For individuals at high risk, baseline sera should be obtained as soon as the exposure is identified, followed by subsequent

draws at 6-week intervals up to 24 weeks post-exposure, adhering to the sequence for laboratory exposures.

- Antimicrobial PEP: Recommendations for antimicrobial post-exposure prophylaxis following a marine mammal exposure are contingent on the risk assessment for the individual exposed. Refer to tables 14, 15, and 16 for guidance on PEP.
- Reporting: Any human illness linked to exposure to zoonotic diseases should be promptly reported to the stranding facility and the National Marine Fisheries Service (NMFS) Regional Office by sending an email to the Regional Stranding Coordinators.

Recreational exposure

Feral swine hunting

- Approximately 25 to 30% of the brucellosis cases reported annually to the CDC in the United States are attributed to B. suis, with almost all diagnoses occurring among feral swine hunters (CDC, unpublished data). Feral swine have been documented in at least 41 states, and serologic surveys indicate endemic B. suis infection in feral swine populations across 13 states (Arkansas, California, Florida, Georgia, Hawaii, Louisiana, Mississippi, Missouri, South Carolina, and Texas). Feral swine hunting is permitted in most states with a feral swine presence. Out-of-state hunters often transport swine meat back to their home states, leading to cases even in regions where B. suis is not endemic in feral swine populations.
- Preventive efforts against B. suis infection should concentrate on educating hunters and fostering collaborations between state and local public health, wildlife and agricultural agencies, and sportsmen's associations. Brochures from the CDC specifically tailored for feral swine hunters are available for public distribution and can be accessed in the Additional Sources of Brucellosis Information section.
- It is crucial to acknowledge that dogs can contract brucellosis from feral swine. Transmission may occur through direct contact with swine or by ingesting uncooked pork or scraps. Even non-hunting dogs can become infected by coming into contact with hunting dogs through urine or during breeding. Individuals who hunt with dogs should be advised not to allow their dogs to play with animal carcasses or consume raw meat. If dogs exhibit symptoms consistent with brucellosis (refer to Additional Sources of Brucellosis Information, Brucellosis in Animals), they should undergo testing for Brucella spp.

Foodborne exposure

Approximately 70 to 75% of annual brucellosis cases reported in the U.S. to the CDC result from B. melitensis and B. abortus. These cases typically occur when individuals consume unpasteurized dairy products originating from countries where brucellosis remains endemic. Currently, high-risk areas include the Mediterranean Basin (Portugal, Spain, Southern France, Italy, Greece, Turkey, and North Africa), Mexico, South and Central America, Eastern Europe, Asia, Africa, the Caribbean, and the Middle East. Prevention efforts should prioritize educating immigrants and international travelers about the risks associated with consuming unpasteurized dairy products from these regions. Feral swine hunters who consume raw or undercooked pork also face a risk of foodborne exposure to brucellosis (via B. suis).

In instances of foodborne brucellosis, systemic symptoms are more commonly reported than gastrointestinal complaints. Some patients may experience nausea, vomiting, and abdominal discomfort, and there have been rare cases of ileitis, colitis, and spontaneous bacterial peritonitis reported.30 Individuals who develop a febrile illness after consuming unpasteurized dairy products or meat from feral swine should be encouraged to submit samples of the food for culture and PCR to confirm the route of transmission.

Brucellosis in pregnant women

Brucellosis during pregnancy poses a heightened risk of spontaneous abortion, especially in the first and second trimesters. Consequently, women should promptly seek medical treatment with appropriate antimicrobials.

The commonly recommended antimicrobial therapy for pregnant women is **rifampin** at a dosage of 15-20 mg/kg per day (maximum 600-900 mg/day) for a duration of 6 weeks. **Rifampin** is categorized as an FDA Pregnancy Category C drug, signifying a lack of sufficient studies or data demonstrating risk in humans, but animal studies have indicated adverse effects on the fetus with the use of this drug.

Additionally, a combination therapy regimen involving **rifampin** (15-20 mg/kg per day, maximum 600-900 mg/day) along with **trimethoprim-sulfamethoxazole** (TMP-SMZ) at 160mg-800 mg twice daily for six weeks has been mentioned in the literature.

- It is crucial to note that TMP-SMZ should not be administered after 36 weeks of pregnancy due to the risk of kernicterus resulting from elevated bilirubin levels. Moreover, the teratogenic potential of various antimicrobials, including rifampin and TMP-SMZ, remains unknown in humans.
- Information regarding the use of doxycycline during pregnancy is limited, and the FDA classifies it as a Pregnancy Category D drug. This classification is based on data extrapolated from the use of tetracycline in both humans and

animals. A Pregnancy Category D designation indicates that there is positive evidence of human fetal risk, but in certain situations, the benefits of drug use may outweigh potential risks. Studies on tetracyclines have shown effects such as infant dental staining, fetal growth delays, and maternal fatty liver. However, reviews of studies on doxycycline use among pregnant women have not demonstrated these findings. The risk-benefit ratio for the use of doxycycline must be carefully considered, especially if rifampin is unavailable or contraindicated.

Neonatal brucellosis

Although neonatal brucellosis cases are infrequent, infection can occur through transplacental transmission of Brucella spp. during a maternal bacteremic phase, exposure to blood, urine, or vaginal secretions during delivery, or through breastfeeding. The majority of documented neonatal brucellosis cases involve B. melitensis, although cases of B. abortus have also been reported.

- Signs and Symptoms: Clinical manifestations typically resemble sepsis and include fever, resistance to feeding, irritability, vomiting, jaundice, respiratory distress, pulmonary infiltrates, hypotension, hyperbilirubinemia, and thrombocytopenia. Progression of the disease state may be evidenced by hepatomegaly, splenomegaly, and lymphadenitis. In some cases, patients may be asymptomatic, or clinical symptoms may present later in infancy.
- Serological Testing: Information from peer-reviewed literature suggests that Brucella spp. may be isolated from neonatal patients with titer levels lower than 1:160.
- Treatment: Dual-combination antimicrobial therapy should be administered for several weeks. Duration and dose of treatment should be determined in consultation with the patient's neonatologist or pediatrician.
- Prevention: As Brucella bacteremia during pregnancy carries the risk of causing spontaneous abortion (particularly during the first and second trimester) or transmission to the infant, pregnant women should avoid consuming unpasteurized dairy products and engaging in high-risk occupational activities such as contact with infected animals or administration of live attenuated Brucella vaccines. Prompt diagnosis and treatment are essential to ensure a healthy pregnancy. Women exposed to Brucella spp. or diagnosed with brucellosis should consult their obstetrician for PEP and treatment options.

Sexual transmission

Since 1966, nine case reports have been published in English literature providing evidence of person-to-person transmission of brucellosis. In each of these cases, a male patient displaying symptoms consistent with brucellosis was believed to have transmitted Brucella spp. to a female partner through sexual intercourse. While such occurrences are rare, it is crucial to acknowledge that sexual partners of infected patients may be at risk of brucellosis exposure.

Organ donations and blood transfusions

While infrequent, transmission of Brucella spp. may also occur through tissue transplantation or blood transfusions. Reported cases of brucellosis caused by blood transfusion are rare, with the earliest case dating back to 1955, and all instances reported outside of the United States. There are documented cases of transmission due to transplantation, including instances attributed to bone marrow donation between siblings. In other published reports of brucellosis in transplant recipients, it is challenging to determine if the infection was acquired from the transplant or through other modes of infection. If a patient who has recently undergone a transfusion or transplant develops symptoms consistent with brucellosis, the CDC Office of Blood, Organ, and Other Tissue Safety should be contacted for assistance in conducting trace-back investigations.

Prevention

Occupational exposures

Exposure to Brucella spp. can occur in various occupational environments, encompassing laboratories, clinical and surgical settings, as well as veterinary settings. In instances involving high-risk exposures it is recommended to implement post-exposure antimicrobial prophylaxis.

Clinicians should communicate with laboratory personnel when dealing with patient specimens that are suspected or are being considered for brucellosis. Laboratory personnel should conduct work involving Brucella spp. within a Class II Biological Safety Cabinet (BSC), utilizing proper PPE and employing primary and secondary barriers. This approach aligns with the Biosafety in Microbiological and Biomedical Laboratories (BMBL), which provides guidance on laboratory containment methods and microbiological procedures. Procedures should be in place to minimize the risk of exposure to spills, splashes, and aerosol-generating events when working with Brucella spp. or other infectious organisms.

In clinical, surgical, and veterinary settings, procedures should be executed judiciously to reduce the occurrence of spills, splashes, and aerosols. Depending on the nature of the procedures performed, PPE should offer ample protection to minimize direct contact with the skin and mucous membranes, as well as exposure

to aerosols. Appropriate PPE may include gloves, closed footwear, eye protection, a face shield (as necessary based on the procedure), and respiratory protection (as necessary depending on the procedure).

Recreational exposures (hunter safety)

Engaging in wild animal hunting poses potential risks of exposure to infectious diseases, including brucellosis. Certain wild animals such as feral swine, elk, moose, bison, deer, and caribou can carry brucellosis and serve as a source of transmission. Predatory animals may also become susceptible to brucellosis after consuming infected prey. When participating in hunting activities, it is crucial to steer clear of contact with animals found dead or visibly unwell. Even seemingly healthy animals may carry brucellosis, emphasizing the importance of employing safe field dressing techniques to protect hunters.

Here are recommended precautions for safe field dressing and handling:

- Utilize clean, sharp knives for field dressing and butchering.
- Wear eye protection and nonporous, disposable gloves (e.g., rubber, nitrile, or latex) when handling carcasses.
- Avoid direct (bare skin) contact with fluids or organs from the animal.
- Steer clear of direct (bare skin) contact with hunting dogs that may have had contact with hunted animals.
- After butchering, dispose of disposable gloves and parts of the carcass that will not be consumed by burning or burying.
- Refrain from feeding dogs raw meat or other parts of the carcass.
- Wash hands promptly with soap and warm water for at least 20 seconds. Dry hands with a clean cloth.
- Clean all tools and reusable gloves with a disinfectant, such as dilute bleach (following safety instructions on the product label).
- Thoroughly cook meat from any animal known to be a possible carrier of brucellosis.
- Be aware that freezing, smoking, drying, and pickling do not eliminate Brucella.

Travel to endemic areas

Brucellosis is prevalent in numerous regions globally. Areas with elevated risk include Mexico, South and Central America, Eastern Europe, Asia, Africa, the Caribbean, the Middle East, and the Mediterranean Basin (encompassing Portugal, Spain, Southern France, Italy, Greece, Turkey, and North Africa). When embarking on travel to these regions, exercise caution and refrain from direct contact with

livestock while also avoiding the consumption of raw animal products. The ingestion of raw or undercooked meat, as well as raw or unpasteurized dairy items, poses a potential risk for Brucella transmission, potentially resulting in illness.

1.3 European Guidelines

1.3.1 Medecins Sans Frontieres (MSF) Clinical Guidelines on the Diagnosis and Treatment of Brucellosis (2022)

The main recommendations from the MSF guidelines on the diagnosis and treatment of brucellosis are summarized below[7].

Clinical features

Acute form (primary infection)

Remittent or intermittent fever (39-40°C) is accompanied by various signs or symptoms such as chills, night sweats, joint and muscle pain, weight loss, fatigue, malaise, and headache. Additionally, adenopathies, particularly in children, may be present. This fever pattern may also be linked to non-specific gastrointestinal issues, cough, hepato and/or splenomegaly, as well as arthritis (particularly in the knee) and orchitis.

Diagnosing brucellosis is challenging due to the wide range of fluctuating and non-specific clinical symptoms. In cases of unexplained fever, consideration of brucellosis is warranted, especially when risk factors such as the consumption of unpasteurized milk products or exposure to livestock (e.g., livestock farmers, veterinarians, butchers, slaughterhouse workers) are present.

Localized form

The initial infection can develop into localized manifestations, sometimes occurring months or even years later, predominantly affecting:

- Osteoarticular system: Involving the sacroiliac joint and frequently affecting joints in the lower limbs; spine complications, including intervertebral disk infection and vertebral osteomyelitis.
- Genito-urinary system: Resulting in conditions such as orchitis and epididymitis.
- Pulmonary system: Leading to bronchitis, pneumonia, and pleurisy.
- Neurological system: Causing complications like meningitis, encephalitis, and polyneuritis.

