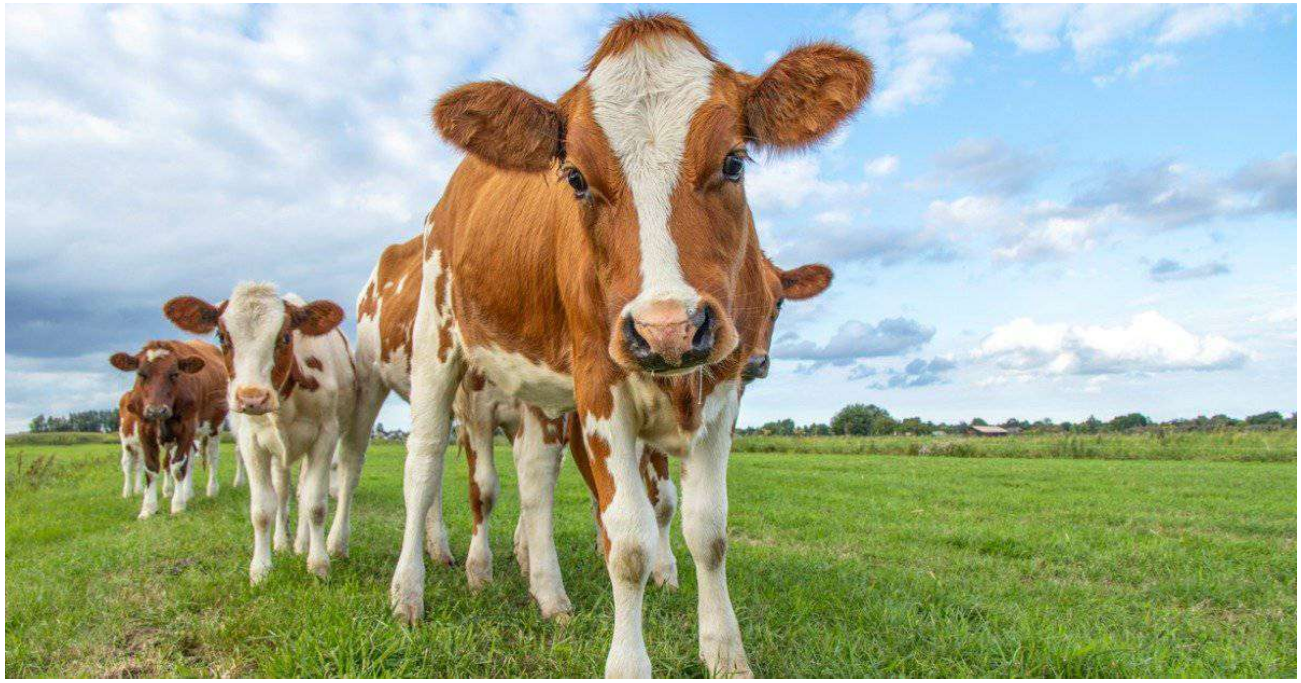
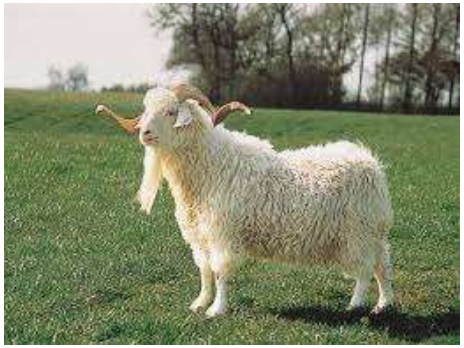
Brucellosis



Brucellosis….

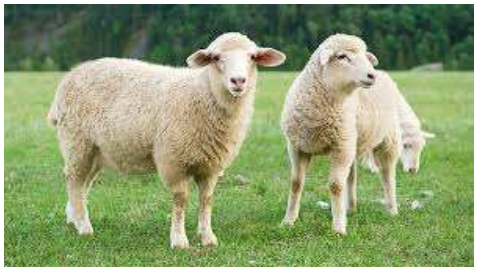


- Undulant fever
- Mediterranean fever
- Malta fever

- A zoonotic infection transmitted to humans from infected animals (cattle, sheep, goats, camels, pigs) by ingestion of food products (unpasteurized dairy products) or by contact with tissue or fluids