Paraclinical investigations

Laboratory

Blood culture stands as the definitive diagnostic method, acknowledged for its accuracy, but it's only effective during the acute phase. The bacteria exhibit slow growth, requiring a period of 7 to 21 days.

Serological tests, including the Rose Bengal, Wright agglutination test, indirect immunofluorescence, ELISA, among others, offer presumptive diagnoses.

When neurological signs or meningitis are present, a lumbar puncture reveals clear cerebrospinal fluid (CSF) with potential indications such as a high white blood cell count, elevated protein concentration in CSF, and decreased CSF glucose.

In regions where malaria is endemic, a rapid test should be employed to rule out this possibility. Additionally, if a cough persists for more than two weeks, tuberculosis should be excluded through sputum smear microscopy.

Radiography

Joint pain, affecting areas such as the hips, knees, ankles, vertebrae, and the sacroiliac joint, manifests with small erosions, joint space narrowing, and occasional destruction. The spine, especially the lumbar region, is frequently involved, leading to spondylodiskitis.

In terms of pulmonary signs, chest X-rays frequently appear normal, although some cases may display indicators such as consolidation, nodules, lymphadenopathy, or pleural effusion.

Treatment

When available, national recommendations should be followed. Treatment options are listed in table 17:

Table 17. MSF Treatment Recommendations

Children under 8 years	Co-trimoxazole + rifampicin Or co-trimoxazole + gentamicin
Children 8 years and over	Doxycycline + rifampicin Or doxycycline + gentamicin
Adults	Doxycycline + rifampicin Or doxycycline + streptomycin or gentamicin
Pregnant/breastfeeding women	Rifampicin

- **Co-trimoxazole** PO for 6 weeks

Children < 8 years: 20 mg SMX + 4 mg TMP/kg (max. 800 mg SMX + 160 mg TMP) 2 times daily

- **Doxycycline** PO for 6 weeks

  Children ≥ 8 years and < 45 kg: 2 to 2.2 mg/kg (max. 100 mg) 2 times daily

  Children ≥ 45 kg and adults: 100 mg 2 times daily

- **Rifampicin** PO for 6 weeks

  Children: 15 to 20 mg/kg (max. 600 mg) once daily
  Adults: 600 to 900 mg once daily

- **Gentamicin** IM for 2 weeks

  Children and adults: 5 mg/kg once daily

- **Streptomycin** IM for 2 weeks

  Adults: 1 g once daily

For localized forms of the infection, same treatment but for a period of 6 weeks to 4 months depending on the focus.

Prevention

It is crucial to wash hands and clothing thoroughly after any contact with animals. Additionally, boiling milk and refraining from consuming unpasteurized milk products are essential preventive measures. Furthermore, it is advisable to ensure thorough cooking of offal.

1.4 International Guidelines

1.4.1 World Health Organization (WHO) Brucellosis in Humans and Animals (2006)

These guidelines published in 2006 were produced by the World Health Organization in collaboration with the Food and Agriculture Organization of the United Nations and World Organization for Animal Health[1].

Etiology

Brucellosis, a bacterial infection originating from various Brucella species, primarily affects cattle, swine, goats, sheep, and dogs. Human transmission typically occurs through direct contact with infected animals, consumption of contaminated animal products, or inhalation of airborne agents. The majority of cases result from consuming unpasteurized milk or cheese from infected goats or sheep. Brucellosis stands out as a prevalent zoonotic disease transmitted by animals, posing significant

public health risks in endemic regions. The ongoing challenges include the expansion of animal industries, urbanization, and insufficient adherence to hygienic practices in animal husbandry and food handling, contributing to the persistent public health threat of brucellosis.

Transmission

Brucellosis is a globally distributed, reportable disease affecting individuals of all ages and genders. In the general population, the majority of cases arise from the consumption of raw milk or its derivatives, particularly fresh cheese, with most instances linked to sheep and goat products. Beyond the general public, the disease is recognized as an occupational hazard for those engaged in the livestock sector. Individuals in close contact with animals, particularly with exposure to blood, placenta, fetuses, and uterine secretions, face an elevated risk of contracting brucellosis. This mode of transmission predominantly impacts farmers, butchers, hunters, veterinarians, and laboratory personnel. Brucella melitensis stands out as the most prevalent species causing human brucellosis globally, partly due to challenges in immunizing free-ranging goats and sheep. Human-to-human transmission remains exceedingly rare.

Prevention and control

Preventing brucellosis hinges on surveillance and mitigating risk factors, with the primary strategy being the eradication of infection in animals. In areas with high prevalence rates, the recommended approach includes vaccinating cattle, goats, and sheep. In regions with low prevalence, serological testing and culling can prove effective. In situations where complete eradication in animals is not feasible, preventing human infection centers on raising awareness, implementing food-safety measures, ensuring occupational hygiene, and maintaining laboratory safety. Pasteurization of milk, both for direct consumption and the production of derivatives like cheese, is a crucial measure to curtail transmission from animals to humans. Educational initiatives emphasizing the avoidance of unpasteurized milk products, along with policies regulating their sale, can be impactful. In agricultural and meat-processing settings, employing protective barriers and adhering to proper handling and disposal practices for afterbirths, animal carcasses, and internal organs constitutes a vital prevention strategy.

Treatment and care

Brucellosis typically manifests with flu-like symptoms such as fever, weakness, malaise, and weight loss, although the disease can present in various atypical forms. In many cases, symptoms are mild, leading to potential oversight in diagnosis. The incubation period varies, spanning from 1 week to 2 months, with an average of 2–4 weeks.

Treatment options encompass **doxycycline** at 100 mg twice daily for 45 days, combined with **streptomycin** at 1 g daily for 15 days.

An alternative therapy involves **doxycycline** (100 mg, twice daily for 45 days) along with **rifampicin** at 15 mg/kg/day (600-900 mg) for 45 days.

While experience suggests that **gentamicin** (5 mg/kg/daily for 7–10 days) may substitute for streptomycin, no direct comparative study between the two regimens is currently available.

Fluoroquinolones may be used for the treatment of brucellosis; however, when used as monotherapy, relapse rates were unacceptably high due to a lack of bactericidal activity. Quinolones should always be used in **combination** with other drugs, such as **doxycycline** or **rifampicin**.

Complications

1. Spondylitis

Osteoarticular complications of brucellosis are common. Some manifestations like sacroiliitis do not require special treatment. Others, such as complicated spondylitis and osteomyelitis may require prolonged therapy, such as the continuation of doxycycline for eight weeks or more.

2. Neurobrucellosis

The main challenge in the treatment of neurobrucellosis consists of achieving high concentrations of drugs in the cerebrospinal fluid (CSF). Since tetracyclines and aminoglycosides do not penetrate the blood/brain barrier well, it is recommended that drugs which achieve this, such as rifampicin or co-trimoxazole, be added to the standard regimen of doxycycline plus streptomycin. A duration of treatment of 6 to 8 weeks is generally recommended, however, prolonged treatments may be needed depending on clinical response.

3. Brucella endocarditis

Infective endocarditis caused by brucellosis is the most fatal of complications seen. Bactericidal concentrations of drugs need to be achieved within the valvular vegetations. Antimicrobial chemotherapy and surgical replacement of the damaged valve are often necessary. The combination of doxycycline plus an aminoglycoside results in rapid killing of the bacteria, and rifampicin or co-trimoxazole are used for their ability to penetrate cell membranes. Prolonged therapy is recommended (at least eight weeks), and therapy should be continued for several weeks after surgery when valve replacement is necessary.

Pregnancy

The optimal treatment for pregnant women, neonates, and children under 8 remains undetermined. All drugs cross the placenta in varying degrees, thus exposing the fetus to potential adverse drug effects. Tetracyclines are contraindicated in pregnancy owing to the potential for permanent staining of fetal dentition, and the susceptibility of pregnant women to drug-induced fatty necrosis of the liver and pancreatitis. Co-trimoxazole has been used in individual cases with reported success. Another alternative is rifampicin therapy for at least 45 days depending on the clinical outcome.

Children less than 8 years of age

For children, potential options include **trimethoprim/sulfamethoxazole** (co-trimoxazole) combined with an **aminoglycoside (streptomycin, gentamycin**) or rifampicin.

WHO response

WHO offers technical guidance to member states by providing standards, information, and recommendations for the control of brucellosis in both humans and animals. The organization actively promotes the coordination and exchange of information between the public health and animal health sectors. In partnership with the Food and Agricultural Organization of the United Nations (FAO), the World Organisation for Animal Health (OIE), and the Mediterranean Zoonoses Control Programme (MZCP), WHO collaborates to assist countries in preventing and managing the disease through the Global Early Warning System for Major Animal Diseases (GLEWS).

1.4.2 Guidelines for the Management of Human Brucellosis in the State of Paraná, Brazil (2017)

A Working Group was established as a resolution of the State of Paraná, Brazil restructure and upgrade the State Protocol on Human Brucellosis. The panel members defined questions to be answered during the management of patients with brucellosis, which included: 1) epidemiological definitions of cases; 2) the most common signs and symptoms; 3) diagnostic tests and interpretation; 4) the treatment and follow-up; 5) definition of therapy failure and cure. The panel members also defined questions to be answered about the management of human exposure to *Brucella* in the following conditions: 1) vaccine exposition; 2) laboratorial; 3) patient contact; 4) workplace with infected animals with brucellosis. The definitions on the strength and quality of the recommendations were the same as those used by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID). The strength of these recommendations was defined as follows: A,

strongly recommended; B, moderately recommended; C, marginally recommended; D, not recommended. The quality of the evidence was defined as follows: level I, at least one properly designed randomized controlled trial; level II, well designed clinical trial without randomization, case-control, or cohort studies; or level III, opinion of respected authorities, case reports, and clinical experience. These recommendations were used for therapy and prophylaxis. The main recommendations on pharmacotherapy are summarized below[8]:

Case definitions

Suspect case: a patient with acute or insidious disease characterized by fever and one or more of the following signs or symptoms: night sweats, arthralgia, headache, fatigue, anorexia, myalgia, arthritis/spondylitis, meningitis, focal or organ involvement (endocarditis, orchitis/epididymitis, hepatomegaly, and splenomegaly). Additionally, the patient had to have a suggestive epidemiological history of contact with contaminated animal products, occupational exposure, or handling animals affected by brucellosis.

Confirmed case: A suspected case, with coinciding laboratory confirmation of brucellosis.

Discarded case: A suspect case with laboratory findings negative for brucellosis and/or a diagnosis confirmed for another disease.

Laboratory diagnosis

Culture is the gold standard method for the diagnosis of human brucellosis. Due to the high risk of laboratory-acquired infection, molecular methods for the speciation and subtyping of *Brucella* isolates have replaced the conventional method. Direct methods include isolation and identification of *Brucella*, immunohistochemistry and detection of nucleic acids using polymerase chain reaction (PCR). Indirect tests detect anti-*Brucella* antibodies which can be positive in patients with a history of brucellosis. The serological response to infection by *Brucella* is influenced by many factors such as the incubation period of the disease, which is highly variable and during which the serology may be negative. However, current serological tests have an accuracy of 95%.

The methods chosen for laboratory diagnosis of brucellosis by this working group were Rose Bengal (serum agglutination), enzyme immunoassay (EIA) IgG and IgM, and real time PCR (figure 2).