- The most common zoonosis worldwide

EPIDEMIOLOGY

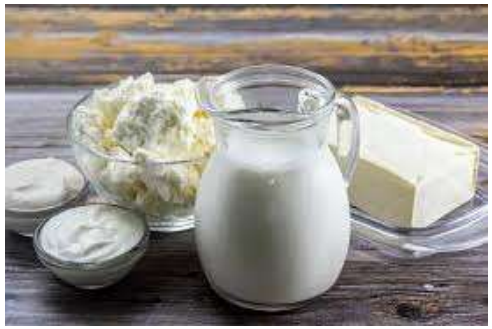


- ✓ Geographic distribution — Endemic areas, countries of the Mediterranean basin, Middle East, Central Asia, China, the Indian subcontinent, sub-Saharan Africa, and parts of Mexico and Central and South America

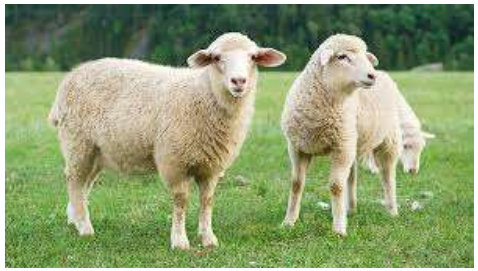
- ✓ All age groups

- ✓ Increasing the prevalence due to growing international tourism, trade, and migration

Transmission



- Consumption of unpasteurized dairy products (especially raw milk, soft cheese, butter, and ice cream) is the most common means of transmission
- Hard cheese, yogurt, and sour milk are less hazardous, since fermentation takes place
- Consumption of raw/undercooked muscle tissue, organ meat (liver& spleen), less common modes of transmission
- Contact of skin/mucous membranes with infected animal tissue (placenta/miscarriage products) or infected animal fluids (blood, urine, milk)
- Inhalation of infected aerosolized particles



- An occupational disease in shepherds, abattoir workers, veterinarians, dairy-industry professionals, and laboratory personnel (workers preparing brucellosis vaccines for animal use)

- Rare, human-to-human transmission via blood transfusion, tissue transplantation, breastfeeding, sexual contact, congenital transmission, and nosocomial infection
- Rare ,Congenital brucellosis. transmission, transplacentally during maternal bacteremia

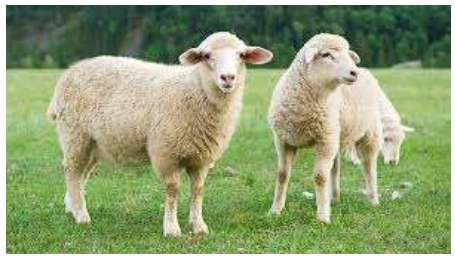
- Neonatal brucellosis may be acquired via contact with body fluids during delivery/via breastfeeding in the postpartum period

MICROBIOLOGY

Four *Brucella* species

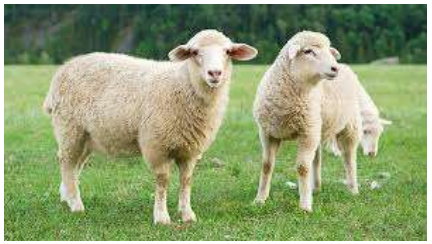
- *B. melitensis* (sheep and goats, camels), *B. abortus* (cattle)
- *B. suis* (swine), *B. canis* (dogs)

- Worldwide, most human cases are caused by *B. melitensi*
- Human infection due to B. melitensis and B. suis, more virulent
- *Brucellae* are small, nonmotile, facultative intracellular aerobic rods, in Gram staining, single, tiny, gram-negative coccobacilli



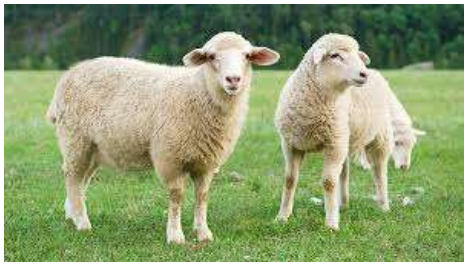
- The semiautomatic blood culture systems (Bactec) ; the presence of *Brucella*, by the third day of incubation
- With automated blood culture systems, most isolates, in one week; no need to incubate bottles longer than two weeks
- Cultures of other fluids/tissues, may take up to three weeks to grow on plated media
- *Brucella* organisms can survive up to two days in milk at ٨°C, three weeks in frozen meat, three months in goat cheese
- *Brucellae* shed in animal excretions may remain viable for >٤٠ days if the soil is damp
- Sensitive to heat, ionizing radiation, most commonly used disinfectants, and pasteurization