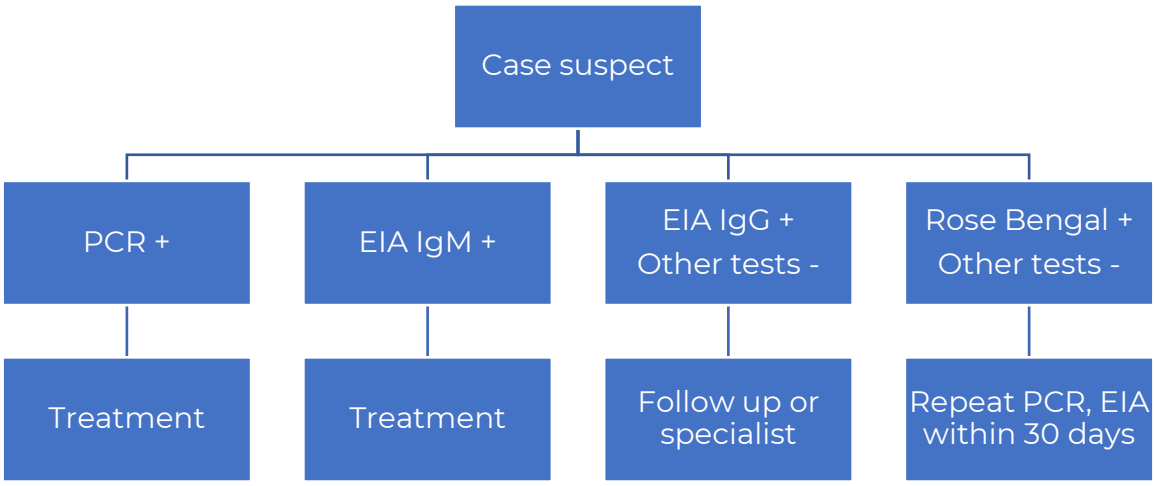

Figure 2. *Management of suspect cases of brucellosis*

Treatment and follow-up

The treatment of choice for each site of infection with brucellosis is detailed in table 18, and recommendations for clinical and laboratory are listed in table 19.

Table 18. Treatment of Brucellosis Patients According to Age, Weight, and Site

Disease		Choice	Duration (days)
Uncomplicated brucellosis (adults or > 30 kg)	1st choice	Doxycycline 100 mg q12h + Gentamycin 5 mg/kg q24h	42 7
	Alternative	Doxycycline 100 mg q12h + Rifampin 300 mg q12h	42 42
Uncomplicated brucellosis (children ≤ 7 years or < 30 kg)		SMX/TMP 40/8 mg/kg 12/12h + Gentamycin 5 mg/kg q24h	42 7
Brucellosis in pregnant women*		SMX/TMP 40/8 mg/kg 12/12h + Gentamycin 5 mg/kg q24h	42 7
Spondylodiscitis**		Doxycycline 100 mg q12h + Gentamycin 5 mg/kg q24h + Rifampin 300 mg q12h	56 14 56
Neurobrucellosis		Doxycycline 100 mg q12h + SMX/TMP 25/5 mg/kg q6h +	56

	Rifampin 300 mg q12h	
Endocarditis***	Doxycycline 100 mg q12h + Gentamycin 5 mg/kg q24h + Rifampin 300 mg q12h	56 7 56

SMX: sulfamethoxazole; TMP: trimethoprim.

*Avoid in the last 4 weeks (change to rifampin).

** The treatment can be longer in those with chronic infection, in general, symptoms for more than 6 weeks.

***Indicative of surgery

Table 19. Clinical and Laboratory Follow-Up of Patients with Brucellosis

Time	Follow-up
Week 1	Evaluate drug adhesion
Week 2	Clinical evaluation, hemogram, creatinine, urea, liver enzymes, erythrocyte sedimentation rate, reactive C protein
Week 4	Clinical evaluation
Week 8	Clinical evaluation, hemogram, creatinine, urea, liver enzymes, erythrocyte sedimentation rate, reactive C protein
Week 12	Clinical evaluation, hemogram, creatinine, urea, liver enzymes, erythrocyte sedimentation rate, reactive C protein
Week 24	Clinical evaluation, hemogram, erythrocyte sedimentation rate, reactive C protein
Month 12	Clinical evaluation
Month 18	Clinical evaluation
Month 24	Clinical evaluation

Post-exposure prophylaxis (PEP)

Exposure to vaccine: for all accidents involving vaccinations, regardless of the vaccine, immediate PEP should be provided to the exposed individual. The drug of choice for PEP was doxycycline, which should be administered in 100 mg doses every 12 hours for 42 days. It is important to promote health education and guidance on the use of Personal Protective Equipment (PPE) to avoid reoccurring accidents.

Exposure to laboratory material: All individuals exposed to contaminated materials must be evaluated for the risk of exposure. The risk is stratified as high, low, or no risk. PEP is indicated for high and low risk exposures. The drug of choice for PEP was doxycycline, which should be administered in 100 mg doses every 12 hours for 21 days. Exposed individuals are followed up for 6 months with sequential serologic

testing (0, 6-, 12-, 18-, and 24-weeks post exposure), observation of symptoms (e.g. weekly), and daily self-fever checks. Table 20 details the laboratory risk levels and indications for PEP.

Table 20. Definition of Risk Levels for Post-Exposure Prophylaxis

Risk level	Person at risk	Risk definition	PEP
High	Individual	Sniffed or opened the culture plate using a maximum of BSL-2 precautions	Yes
	Person performing activity and any person within a 5ft. radius	Work with a *Brucella* isolate, sniffed or opened the culture plate, mouth pipetted specimen material, worked in a Class II biosafety cabinet or on open bench without using BSL-3 precautions	Yes
	All persons present in laboratory room	Occurrence of widespread aerosol generating procedures*	Yes
Low	All persons present in laboratory room at distance greater than 5ft. from activity	Present in the lab at the time of manipulation of a *Brucella* isolate on an open bench, but who do not have high risk exposures as defined above	May consider
None	All persons present in laboratory room	Handling and testing of a *Brucella* isolate in a Class II biosafety cabinet using BSL-3 precautions	None

PEP: post-exposure prophylaxis; BSL: biosafety level.

*Centrifuging without sealed carriers, vortexing, sonicating, accidents resulting in spillage or splashes (i.e. breakage of tube containing specimen).

1.5 Systematic Reviews & Meta Analyses

Table 21 tackles 3 systematic reviews and meta-analyses issued in **2022-2023** for Brucellosis.

Table 21. Systematic Review and Meta-Analyses for Brucellosis

Study	Author (year)	Primary Objective	Outcomes	Results
1	Beig et al. (2024)[9]	Determine the overall prevalence of fluoroquinolone resistance in B. melitensis and B. abortus isolates and identify any trends or patterns in the prevalence of resistance.	Data extracted included first author(s), year of publication, country, antimicrobial susceptibility technique (AST) (disc diffusion, E-test, agar dilution, broth dilution), AST guideline (CLSI, non-CLSI), source of isolates (human samples, animal samples), species (unidentified, B. melitensis, B. abortus)	The resistance rates to ofloxacin, sparfloxacin, fleroxacin, pefloxacin, and lomefloxacin were 2%, 1.6%, and 4.6%, respectively. Based on in vitro investigations, this systematic review and meta-analysis concluded that fluoroquinolones are effective against Brucella spp. Due to resistance to first-line treatment, recurrence, and toxicity of old medicines, standardization of the AST method for Brucella is essential, and studying new methods is crucial.
2	Huang et al. (2023)[10]	Assess efficacy of triple antibiotics therapy for human brucellosis	The differences in efficacy and side effects between triple antibiotics therapy and dual antibiotics therapy in the treatment of brucellosis.	Triple antibiotics showed better efficacy than dual antibiotics. The occurrence of side effects in individuals with brucellosis undergoing treatment with a combination of three antibiotics did not show a statistically significant distinction compared to brucellosis patients treated

				with a combination of two antibiotics.
3	Li et al. (2023)[11]	Follow-up outcomes of asymptomatic brucellosis	• Appearing symptomatic: fever, sweating, fatigue, headache, myalgia, or arthralgia • Maintaining asymptomatic: asymptomatic disease with high SAT titer • Decreased SAT titer: asymptomatic disease with low or negative SAT titer.	• The pooled prevalence of appearing symptomatic in the last decade was significantly higher than that in the period 1990–2009. • Most asymptomatic patients were men because they are more likely to work in high-exposure occupations such as veterinarians, slaughter workers, or herders. Asymptomatic brucellosis has both occupational and familial clusters. • Attention should be paid to the prevalence of brucellosis seropositivity in student groups in endemic areas, and if necessary, preventive medication can be used for those with high titer. • Education and public awareness of asymptomatic brucellosis should be strengthened to reduce the contact with infected animals and consumption of

				unpasteurized animal products.

Section 2.0 Drug Therapy

2.1 Tetracyclines

2.1.1 Doxycycline[12]

Table 22. Doxycycline Drug Information

SCIENTIFIC NAME **Doxycycline**[13]	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes 06/2005
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	A23
Drug Class	Antibiotic
Drug Sub-class	Tetracycline derivative
ATC Code	Oral: J01AA02
Pharmacological Class (ASHP)	Antibiotic, Tetracycline Derivative
DRUG INFORMATION	
Dosage Form	Tablet, Capsule Syrup Powder and solvent for solution for injection
Route of Administration	Oral
Dose (Adult) [DDD]*	Oral: IR and most ER formulations: 100 to 200 mg/day in 1 to 2 divided doses. Note: 60mg of modified polymer-coated tablet is equivalent to 50 mg conventional delayed-release tablet and 120 mg of modified polymer-coated tablet is equivalent to 100 mg conventional delayed-release tablet.
Maximum Daily Dose Adults*	The maximum dosage is **300 mg/day**, except in the case of acute gonorrheal

	infection, which is often treated with 600 mg/day for five days
Dose (pediatrics)	Doxycycline was traditionally avoided in ages < 8 years, but use has more recently been accepted for short courses (<21 days) for all ages when necessary. **Brucellosis**: Children ≥ 8 years and Adolescents: Oral: 2.2 mg/kg/dose twice daily for at least 6 weeks; maximum dose: 100 mg/dose; use in combination with rifampin; for serious infections, gentamicin should be added for initial 1 to 2 weeks and therapy may be extended for up to 4 to 6 months
Maximum Daily Dose Pediatrics*	200 mg/day only for children more than 8 year of age
Adjustment	**Altered Kidney Function:** The renal dosing recommendations are based upon the best available evidence and clinical expertise. **Mild to severe impairment:** No dosage adjustment necessary **Hemodialysis, intermittent (thrice weekly):** Poorly dialyzed (0% to 5%); no supplemental dose or dosage adjustment necessary. **Peritoneal dialysis:** Poorly dialyzed; no dosage adjustment necessary **CRRT:** No dosage adjustment necessary. **PIRRT** (e.g., sustained, low-efficiency diafiltration): No dosage adjustment necessary **Hepatic Impairment:** There are no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits*	Age, CU
AGE (Age Edit)	To be used in adults and children more than 8 year of age

CU (Concurrent Use Edit)	Doxycycline is to be given in combination with other agents (e.g., TMP/SMX, rifampicin)
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	N/A
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	N/A
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common:** headache, blurred vision, Oral candidiasis, Skin hyperpigmentation/dental discoloration **Most serious**: Intracranial hypertension, diplopia, vision loss, Superinfection Bone growth suppression Esophagitis, esophageal ulcer Photosensitivity
Drug Interactions*	**Category X:** BCG (Intravesical) Retinoic Acid Derivatives Strontium Ranelate
Special Population	**Neonatal**: Preterm neonates receiving oral tetracycline experienced a reversible decrease in fibular growth rate; data with doxycycline are unavailable; use caution **Pediatric**: Due to risks of permanent tooth staining, manufacturers generally recommend using tetracycline antibiotics in patients <8 years of age only when benefits outweigh the risks; however, studies have not validated the concern for tooth staining with short-term use of doxycycline (<21 days) and short-term use is considered acceptable in children regardless of age
Pregnancy	Tetracyclines cross the placenta

	A single prophylactic dose of doxycycline can be used in pregnant patients; the use of treatment doses should be individualized. Permanent discoloration of teeth (yellow, gray, brown) can occur following in utero exposure and is more likely to occur following long-term or repeated exposure.
Lactation	WHO states that maternal use of doxycycline should be avoided if possible but that a single dose or the short-term use of doxycycline is probably safe. There exists a possibility of dental staining and inhibition of bone growth in the infant, especially with prolonged use
Contraindications	Hypersensitivity to doxycycline, other tetracyclines, or any component of the formulation.
Monitoring Requirements	CBC, renal and liver function tests periodically with prolonged therapy. Patients with no risk factors for chronic Q fever should undergo clinical and serological evaluation 6 months after diagnosis of acute Q fever to identify possible progression to chronic disease. Postpartum women treated during pregnancy for acute Q fever, others who are at high risk for progression to chronic disease or when used as part of treatment for chronic Q fever infection unrelated to endocarditis or vascular infection (e.g., osteoarticular infections or chronic hepatitis), assess serologic response at 3, 6, 12, 18, and 24 months after diagnosis of acute Q fever (or after delivery in pregnant women)
Precautions	**Disease-related concerns**

	Oral candidiasis: Safety and effectiveness have not been established for treatment of periodontitis in patients with coexistent oral candidiasis; use with caution in patients with a history or predisposition to oral candidiasis. **Dosage form specific issues:** Sulfite sensitivity: Syrup may contain sodium metabisulfite, which may cause allergic reactions in certain individuals (e.g., asthmatic patients).
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of **Brucellosis treatment** options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Doxycycline.**

Table 23. Doxycycline HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Doxycycline	NICE	N/A
	CADTH	N/A
	HAS[14]	Octobre 2016: The medical service provided by doxycycline remains significant for brucellosis
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT – DOXYCYCLINE

The use of doxycycline is commonly recommended for the treatment of brucellosis. The WHO guidelines **suggest** a specific regimen for adults and children over 8 years of age. The **recommended** treatment involves:

Doxycycline: 100 mg orally twice daily (in combination with other agents).