SYMPTOMS



- *Brucellae* are taken up by local tissue lymphocytes, enter the circulation via regional lymph nodes, and seed throughout the body, with tropism for the reticuloendothelial system
- The incubation period, ۲-۴ wks; may be, several months
- Insidious onset of fever, malaise, night sweats (a strong, peculiar, moldy odor), and arthralgias (table ۳)
- The spiking fever, rigors, or may be relapsing, mild, protracted
- Weight loss, arthralgia, low back pain, headache, dizziness, anorexia, dyspepsia, abdominal pain, cough, and depression
- Physical findings, variable and nonspecific; hepatomegaly, splenomegaly, and/or lymphadenopathy

Complications



- Infection involving one/more focal sites
- The likelihood of focal involvement, ۶-۹۲%(۲۰%)
- More frequently in adults than in children

Osteoarticular disease, the most common form (٧٠%)

- Peripheral arthritis, sacroiliitis, and spondylitis. The sacroiliac (٨٠%of those with osteoarticular disease) and spinal joints (up to ٥٤%)
- Sacroiliitis, in young adults ; unilat.(٨٠%)Peripheral arthritis and sacroiliitis occur in acute disease, involves the knees, hips, and ankles
- Prosthetic joints can also be affected
- Spondylitis, a serious complication of brucellosis; in older patients and patients with prolonged illness prior to treatment
- The lumbar vertebrae, more frequently than the thoracic and cervical vertebrae, paravertebral, epidural, and psoas abscesses . Spondylitis is frequently associated with residual damage following treatment

Genitourinary involvement, the second most common form;(١٠%)

- Orchitis and/or epididymitis, the most common presentation; prostatitis and testicular abscess
- Cystitis, interstitial nephritis, glomerulonephritis, and renal abscess
- In pregnant women, the risk of spontaneous abortion, intrauterine fetal death, premature delivery, and intrauterine infection with possible fetal death

Neurologic involvement, (١٠%)

- Meningitis (acute/chronic), encephalitis, brain abscess, myelitis, radiculitis, and/or neuritis (with involvement of cranial/peripheral nerves)

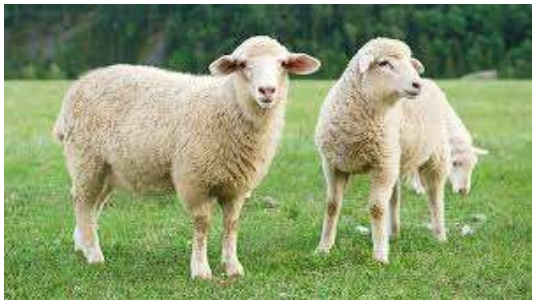
Cardiovascular involvement,٣%

- Endocarditis, myocarditis, pericarditis, endarteritis thrombophlebitis, and/or mycotic aneurysm of the aorta/ventricle

- Endocarditis, the most common cardiovascular complication (١-٢%) the main cause of death attributable to brucellosis

- Pulmonary involvement, (٢%) . Bronchitis, interstitial pneumonitis, lobar pneumonia, lung nodules, pleural effusion, hilar lymphadenopathy, empyema, abscesses
- Intra-abdominal manifestations, rare; hepatic/splenic abscess, cholecystitis, pancreatitis, ileitis, colitis, and peritonitis
- Ocular involvement, rare; uveitis, keratoconjunctivitis, corneal ulcers, iridocyclitis, nummular keratitis, choroiditis, optic neuritis, papilledema, and endophthalmitis
- Dermatologic manifestations, ١٠%) macular, maculopapular, scarlatiniform, papulonodular, and erythema nodosum-like eruptions, ulcerations, petechiae, purpura, granulomatous vasculitis, and abscesses

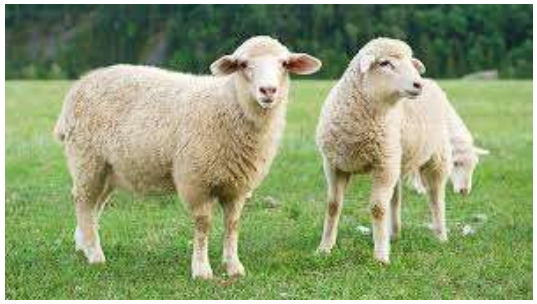
Chronic Brucellosis



Clinicians typically consider patients with clinical manifestations for more than one year after the diagnosis of brucellosis is established to have chronic brucellosis