This doxycycline regimen is typically administered for a duration of 6 weeks. The antibiotic is known for its effectiveness against Brucella species. It is crucial for patients to adhere to the prescribed treatment plan and complete the full course of medication to ensure optimal efficacy and to minimize the risk of relapse.

2.2 Antitubercular Agents

2.2.1 Rifampicin[15]

Table 24. Rifampicin Drug Information

SCIENTIFIC NAME Rifampicin[16]	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes 2017
MHRA	Yes
PMDA	N.A
Indication (ICD-10)	A23
Drug Class	Antitubercular Agent
Drug Sub-class	
ATC Code	J04AB02
Pharmacological Class (ASHP)	Antitubercular Agent
DRUG INFORMATION	
Dosage Form	Capsule
Route of Administration	Oral use
Dose (Adult) [DDD]*	Treatment: Oral: 600 to 900 mg once daily as part of an appropriate combination regimen. Duration is 6 weeks for uncomplicated nonfocal infection and at least 12 weeks for spondylitis, neurobrucellosis, and endocarditis. Postexposure prophylaxis (high-risk laboratory exposure): Note: For exposure to Brucella abortus RB51, use an alternative prophylactic regimen due to resistance.

	Oral: 600 mg once daily in combination with doxycycline for 3 weeks
Maximum Daily Dose Adults*	600mg /day
Dose (pediatrics)	Limited data available: Children and Adolescents: Oral: 15 to 20 mg/kg/day in 1 to 2 divided doses as part of an appropriate combination regimen; Duration is ≥ 6 weeks and dependent on patient specific factors including site of infection and presence of complications
Maximum Daily Dose Pediatrics*	Maximum dose: 600 mg/day
Adjustment	**Altered Kidney Function:** At rifampin doses ≤600 mg/day, reduced clearance by the kidney is compensated for by biliary excretion. However, at rifampin doses ≥900 mg/day, the hepatic excretory pathway is saturated and higher concentrations of rifampin are noted in patients with reduced kidney function. **Altered kidney function:** CrCl >15 mL/minute: No dosage adjustment necessary. CrCl <15 mL/minute: No dosage adjustment necessary for usual indication-specific doses ≤600 mg/day. For usual indication-specific doses ≥900 mg/day, consider limiting dose to 600 mg/day or monitoring more closely for adverse effects except when used for meningococcal chemoprophylaxis (no adjustment necessary due to short duration of therapy). **Hemodialysis, intermittent (thrice weekly):** Not significantly dialyzable; no dosage adjustment necessary for usual indication-specific doses ≤600 mg/day. For usual indication-specific doses ≥900 mg/day, consider limiting dose to 600

	mg/day or monitoring more closely for adverse effects except when used for meningococcal chemoprophylaxis (no adjustment necessary due to short duration of therapy). **Peritoneal dialysis:** Not significantly dialyzable; no dosage adjustment necessary for usual indication-specific doses ≤600 mg/day. For usual indication-specific doses ≥900 mg/day, consider limiting dose to 600 mg/day or monitoring more closely for adverse effects except when used for meningococcal chemoprophylaxis (no adjustment necessary due to short duration of therapy). **CRRT:** No dosage adjustment necessary. **PIRRT (e.g., sustained, low efficiency diafiltration):** No dosage adjustment necessary. **Hepatic Impairment:** There are no dosage adjustments provided in manufacturer's labeling; use with caution. **Hepatotoxicity during treatment:** New or worsening hepatic damage: Discontinue rifampin.
Prescribing edits*	CU
AGE (Age Edit)	N/A
CU (Concurrent Use Edit)	Rifampicin is to be given in combination with other agents (e.g., doxycycline, TMP/SMX)
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	N/A
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	N/A
EU (Emergency Use Only)	N/A

PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common:** Hypersensitivity reactions, both immediate (urticaria, angioedema, anaphylaxis) and delayed have been reported. Flu-like symptoms Hypotension Abdominal cramps **Most serious**: Clostridioides difficile infection Hematologic effects Hepatotoxicity
Drug Interactions*	**Category X:** Abemaciclib Abrocitinib Adagrasib Alpelisib Antihepaciviral Combination Products Apixaban Apremilast Aprepitant Artemether and Lumefantrine Asunaprevir Atazanavir Atovaquone Avacopan Avanafil Avapritinib Axitinib BCG (Intravesical) Bedaquiline Berotralstat Bictegravir Bortezomib Bosutinib Brigatinib Cabotegravir Capmatinib

	Cariprazine Ceritinib Cholera Vaccine Cobicistat Cobimetinib Copanlisib Crizotinib Dabigatran Etexilate Daclatasvir Daridorexant Darolutamide Darunavir Dasabuvir Deflazacort Delamanid Delavirdine Dexlansoprazole Doravirine DOXOrubicin (Conventional Dronedarone Duvelisib Edoxaban Elacestrant Elagolix, Estradiol, and Norethindrone Elbasvir and Grazoprevir Elexacaftor, Tezacaftor, and Ivacaftor Eliglustat Elvitegravir Encorafenib Entrectinib Erdafitinib Esomeprazole Etrasimod Etravirine Fecal Microbiota (Live) (Oral) Fecal Microbiota (Live) (Rectal) Fedratinib Fexinidazole Fimasartan

	Finerenone Flibanserin Fosamprenavir Fosaprepitant Fosnetupitant Fostamatinib Fostemsavir Fruquintinib Futibatinib Gemigliptin Gepirone Gilteritinib Glasdegib Glecaprevir and Pibrentasvir Halothane Ibrexafungerp Ibrutinib Idelalisib Indinavir Infigratinib Isavuconazonium Sulfate Istradefylline Itraconazole Ivabradine Ivacaftor Ivosidenib Ixazomib Lansoprazole Ledipasvir Lemborexant Lenacapavir Leniolisib Letermovir Levoketoconazole Lopinavir Lorlatinib Lumacaftor and Ivacaftor Lumateperone Lurasidone

	Lurbinectedin Macimorelin Macitentan Maribavir Mavacamten Midostaurin Mitapivat Mobocertinib Naldemedine Naloxegol Neratinib Netupitant Nevirapine Nilotinib NiMODipine Nintedanib Nirmatrelvir and Ritonavir Nisoldipine Olaparib Olutasidenib Omaveloxolone Omeprazole Orelabrutinib Ozanimod Pacritinib Palbociclib Palovarotene Panobinostat PAZOPanib Pemigatinib Pexidartinib Pimavanserin Piperaquine Pirtobrutinib Ponesimod Praziquantel Pretomanid QuiNINE Quizartinib

	Ranolazine Regorafenib Relugolix, Estradiol, and Norethindrone Revefenacin Ribociclib Rilpivirine Ripretinib Ritlecitinib Rivaroxaban Ritonavir Roflumilast (Systemic Rolapitant RomiDEPsin Sacituzumab Govitecan Samidorphan Saquinavir Selpercatinib Selumetinib Simeprevir Siponimod Sirolimus (Protein Bound) Sofosbuvir Sonidegib SORAfenib Sotorasib Sparsentan Tamoxifen Tasimelteon Taurursodiol Tazemetostat Tenofovir Alafenamide Tezacaftor and Ivacaftor Ticagrelor Tipranavir Tivozanib Tofacitinib Tolvaptan Toremifene Trabectedin

	Tucatinib Ubrogepant Ulipristal Upadacitinib Valbenazine Vandetanib Velpatasvir Venetoclax VinCRIStine (Liposomal) Vinflunine Voclosporin Vonoprazan Vorapaxar Voriconazole Voxilaprevir Zanubrutinib Zavegepant Zuranolone
Special Population	**Older Adult Considerations** A medication list evaluation is necessary for older adults starting rifampin, secondary to the increased risk of drug-interactions and polypharmacy. Additional monitoring may be necessary. **Reproductive Considerations** Rifampin may decrease the effectiveness of hormonal contraceptives.
Pregnancy	Rifampin crosses the human placenta. Postnatal hemorrhages have been reported in the infant and mother with administration during the last few weeks of pregnancy. Rifampin is used off-label for the treatment of brucellosis infection. Brucellosis infection may increase the risk of spontaneous abortion; rifampin is recommended for the treatment of brucellosis infection during pregnancy.

Lactation	Due to the potential for serious adverse reactions in the breastfeeding infant, the manufacturer recommends a decision be made whether to discontinue breastfeeding or to discontinue the drug, considering the importance of treatment to the mother.
Contraindications	Hypersensitivity to rifampin, any rifamycins, or any component of the formulation; concurrent use of atazanavir, darunavir, fosamprenavir, lurasidone, praziquantel, ritonavir/saquinavir, saquinavir, or tipranavir. Significant drug interactions exist, requiring dose/frequency adjustment or avoidance. Consult drug interactions database for more information. Canadian labeling: Additional contraindications (not in US labeling): Jaundice associated with reduced bilirubin excretion; premature and newborn infants; breastfeeding women; hepatic function impairment.
Monitoring Requirements	Baseline LFTs (AST, ALT, bilirubin), serum creatinine, CBC; periodic (every 2 to 4 weeks during therapy) monitoring of liver function in patients with preexisting hepatic impairment and periodic monitoring of serum creatinine and CBC in patients with baseline abnormalities. Monitor for signs/symptoms of liver injury (especially in prolonged therapy or with concurrent hepatotoxic drugs). Monitor mental status, sputum culture, chest X-ray 2 to 3 months into treatment, and for signs/symptoms of hypersensitivity (e.g., fever, lymphadenopathy, eosinophilia,

	neutropenia, rash, hypotension, acute bronchospasm, conjunctivitis, flu-like syndrome). Monitor coagulation tests during treatment in patients at risk of vitamin K deficiency (e.g., chronic liver disease, poor nutritional status, prolonged use of antibacterial agents or anticoagulants). Check platelets, renal function tests, serum lactate dehydrogenase, blood film for schistocytes (erythrocyte fragmentation), ADAMTS13 activity, and anti- ADAMTS13-antibody determination in patients with suspected thrombotic microangiopathy, thrombotic thrombocytopenic purpura, or hemolytic uremic syndrome. Monitor for symptoms of interstitial lung disease/pneumonitis.
Precautions	**Disease-related concerns:** Diabetes mellitus: Use with caution in patients with diabetes mellitus; management of diabetes may be more difficult in patients taking rifampin. Hepatic impairment: Use with caution in patients with hepatic impairment. Meningococcal disease: Do not use for treatment of meningococcal disease, only for short-term treatment of asymptomatic carrier states. Porphyria: Use with caution in patients with porphyria; exacerbations have been reported due to enzyme-inducing properties. **Other warnings/precautions:** Compliance: Monitor for compliance in patients on intermittent therapy.

	Contact lenses: Remove soft contact lenses during therapy since permanent staining may occur. Discoloration: Teeth (may be permanent), urine, feces, saliva, sweat, and tears may be discolored (yellow, orange, red, or brown). **Food Interactions** Food decreases the extent of absorption; rifampin concentrations may be decreased if taken with food. Management: Administer on an empty stomach with a glass of water (ie, 1 hour prior to, or 2 hours after meals or antacids). **Test Interactions** May interfere with urine detection of opioids (false-positive); positive Coombs' reaction [direct], rifampin inhibits standard assay's ability to measure serum folate and B; transient increase in LFTs and decreased biliary excretion of contrast media
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of **Brucellosis treatment** options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Rifampicin.**

Table 25. Rifampicin HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Rifampicin	NICE	N/A
	CADTH	N/A
	HAS[17]	Juillet 2015: Positive Recommendation: Opinion in favor of maintaining reimbursement in the treatment of brucellosis
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT – RIFAMPICIN

Rifampicin stands as the **primary treatment** for brucellosis during pregnancy, and the WHO recommends rifampicin as the initial approach. While it may be used as monotherapy, it is commonly administered in combination with other agents such as TMP/SMX or doxycycline, as the use of monotherapy in brucellosis treatment, particularly in pregnant women, remains a subject of uncertainty. Definitive conclusions on the suitability of this option for treating brucellosis in pregnant women await further randomized studies to provide clarity.

2.3 Sulfonamide Derivatives

2.3.1 Sulfamethoxazole/Trimethoprim[18]

Table 26. Sulfamethoxazole/Trimethoprim

SCIENTIFIC NAME SULFAMETHOXAZOLE/TRIMETHOPRIM[19]	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes 2001
EMA	Yes 2019
MHRA	N.A 2013
PMDA	Yes
Indication (ICD-10)	A23
Drug Class	Antibiotic
Drug Sub-class	Sulfonamide Derivative
ATC Code	J01EE01

Pharmacological Class (ASHP)	Antibiotic
DRUG INFORMATION	
Dosage Form	Syrup Tablet Solution Oral suspension
Route of Administration	Oral IV
Dose (Adult) [DDD]*	Note: Weight-based dosing recommendations are based on the trimethoprim component. Each double-strength (DS) tablet contains trimethoprim 160 mg and sulfamethoxazole 800 mg. Each single-strength (SS) tablet contains trimethoprim 80 mg and sulfamethoxazole 400 mg. Oral: 1 to 2 double-strength tablets every 12 to 24 hours. IV: 8 to 20 mg/kg/day (trimethoprim component) divided every 6 to 12 hours. Neurobrucellosis: Oral: One double-strength tablet twice daily for ≥12 weeks (may be needed for up to 6 months) as part of an appropriate combination regimen. Uncomplicated (nonfocal): Oral: One double-strength tablet twice daily for 6 weeks as part of an appropriate combination regimen. Postexposure prophylaxis (high-risk laboratory exposure): Oral: One double strength tablet twice daily for 3 weeks as part of an appropriate combination regimen.
Maximum Daily Dose Adults*	The total daily dose should not exceed 320 mg trimethoprim and 1600 mg sulfamethoxazole
Dose (pediatrics)	**General dosing**: Infants ≥2 months, Children, and Adolescents: Oral, IV: 8 to

	12 mg TMP/kg/day in divided doses every 12 hours; maximum dose: 160 mg TMP/dose Brucellosis: Limited data available: Note: Recommended in patients <8 years of age for whom prolonged use of doxycycline is not recommended or in older patients if tetracyclines are contraindicated. Infants ≥2 months, Children, and Adolescents: Oral: 8 to 12 mg TMP/kg/day in divided doses every 12 hours in combination with rifampin for ≥6 weeks. For serious infections, gentamicin should be added for the initial 1 to 2 weeks and therapy may be extended for up to 4 to 6 months
Maximum Daily Dose Pediatrics*	Total daily dose should not exceed 320 mg of trimethoprim and 1.6 g of sulfamethoxazole.
Adjustment	**Altered Kidney Function:** Refer to tables below. **Hepatic Impairment:** Hepatic impairment prior to treatment initiation: Child-Turcotte-Pugh class A to C: No dosage adjustment necessary. Dosage adjustment in patients with chronic, worsening hepatic function during treatment (e.g., progression from Child-Turcotte-Pugh class A to B): Progression from baseline to Child-Turcotte-Pugh class A to C: No dosage adjustment necessary; however, avoid use in patients with suspected or confirmed sulfamethoxazole-induced liver injury unless the benefits outweigh the risks.

	Acute worsening of hepatic function (e.g., requiring hospitalization): No dosage adjustment necessary; however, consider discontinuation of sulfamethoxazole/trimethoprim therapy in patients with suspected sulfamethoxazole induced liver injury unless the benefits outweigh the risks
Prescribing edits*	CU
AGE (Age Edit)	N/A
CU (Concurrent Use Edit)	TMP/SMX is to be given in combination with other antibiotic (rifampicin or gentamycin)
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	N/A
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	N/A
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common:** diarrhea, abdominal pain, urticaria, anorexia **Most serious**: Hepatotoxicity, agranulocytosis, hemolytic anemia, leukopenia, and thrombocytopenia, Hyperkalemia, Hypoglycemia, Hyponatremia
Drug Interactions*	**Category X:** Aminolevulinic Acid (Systemic) BCG (Intravesical) Cholera Vaccine Dofetilide Fecal Microbiota (Live) (Ora) Fecal Microbiota (Live) (Rectal) Leucovorin Calcium-Levoleucovorin Mecamylamine Methenamine

	MetroNIDAZOLE (Systemic) Ornidazole Potassium P-Aminobenzoate Procaine Secnidazole
Special Population	Older adult: Use with caution in older adult patients; greater risk for more severe adverse reactions. Patients with potential for folate deficiency: Use with caution in patients with potential folate deficiency (malnourished, chronic antiseizure therapy, or elderly). Porphyria: Avoid use in patients with porphyria. Slow acetylators: May be more prone to adverse reactions. Pediatric Considerations Sulfa antibiotics have been shown to displace bilirubin from protein binding sites which may potentially lead to hyperbilirubinemia and kernicterus in neonates and young infants; do not use in neonates; avoid use in infants <2 months unless other options are not available
Pregnancy	Sulfamethoxazole/trimethoprim may be used as part of a treatment regimen when brucellosis is diagnosed during pregnancy (not the preferred treatment in nonpregnant patients). Untreated maternal brucellosis infection may cause adverse pregnancy outcomes including spontaneous abortion or transmission to the infant. Treatment with sulfamethoxazole/trimethoprim is not recommended after 36 weeks' gestation due to the risk of kernicterus.

Lactation	The manufacturer recommends that caution be used if administered to persons who are breastfeeding, especially if breastfeeding infants are ill, jaundiced, premature, or stressed due to the potential risk of bilirubin displacement and kernicterus. Avoid use of sulfamethoxazole in persons who are breastfeeding an infant with G6PD deficiency or hyperbilirubinemia. The WHO considers sulfamethoxazole and trimethoprim compatible with breastfeeding in older, healthy, full-term infants with monitoring of the infant for jaundice and hemolysis
Contraindications	Hypersensitivity to any sulfa drug, trimethoprim, or any component of the formulation; history of drug induced-immune thrombocytopenia with use of sulfonamides or trimethoprim; megaloblastic anemia due to folate deficiency; infants <2 months (manufacturer's labeling), infants <4 weeks; marked hepatic damage or severe renal disease (if patient not monitored); concomitant administration with dofetilide. Significant drug interactions exist, requiring dose/frequency adjustment or avoidance. Consult drug interactions database for more information. Canadian labeling: Additional contraindications (not in US labeling): Blood dyscrasias; pregnancy; breastfeeding; premature infants; acute porphyria
Monitoring Requirements	CBC, electrolytes, renal function
Precautions	**Disease-related concerns:** Asthma/Allergies: Use with caution in patients with allergies or asthma.

	Hepatic impairment: Use with caution in patients with hepatic impairment. Renal impairment: Use with caution in patients with renal impairment; dosage adjustment recommended. Maintain adequate hydration to prevent crystalluria. Thyroid dysfunction: Use with caution in patients with thyroid dysfunction **Dosage form specific issues:** Benzyl alcohol and derivatives: Some dosage forms may contain benzyl alcohol; large amounts of benzyl alcohol (≥99 mg/kg/day) have been associated with a potentially fatal toxicity ("gasping syndrome") Propylene glycol: Some dosage forms may contain propylene glycol; large amounts are potentially toxic and have been associated hyperosmolality, lactic acidosis, seizures, and respiratory depression neonates • Sulfite sensitivity: Injection may contain sodium metabisulfite, a sulfite that may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible persons
Black Box Warning	N/A
REMS*	N/A

Both oral and IV TMP/SMX should be adjusted based on renal function (tables 24 and 25)[18].

Table 27. Oral TMP/SMX Dose Adjustments for Kidney Impairment

CrCl (mL/min)	If usual recommended dose is 1 DS tablet every 24 hours or 3 times per week	If usual recommended dose is 1 DS tablet every 12 hours	If usual recommended dose is 2 DS tablets every 12 hours	If usual recommended dose is 2 DS tablets every 8 hours
> 30	No dosage adjustment necessary			
15 to 30	Reduce dose to 50% of usual dose. Example: 1 SS tablet every 24 hours or 3 times per week.	Reduce dose to 50% of usual dose. Example: 1 DS tablet once, followed by 1 SS tablet every 12 hours.	Reduce dose to 50% of usual dose. Example: 1 DS tablet every 12 hours.	Reduce dose to 50% of usual dose. Example: 2 DS tablets every 12 hours.
< 30	Reduce dose to 25 to 50% of usual dose. Use with caution and appropriate monitoring. Example: 1 SS tablet every 24 hours or 3 times per week.	Reduce dose to 25 to 50% of usual dose. Use with caution and appropriate monitoring. Example: 1 DS tablet once, followed by 1 SS tablet every 12 or 24 hours.	Reduce dose to 25 to 50% of usual dose. Use with caution and appropriate monitoring. Example: 1 DS tablet every 12 hours or 1 DS tablet once, followed by 1 SS tablet every 12 hours.	Reduce dose to 25 to 50% of usual dose. Use with caution and appropriate monitoring. Example: 1 to 2 DS tablets every 12 hours or 2 DS tablets every 24 hours.

Table 28. Intravenous TMP/SMX Dose Adjustments for Kidney Impairment

CrCl (mL/min)	If usual recommended daily dose is 10 mg/kg/day (TMP component)	If usual recommended daily dose is 8 to 12 mg/kg/day (TMP component)	If usual recommended daily dose is 15 to 20 mg/kg/day (TMP component)
> 30	No dosage adjustment necessary		
15 to 30	Reduce dose to 50% of usual dose. Example: 5 mg/kg once daily	Reduce dose to 50% of usual dose. Example: 4 to 6 mg/kg/**day** in 2 divided doses	Reduce dose to 50% of usual dose. Example: 7.5 to 10 mg/kg/**day** in 2 to 4 divided doses
< 30	Reduce dose to ~25 to 50% of usual dose. Use with caution and appropriate monitoring. Example: 2.5 to 5 mg/kg once daily. **Note:** When treating toxoplasmosis encephalitis, use 5 mg/kg once daily or use alternative agent	Reduce dose to ~25 to 50% of usual dose. Use with caution and appropriate monitoring. Example: 2 to 3 mg/kg once daily **or** 4 to 6 mg/kg every 24 to 48 hours	Reduce dose to ~25 to 50% of usual dose. Use with caution and appropriate monitoring. Example: 4 to 5 mg/kg once daily **or** 7.5 to 10 mg/kg every 24 to 48 hours

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of **Brucellosis treatment** options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for SULFAMETHOXAZOLE, TRIMETHOPRIM**

Table 29. TMP/SMX HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
SULFAMETHOXAZOLE, TRIMETHOPRIM	NICE	N/A
	CADTH	N/A
	HAS	N/A
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT – SULFAMETHOXAZOLE/TRIMETHOPRIM

Sulfamethoxazole/trimethoprim, abbreviated as SMX/TMP or co-trimoxazole, is another antibiotic combination that may be used in the treatment of brucellosis.

Sulfamethoxazole/Trimethoprim: The specific dosage and duration can vary but may involve a combination of sulfamethoxazole 800 mg and trimethoprim 160 mg, given orally twice daily.

This combination therapy is often considered in cases where other antibiotics may not be suitable or in instances of resistance to other commonly used antibiotics.