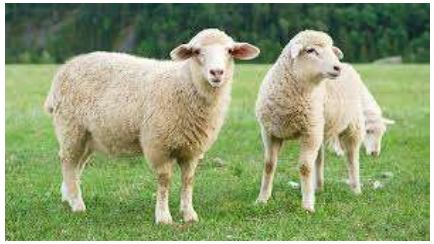
- Those with a focal complication (spondylitis, osteomyelitis, tissue abscess, uveitis) and objective evidence of infection elevated antibody titers and/or recovery of *Brucellae* from blood/ tissue culture)
- Those with persistent symptoms in the absence of objective signs of infection (positive serology/ cultures); malaise, psychiatric complaints (depression, anxiety, emotional lability), insomnia, sexual disturbances, tremor, arthralgias

Relapse

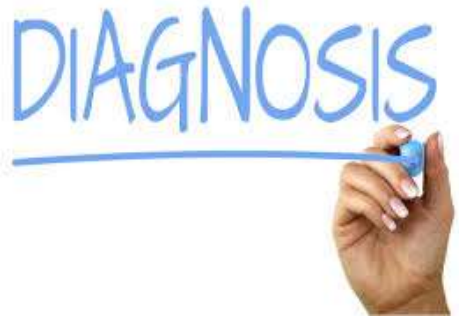


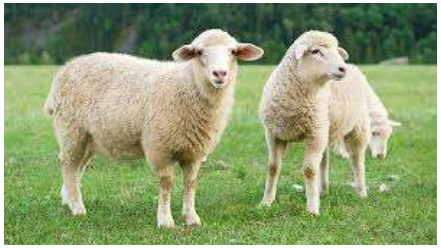
- ۵-۱۵%
- Occurs within the first six months following completion of treatment, up to ۱۲ months later
- ✓ An inadequate antibiotic regimen, inadequate duration of antibiotic therapy, lack of adherence, or localized foci of infection(in the absence of the preceding factors)
- ✓ Relapse due to antibiotic resistance is rare
- ✓ In a multivariate model for predicting relapse, Temperature ≥۳۸/۳°C, duration of symptoms <۱۰ days prior to treatment, and positive blood cultures at baseline
- In areas with ongoing exposure, differentiation between relapse and reinfection can be difficult

Laboratory Findings



- Elevated transaminases, anemia, leukopenia/leukocytosis with relative lymphocytosis, and thrombocytopenia (table ٣)
- The synovial fluid WBC ≤١٥’٠٠٠ cells/microL (lymphocyte-predominant)
- CSF, a pleocytosis (١٠ -٢٠٠ white blood cells, predominantly PMN), mild to moderately elevated protein level and hypoglycorrhachia
- CSF adenosine deaminase (ADA) level, a useful adjunctive test for diagnosis of CNS brucellosis
- Elevated CSF ADA levels, be observed in the setting of tuberculosis and other infections, and there is no clear threshold to distinguish neurobrucellosis from meningitis caused by other infectious agents
- Brucella in CSF culture, ٤-٣٨%
- Antibody/agglutination testing of spinal fluid, establish the diagnosis
- Pyuria ; the organism may be grown in urine culture


DIAGNOSIS

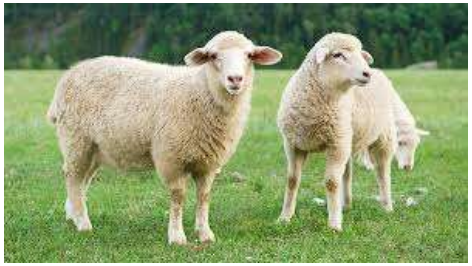


Clinical approach

- Brucellosis should be suspected in patients with relevant signs and symptoms (fever, malaise, night sweats, and arthralgia) in the setting of relevant epidemiologic exposure (consumption of unpasteurized dairy products, animal exposure in an endemic area, and/or occupational exposure)

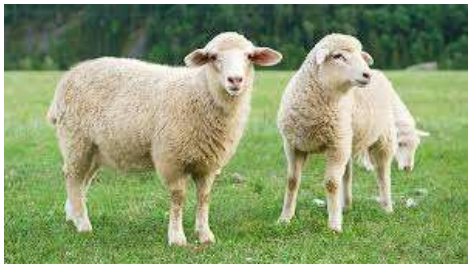
A definitive diagnosis of brucellosis may be made via either of the following:

- Culture of the organism from blood, body fluids (urine, cerebrospinal fluid, synovial fluid, and pleural fluid), or tissue (bone marrow/ liver biopsy).time consuming and hazardous (table ٢)
- A fourfold/greater rise in *Brucella* antibody titer between acute and convalescent phase serum specimens obtained ≥٢ weeks apart