2.4 Aminoglycosides

2.4.1 Gentamycin[20]

Table 30. Gentamycin Drug Information

SCIENTIFIC NAME Gentamycin	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes 2018
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	A23
Drug Class	Antibiotic
Drug Sub-class	Aminoglycoside
ATC Code	J01GB03
Pharmacological Class (ASHP)	Antibiotic
DRUG INFORMATION	

Dosage Form	Solution for injection
Route of Administration	IV, IM
Dose (Adult) [DDD]*	Note: Additional agents or other regimens are preferred for neurobrucellosis and infection in patients who are pregnant Endocarditis: IV, IM: 5 mg/kg/day in 1 to 3 divided doses for 4 weeks as part of an appropriate combination regimen. Spondylitis: IV, IM: 5-7.5 mg/kg once daily for 7 to 14 days as part of an appropriate combination regimen. Uncomplicated (nonfocal): IV, IM: 5 mg/kg once daily for 7 to 10 days as part of an appropriate combination regimen
Maximum Daily Dose Adults*	500mg /day
Dose (pediatrics)	Children, and Adolescents: IM, IV: 2 to 2.5 mg/kg/dose every 8 hours
Maximum Daily Dose Pediatrics*	max dose 560mg ONCE a day [21]
Adjustment	**Altered Kidney Function:** Use with caution in patients with CrCl <40 mL/minute; high-dose, extended interval dosing may still be considered, especially in patients with severe sepsis/shock or those infected with multidrug-resistant gram-negative organisms. IV: Initial dose: 5 to 7 mg/kg. Subsequent doses and frequency of administration should be determined based on therapeutic drug monitoring; regimens may vary; The following recommendations may serve as a general guideline after the initial dose: CrCl ≥60 mL/minute: IV: Administer every 24 hours; adjust dose and/or interval based on gentamicin serum concentrations.

	CrCl 40 to <60 mL/minute: IV: Administer every 36 hours; adjust dose and/or interval based on gentamicin serum concentrations. CrCl 20 to <40 mL/minute: IV: Administer every 48 hours; adjust dose and/or interval based on gentamicin serum concentrations. CrCl <20 mL/minute: IV: Administer usual dose once, then determine subsequent dose and interval based on serum concentration monitoring. **Hepatic Impairment:** There are no dosage adjustments provided in the manufacturer's labeling
Prescribing edits*	CU
AGE (Age Edit)	N/A
CU (Concurrent Use Edit)	Gentamicin is to be given in combination with another antibiotic (TMP/SMX or doxycycline)
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	N/A
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	N/A
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common:** **Most serious**: Hypersensitivity: Cross-sensitivity to other aminoglycosides Nephrotoxicity Neurotoxicity/Ototoxicity Neuromuscular blockade and respiratory paralysis
Drug Interactions*	**Category X:** Agalsidase Alfa Aminoglycosides

	Ataluren Bacitracin (Systemic) BCG (Intravesical Cholera Vaccine CISplatin Fecal Microbiota (Live) (Oral) Fecal Microbiota (Live) (Rectal): Foscarnet Mannitol (Systemic) Mecamylamine Methoxyflurane Netilmicin (Ophthalmic) Polymyxin B
Special Population	Patients with genomic variants in MT-RNR1: Carriers of certain variants in the MT-RNR1 gene may be at increased risk for aminoglycoside-induced ototoxicity, including potentially significant hearing loss that may be irreversible, even when serum levels are within the normal range. Pregnancy: [US Boxed Warning]: Aminoglycosides may cause fetal harm if administered to a pregnant woman. Use with caution in pediatric patients on extracorporeal membrane oxygenation (ECMO).
Pregnancy	Aminoglycosides can cause fetal harm when administered to a pregnant woman.
Lactation	The WHO considers gentamicin to be compatible with breastfeeding. Infants should be monitored for thrush and diarrhea.
Contraindications	Hypersensitivity to gentamicin, other aminoglycosides, or any component of the formulation.
Monitoring Requirements	Urinalysis, urine output, BUN, serum creatinine, plasma gentamicin levels (as appropriate to dosing method). Levels

	are typically obtained before and after the third dose in conventional dosing. Hearing should be tested before, during, and after treatment; particularly in those at risk for ototoxicity or who will be receiving prolonged therapy (>2weeks). Some penicillin derivatives may accelerate the degradation of aminoglycosides in vitro. This may be clinically significant for certain penicillin (ticarcillin, piperacillin, carbenicillin) and aminoglycoside (gentamicin, tobramycin) combination therapy in patients with significant renal impairment. Close monitoring of aminoglycoside levels is warranted.
Precautions	**Concurrent drug therapy issues:** Neurotoxic and/or nephrotoxic drugs: [US Boxed Warning]: Avoid concomitant or sequential use of other neurotoxic and/or nephrotoxic drugs (e.g., cisplatin, polymyxin B, colistin, vancomycin, other aminoglycosides). Potent diuretics: [US Boxed Warning]: Avoid concomitant use with potent diuretics (e.g., ethacrynic acid, furosemide) since diuretics themselves may cause ototoxicity and may enhance aminoglycoside toxicity. **Other warnings/precautions:** Long-term use: Risk of toxicity is increased with extended duration of administration; additional monitoring may be required with long-term use. Surgical irrigation: May be almost completely systemically absorbed after local irrigation and/or topical application (except to the urinary bladder) during surgical procedures.

	Consider potential for nephrotoxicity, neuromuscular blockade, ototoxicity, and respiratory paralysis when administering aminoglycosides in this manner.
Black Box Warning	Nephrotoxicity, ototoxicity, neurotoxicity Aminoglycosides can cause fetal harm when administered to a pregnant woman.
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of **Brucellosis treatment** options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Gentamycin**

Table 31. Gentamycin HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Gentamycin	NICE	N/A
	CADTH	N/A
	HAS	N/A
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT- Gentamycin

Gentamicin is an aminoglycoside antibiotic that can be considered for the treatment of brucellosis, particularly as an alternative to streptomycin. The specific recommendations for gentamicin use in brucellosis treatment may vary, and the choice of antibiotics is often influenced by factors such as the severity of the infection, regional resistance patterns, and individual patient characteristics.

In the context of brucellosis treatment, a common regimen involving gentamicin might include:

Gentamicin: Given intramuscularly (IM) or intravenously (IV) with a dosage and duration specified by the healthcare provider. Dosage typically ranges from 5 to 7 mg/kg per day, divided into two or three doses.

Gentamicin is often used in combination with other antibiotics, such as doxycycline or rifampicin, to enhance efficacy and reduce the risk of relapse. The duration of treatment and the specific combination of antibiotics depend on the individual patient's condition and the healthcare provider's assessment.

2.5 Fluoroquinolones

2.5.1 Ciprofoxacin[22]

Table 32. Ciprofloxacin Drug Information

SCIENTIFIC NAME Ciprofloxacin	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes 2008
MHRA	Yes 2019
PMDA	Yes 2016
Indication (ICD-10)	A23
Drug Class	Antibiotic
Drug Sub-class	Fluoroquinolone
ATC Code	J01MA02 S02AA15
Pharmacological Class (ASHP)	Antibiotic, Fluoroquinolone
DRUG INFORMATION	
Dosage Form	Film-coated tablet, Tablet Solution for infusion Solution
Route of Administration	Oral use Parenteral use
Dose (Adult) [DDD]*	500mg twice daily for 6 weeks with Rifampicin or Doxycycline
Maximum Daily Dose Adults*	maximum daily dose 1200 mg
Dose (pediatrics)	Oral: Immediate release: 10 to 20 mg/kg/dose every 12 hours IV: 10 mg/kg/dose every 8 to 12 hours
Maximum Daily Dose Pediatrics*	Oral: 1500mg per day IV: maximum dose: 400 mg/dose

Adjustment	**Altered Kidney Function:** Refer to table below **Hepatic Impairment:** Initial or dose titration in patients with preexisting liver cirrhosis or dosage adjustment in patients with chronic, worsening hepatic function during treatment: Child-Turcotte-Pugh class A through C: IV, Oral: No dosage adjustment necessary. Acute worsening of hepatic function (eg, requiring hospitalization): No dosage adjustment necessary; however, consider discontinuation of ciprofloxacin therapy in patients with suspected ciprofloxacin-induced liver injury unless the benefits outweigh the risks
Prescribing edits*	CU
AGE (Age Edit)	N/A
CU (Concurrent Use Edit)	Ciprofloxacin is to be given in combination with another antibiotic (e.g., doxycycline, rifampicin)
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	N/A
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	N/A
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common:** Clostridioides difficile infection (Diarrhea), nausea, candidadis Phototoxicity/photoallergy (skin rash) **Most serious**: Aortic aneurysm/aortic dissection

	Arthropathy/arthralgia CNS effects/neuroexcitation (dizziness, hallucinations, seizures)
Drug Interactions*	**<u>Category X:</u>** Agomelatine Aminolevulinic Acid (Systemic) BCG (Intravesical) Cholera Vaccine Fecal Microbiota (Live) (Oral) Fecal Microbiota (Live) (Rectal) Fezolinetant Lomitapide Meptazinol Nadifloxacin Pimozide Strontium Ranelate Taurursodiol TiZANidine
Special Population	Older adult: Adverse effects (eg, tendon rupture, QT changes) may be increased in elderly patients. G6PD deficiency: Hemolytic reactions may (rarely) occur with fluoroquinolone use in patients with G6PD deficiency. Pediatric: Adverse effects, including those related to joints and/or surrounding tissues, are increased in pediatric patients and therefore, ciprofloxacin should not be considered as drug of choice in children (exception is anthrax treatment).
Pregnancy	Based on available data, an increased risk of major birth defects, miscarriage, or other adverse fetal and maternal outcomes have not been observed following ciprofloxacin use during pregnancy.
Lactation	In general, quinolone antibiotics should be avoided in breastfeeding patients if alternative agents are available.

Contraindications	Hypersensitivity to ciprofloxacin, any component of the formulation, or other quinolones; concurrent administration of tizanidine. Significant drug interactions exist, requiring dose/frequency adjustment or avoidance. Consult drug interactions database for more information. Canadian labeling: Additional contraindications (not in the US labeling): Concurrent administration of agomelatine.
Monitoring Requirements	CBC, renal and hepatic function during prolonged therapy, altered mental status, signs and symptoms of tendinopathy (tendon pain, swelling, inflammation, or rupture) or peripheral neuropathy; signs and symptoms of disordered glucose regulation (especially in patients with diabetes mellitus); rash; signs and symptoms of hypersensitivity reaction. **Nursing Physical Assessment/Monitoring** Check ordered labs and report any abnormalities. Monitor for hypersensitivity reactions (severe reactions, including anaphylaxis, have occurred with quinolone therapy). Instruct patient to report signs and symptoms of tendinopathy (pain or swelling of joints, unable to bear weight on a joint, or feeling a snap or pop).
Precautions	**Concerns related to adverse effects:** Crystalluria: Rarely, crystalluria has occurred; urine alkalinity may increase the risk. Ensure adequate hydration during therapy. Superinfection: Prolonged use may result in fungal or bacterial superinfection.

	Disease-related concerns: Renal impairment: Use with caution in patients with renal impairment; dosage adjustment required. Syphilis: Since ciprofloxacin is ineffective in the treatment of syphilis and may mask symptoms, all patients should be tested for syphilis at the time of gonorrheal diagnosis and 3 months later.
Black Box Warning	Fluoroquinolones have been associated with disabling and potentially irreversible serious adverse reactions that have occurred together, including: tendinopathy and tendon rupture, peripheral neuropathy, and CNS effects Exacerbation of myasthenia gravis.
REMS*	N/A

Table 33. Ciprofloxacin Dosage Adjustments in Altered Kidney Function

CrCl (mL/minute)	Oral, immediate release	Oral, extended release	IV
CrCl >50 to <130	500 to 750 mg every 12 hours	1 g every 24 hours	400 mg every 8 to 12 hours
CrCl 30 to 50	250 to 500 mg every 12 hours	1 g every 24 hours	400 mg every 8 to 12 hours
CrCl <30	500 mg every 24 hours	500 mg every 24 hours	200 to 400 mg every 12 to 24 hours
Hemodialysis, intermittent (thrice weekly)	250 to 500 mg every 24 hours	500 mg every 24 hours	200 to 400 mg every 24 hours
Peritoneal dialysis	250 to 500 mg every 24 hours	500 mg every 24 hours	200 to 400 mg every 24 hours

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of **Brucellosis treatment** options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies

in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Ciprofloxacin.**

Table 34. Ciprofloxacin HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Ciprofoxacin	NICE	N/A
	CADTH	N/A
	HAS	N/A
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT- Ciprofloxacin

Ciprofloxacin is a fluoroquinolone antibiotic that may be considered in the treatment of brucellosis, especially in cases where other antibiotics are not suitable or in regions with specific resistance patterns.

A typical regimen for brucellosis treatment involving ciprofloxacin might include: Ciprofloxacin: Given orally with a dosage of 500 mg to 750 mg twice daily.

Ciprofloxacin is sometimes used in combination with other antibiotics, such as doxycycline or rifampicin, depending on the healthcare provider's assessment of the specific case.

2.6 Cephalosporins

2.6.1 Ceftriaxone[23]

Table 35. Ceftriaxone Drug Information

SCIENTIFIC NAME Ceftriaxone	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes 2014
MHRA	Yes 2009
PMDA	Yes 2007
Indication (ICD-10)	A23

Drug Class	Antibiotic
Drug Sub-class	Cephalosporin (Third Generation)
ATC Code	J01DD04
Pharmacological Class (ASHP)	Antibiotic, Cephalosporin (Third Generation)
DRUG INFORMATION	
Dosage Form	Solution for injection Solution Powder and solvent for suspension for injection Powder for solution for injection
Route of Administration	IV IM
Dose (Adult) [DDD]*	Neurobrucellosis (off-label use): IV: 2 g every 12 hours for 4 to 6 weeks as part of an appropriate combination regimen
Maximum Daily Dose Adults*	The total daily dose should not exceed 4 g
Dose (pediatrics)	General dosing: Infants, Children, and Adolescents: IM, IV: 50 to 75 mg/kg/day in divided doses every 12 to 24 hours; higher doses recommended in certain infections. In neurobrucellosis, the recommended dose is 100 mg/kg/day divided every 12 to 24 hours.
Maximum Daily Dose Pediatrics*	2,000 mg/day
Adjustment	**Altered Kidney Function:** Altered kidney impairment: IM, IV: CrCl >15 mL/minute: No dosage adjustment necessary. CrCl <15 mL/minute: No dosage adjustment necessary. Use of >2 g/day has not been studied and should be done with close monitoring, especially in patients with concurrent hepatic dysfunction (decreased biliary excretion).

	Hepatic Impairment: Child-Turcotte-Pugh class A through C: No dosage adjustment necessary
Prescribing edits*	CU, ST
AGE (Age Edit)	N/A
CU (Concurrent Use Edit)	Ceftriaxone is to be given in combination with another antibiotic (doxycycline)
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	N/A
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	To be used as an alternative option in place of gentamicin as part of a combination regimen.
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common:** Black, tarry stools, shortness of breath. sores, ulcers, swollen glands. unusual bleeding or bruising **Most serious**: Ceftriaxone-calcium precipitation Clostridioides difficile infection Hemolytic anemia Kernicterus
Drug Interactions*	**Category X:** BCG (Intravesical) Cholera Vaccine Fecal Microbiota (Live) (Oral) Fecal Microbiota (Live) (Rectal)
Special Population	Pediatric patients: High-risk medication: KIDs List: Ceftriaxone, when used in neonates, is identified on the Key Potentially

	Inappropriate Drugs in Pediatrics (KIDs) list and should be used with caution due to risk of kernicter Neonates: Use extreme caution in neonates due to risk of hyperbilirubinemia, particularly in premature infants (contraindicated in hyperbilirubinemic neonates and neonates <41 weeks postmenstrual age.
Pregnancy	Based on available data, cephalosporin antibiotics are generally considered compatible for use during pregnancy.
Lactation	In general, antibiotics that are present in breast milk may cause nondose-related modification of bowel flora. Monitor infants for GI disturbances. Ceftriaxone is considered compatible with breastfeeding when used in usual recommended doses.
Contraindications	Hypersensitivity to ceftriaxone, any component of the formulation, or other cephalosporins; do not use in hyperbilirubinemic neonates, particularly those who are premature since ceftriaxone is reported to displace bilirubin from albumin binding sites; concomitant use with intravenous calcium-containing solutions/products in neonates (≤28 days); IV use of ceftriaxone solutions containing lidocaine. Significant drug interactions exist, requiring dose/frequency adjustment or avoidance. Consult drug interactions database for more information.
Monitoring Requirements	Prothrombin time/INR. Observe for signs and symptoms of anaphylaxis. Test-of-cure 7 to 14

	days after initial treatment of pharyngeal gonorrhea Nursing Physical Assessment/Monitoring Check ordered labs and report any abnormalities. Monitor closely for signs of hypersensitivity reaction (shortness of breath, dyspnea, chest pain, complaints of difficulty swallowing or throat tightness, or change in vital signs), especially with the first dose. Monitor for severe or bloody diarrhea and send a specimen to the lab for C. difficile. Never connect IV infusion of drug to an infusion containing calcium as precipitate can form. Flush IVs well if administering calcium and ceftriaxone sequentially
Precautions	**Disease-related concerns:** Renal/hepatic impairment (concurrent): Use with caution in patients with concurrent hepatic dysfunction (impaired biliary excretion) and severe kidney disease; dosing adjustments may be recommended.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of **Brucellosis treatment** options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Ceftriaxone.**

Table 36. Ceftriaxone HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Ceftriaxone	NICE	N/A
	CADTH	N/A
	HAS	N/A
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT- Ceftriaxone

Ceftriaxone is a third-generation cephalosporin antibiotic. In acute neuro-brucellosis, ceftriaxone 2g IV once a day is an option when added to initial treatment (due to its excellent CNS penetration). While local studies report the efficacy of ceftriaxone in treating complicated brucellosis conditions like neurobrucellosis and orchitis, further research is needed before considering ceftriaxone as a first-line therapy for human brucellosis.

2.8 Other Drugs

2.8.1 Streptomycin[124]

Streptomycin was approved by FDA in 1947 and by EMA in November 2001; however, it is currently **not SFDA-registered**.

WHO guidelines advocate the following brucellosis treatment approach for adults and children aged 8 years and above suffering from acute brucellosis: 100 mg of Doxycycline orally twice a day for a duration of 6 weeks and 1 g/day of streptomycin IM for 2-3 weeks.

This regimen is considered more efficacious, particularly in preventing relapse; gentamicin can be employed as an alternative to streptomycin, displaying comparable effectiveness.

Section 3.0 Key Recommendations Synthesis

Rifampicin and **TMP/SMX** for children below 8 years of age. **Doxycycline** and TMP/SMX or rifampicin for children older than 8 years of age. This combination has been shown to have the highest success rate and should be used in children above 8 years to avoid the staining of the teeth in younger children. (Grade A)

Brucellosis is a common infection caused by Brucella bacteria species and can infect both people and animals. It is spread by eating infected food products and through direct contact with infected animals. (Grade A)

Current recommended treatment regimens involve the use of two or more antibiotics in order to avoid relapses occurring and to prevent prolonged use of these drugs, which may lead to problems of drug resistance arising. (Grade A)

Depending on the timing of treatment and severity of illness, recovery may take a few weeks to several months. (Grade A)

Death from brucellosis is rare, occurring in no more than 2% of all cases. (Grade A)

For most presentations of the disease, combination treatment with doxycycline and rifampicin or an **aminoglycoside** is recommended as first line treatment. (Grade A)

Quinolone-based treatments seem to have a role in modern clinical practice as alternatives to standard therapy for patients with relapse of brucellosis after treatment with another regimen, as well as in patients in whom toxicity has developed due to the use of some of the older agents (Grade B)

For certain presentations, including endocarditis, joint infections and CNS infections, a more prolonged course of multiple antibiotics is required. In acute neuro brucellosis, **ceftriaxone** 2g IV once a day in combination with another effective drug such as doxycycline is the preferred treatment. (Grade A)

Section 4.0 Conclusion

The recommendations provided in this report are intended to assist in the management of Brucellosis.

These recommendations should be used to support and not supplant decisions in individual patient management.

Section 5.0 References

1. Corbel MJ, World Health Organization., Food and Agriculture Organization of the United Nations., International Office of Epizootics. *WHO-Brucellosis in Humans and Animals-2006*. World Health Organization; 2006.
2. Al Anazi M, AlFayyad I, AlOtaibi R, Abu-Shaheen A. Epidemiology of Brucellosis in Saudi Arabia. *Saudi Med J*. 2019;40(10):981-988. doi:10.15537/smj.2019.10.24027
3. Alshaalan MA, Alalola SA, Almuneef MA, et al. Brucellosis in children: Prevention, diagnosis and management guidelines for general pediatricians endorsed by the Saudi Pediatric Infectious Diseases Society (SPIDS). *Int J Pediatr Adolesc Med*. 2014;1(1):40-46. doi:10.1016/j.ijpam.2014.09.004
4. Alharbi RA. Brucellosis trends in Majmaah city, Riyadh, Saudi Arabia: A trend of 5-year retrospective study (2016-2020). *International Journal of ADVANCED AND APPLIED SCIENCES*. 2022;9(12):85-88. doi:10.21833/ijaas.2022.12.011
5. Alshaalan M, Al Zamil F, Almaghrabi RH, Al Dubisi F, Aljehani S. *Brucella Infection: A Manual Guide and Atlas From Saudi Pediatric Infectious Disease Society*.; 2022.
6. for Disease Control C. *BRUCELLOSIS REFERENCE GUIDE: CDC-USA-2017*.; 2017. http://www.selectagents.gov/
7. Brucellosis | MSF Medical Guidelines. Accessed January 19, 2024. https://medicalguidelines.msf.org/en/viewport/CG/english/brucellosis-16689930.html
8. Tuon FF, Cerchiari N, Cequinel JC, et al. Guidelines for the management of human brucellosis in the State of Paraná, Brazil. *Rev Soc Bras Med Trop*. 2017;50(4):458-464. doi:10.1590/0037-8682-0319-2016
9. Beig M, Moradkasani S, Goodarzi F, Sholeh M. Prevalence of Brucella melitensis and Brucella abortus Fluoroquinolones Resistant Isolates: A Systematic Review and Meta-Analysis. *Vector Borne Zoonotic Dis*. 2024;24(1):1-9. doi:10.1089/vbz.2023.0063
10. Huang S, Wang H, Li F, et al. Better efficacy of triple antibiotics therapy for human brucellosis: A systematic review and meta-analysis. *PLoS Negl Trop Dis*. 2023;17(9):e0011590. doi:10.1371/journal.pntd.0011590
11. Li F, Du L, Zhen H, et al. Follow-up outcomes of asymptomatic brucellosis: meta-analysis-china-2023. *Emerg Microbes Infect*. 2023;12(1). doi:10.1080/22221751.2023.2185464
12. *Doxycycline*.; 2023. https://www.ashp.org/Drug-Shortages/Current-Shortages

13. *International Nonproprietary Names (INN).*; 2023. https://www.ashp.org/Drug-Shortages/Current-Shortages

14. apegorier. *HAS-Direction de l'Evaluation Médicale, Economique et de Santé Publique COMMISSION DE LA TRANSPARENCE-Doxycycline-2016.*; 2016.

15. *Rifampicin.*; 2023.

16. *Rifampicin [RifAMPin] Anatomic Therapeutic Chemical (ATC) Classification Pharmacologic Category.*; 2023.

17. apegorier. *HAS-Direction de l'Evaluation Médicale, Economique et de Santé Publique Rifampicin-2015.*; 2015. http://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Revision-

18. *Co-Trimoxazole [Sulfamethoxazole and Trimethoprim].*; 2023.

19. Lexicomp. 2023. Published 2023. Accessed June 15, 2023. https://login.ezproxy.lau.edu.lb:2443/login?qurl=https://online.lexi.com%2flco%2faction%2fdoc%2fretrieve%2fdocid%2fmultinat_f%2f4668145%3fcesid%3d6yvIzRFAUiX%26searchUrl%3d%252Flco%252Faction%252Fsearch%253Fq%253Dixabepilone%2526t%253Dname%2526acs%253Dtrue%2526acq%253Dixabe

20. *Gentamicin.*; 2023. https://www.ashp.org/Drug-Shortages/Current-Shortages

21. *Paediatric Medication Guideline.*; 2023. www.cdc.gov/growthcharts

22. *Ciprofloxacin (Systemic).*; 2023. https://www.ashp.org/Drug-Shortages/Current-Shortages

23. *Ceftriaxone.*; 2023.

24. Streptomycin. Published online 2023.

Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

I. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

Some covered drugs may have additional requirements, rules or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses and sequence of therapy

Appendix B. Level of Evidence Description

I- Level of Evidence Adopted:

Grade of research	
A	Strongly recommend; good evidence
B	Recommend; at least fair evidence
C	No recommendation for or against; balance of benefits and harms too close to justify a recommendation
D	Recommend against; fair evidence is ineffective, or harm outweighs the benefit
E	Evidence is insufficient to recommend for or against routinely; evidence is lacking or of poor quality; benefits and harms cannot be determined
Level of evidence	
Level I	Meta-analysis of multiple studies
Level II	Experimental studies
Level III	Well-designed, quasi-experimental studies
Level IV	Well-designed, non-experimental studies
Level V	Case reports and clinical examples

Appendix C. PubMed Search

Query	Filters	Search Details	Results
((((((((((((((((Brucellosis[MeSH Terms]) OR (Brucelloses[Title/Abstract])) OR (Malta Fever[Title/Abstract])) OR (Fever, Malta[Title/Abstract])) OR (Gibraltar Fever[Title/Abstract])) OR (Fever, Gibraltar[Title/Abstract])) OR (Rock Fever[Title/Abstract])) OR (Fever, Rock[Title/Abstract])) OR (Cyprus Fever[Title/Abstract])) OR (Fever, Cyprus[Title/Abstract])) OR (Brucella Infection[Title/Abstract])) OR (Brucella Infections[Title/Abstract])) OR (Infection, Brucella[Title/Abstract])) OR (Undulant Fever[Title/Abstract])) OR (Fever, Undulant[Title/Abstract])) OR (Brucellosis, Pulmonary[Title/Abstract])) OR (Brucelloses, Pulmonary[Title/Abstract])) OR (Pulmonary Brucelloses[Title/Abstract])) OR (Pulmonary Brucellosis[Title/Abstract])	Guideline, in the last 5 years	("Brucellosis"[MeSH Terms] OR "Brucelloses"[Title/Abstract] OR "malta fever"[Title/Abstract] OR "fever malta"[Title/Abstract] OR "gibraltar fever"[Title/Abstract] OR "fever gibraltar"[Title/Abstract] OR "rock fever"[Title/Abstract] OR (("Fever"[MeSH Terms] OR "Fever"[All Fields] OR "fevers"[All Fields]) AND "Rock"[Title/Abstract]) OR "cyprus fever"[Title/Abstract] OR "fever cyprus"[Title/Abstract] OR "brucella infection"[Title/Abstract] OR "brucella infections"[Title/Abstract] OR "infection brucella"[Title/Abstract] OR "undulant fever"[Title/Abstract] OR "fever undulant"[Title/Abstract] OR "brucellosis pulmonary"[Title/Abstract] OR (("Brucellosis"[MeSH Terms] OR "Brucellosis"[All Fields] OR "Brucelloses"[All Fields]) AND "Pulmonary"[Title/Abstract]) OR (("lung"[MeSH Terms] OR "lung"[All Fields] OR	0

		"Pulmonary"[All Fields]) AND "Brucelloses"[Title/Abstract]) OR "pulmonary brucellosis"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))	
brucellosis	Guideline, in the last 5 years	("brucellosis"[MeSH Terms] OR "brucellosis"[All Fields] OR "brucelloses"[All Fields]) AND ((y_5[Filter]) AND (guideline[Filter]))	0

Appendix D. Treatment Algorithms[1, 5,7]

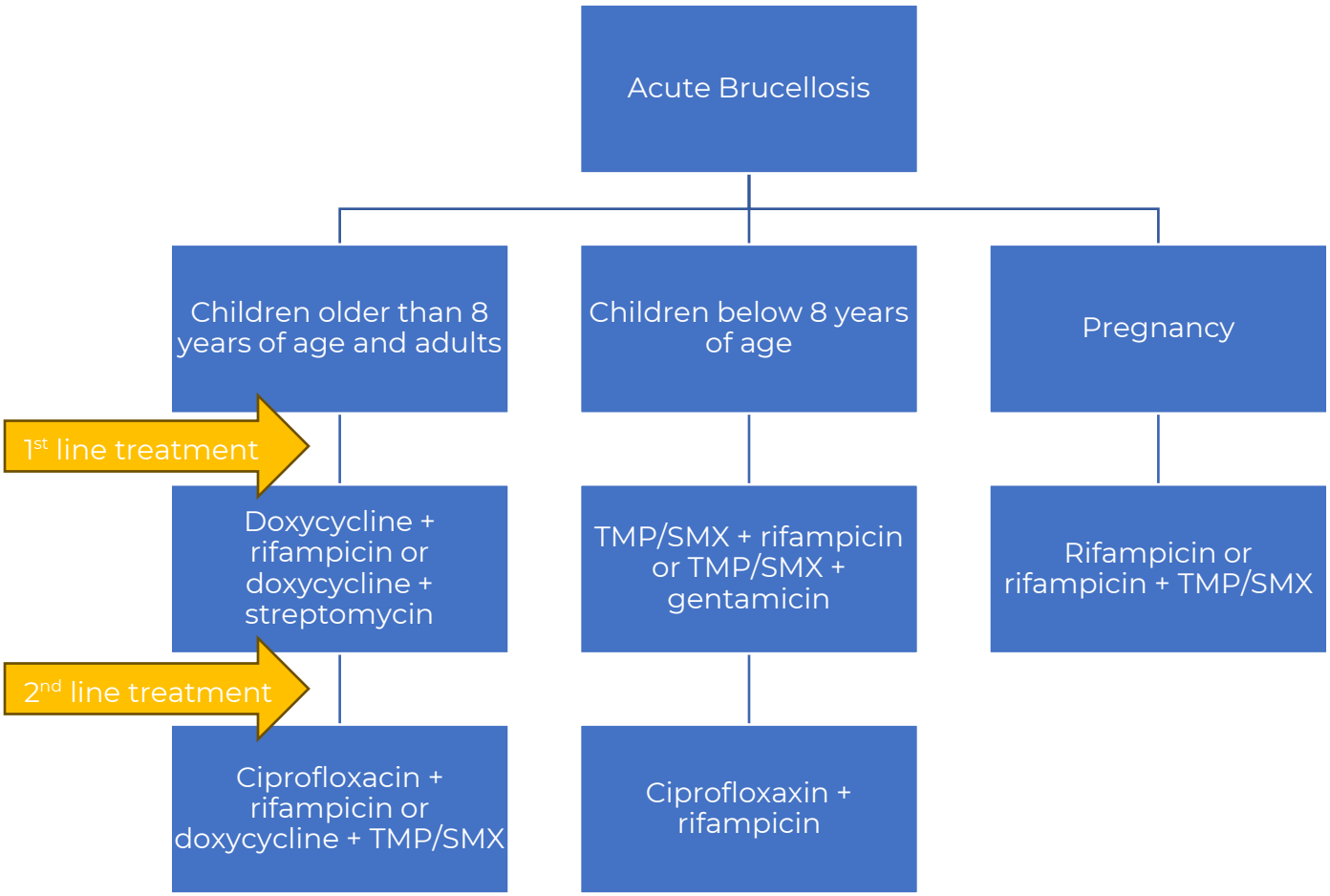

Figure 3. *Treatment algorithm for the management of acute brucellosis*

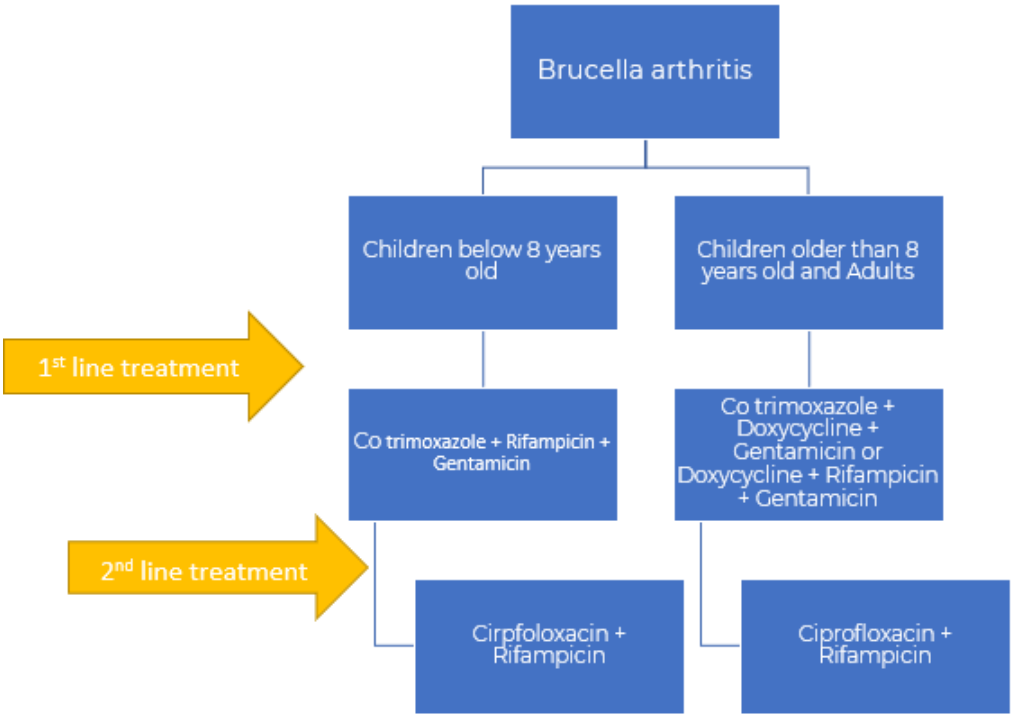

Figure 4. *Treatment algorithm for the management of brucella arthritis*

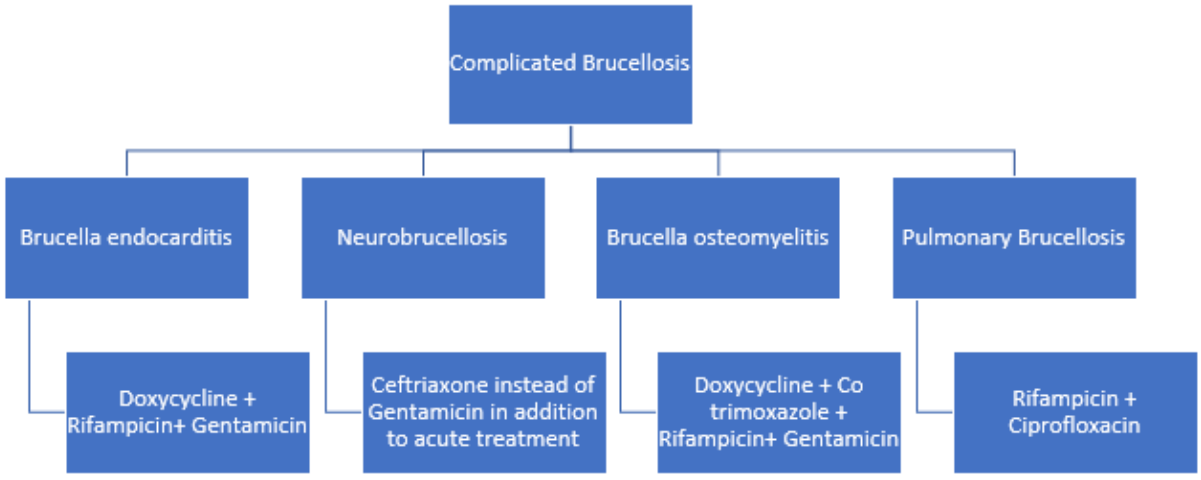

Figure 5. *Treatment algorithm for the management of complicated brucellosis*