A presumptive diagnosis of brucellosis may be made via either of the following:

- *Brucella* total antibody titer ≥١:١٦٠ by standard tube agglutination test (SAT) in serum specimen obtained after onset of symptoms
- Detection of *Brucella* DNA in a clinical specimen by polymerase chain reaction assay



For patients with suspected brucellosis, blood cultures and serologic testing should be performed

- Complete blood count, liver function tests, non specific tests
- Laboratory workers should be informed about the diagnostic possibility of brucellosis in order to implement special culture techniques and appropriate precautions (table ٢).
- For patients with negative blood cultures and negative serologic studies, further investigation should be guided by the clinical presentation

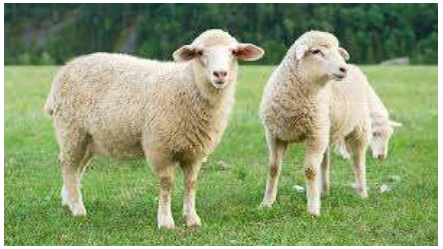
- Patients with signs and symptoms of osteoarticular disease, synovial fluid analysis and radiographic imaging

- Patients with neurologic manifestations, lumbar puncture; this procedure usually does not enable definitive diagnosis, may be useful to distinguish brucellosis from other causes of disease
- Bone marrow biopsy for culture and histopathology
- Not diagnostic bone marrow, liver involvement (based on liver function tests and/or radiographic imaging), liver biopsy .

Diagnostic Tests

- Culture — The sensitivity ,١٥-٧٠%
- Automated blood culture systems, most effective
- Blood cultures, negative in chronic disease
- Bone marrow culture is more sensitive than blood culture and is considered the gold standard for diagnosis of brucellosis (٩٢%) a shorter time to detection than blood culture, not diminished sensitivity by prior antibiotic use
- Serologic tests, enable antibody detection against lipopolysaccharide/ other antigens
- It must be interpreted in context of clinical presentation and epidemiologic data
- The most common tests are SAT and ELISA

Additional Tests

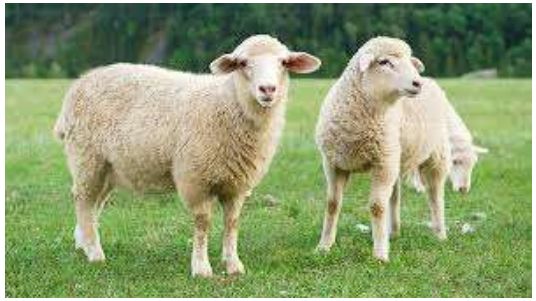


- ✓ Screening tests: (Rose Bengal agglutination test) sensitivity٨٧%, specificit١٠٠%

Tests in complicated and/or chronic infection

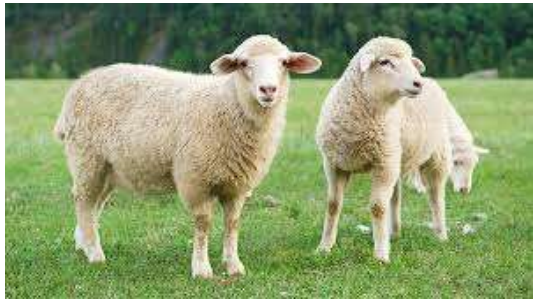
- ✓ The ٢-mercaptoethanol (٢-ME) agglutination test and the indirect Coombs test
- ✓ Use a combination of two serologic tests (SAT with ٢-ME, SAT with indirect Coombs, or ELISA for immunoglobulin [IgG and IgM)
- ✓ In acute disease, any of the assays may be positive; in chronic or complicated disease, SAT may be negative while ٢-ME, Coombs, and ELISA IgG may be positive
- ✓ Positive SAT titers consist of >١:١٦٠ outside endemic regions and >١:٣٢٠ within endemic areas

- Evolution of titers (a fourfold or greater rise in titer between acute and convalescent phase serum specimens obtained ≥٢ weeks apart) may be used as a diagnostic tool ; however, this definition is clinically impractical and may delay therapy
- The sensitivity and specificity of SAT are high ٩٥% and ١٠٠%
- In patients with chronic *Brucella* infection, nonagglutinating antibodies progressively become more abundant than the agglutinating ones and the SAT may give false-negative results
- SAT may not be used for diagnosis of *B. canis* infection; *B. canis* serology should be requested specifically if brucellosis is suspected but the SAT is negative, or if there is clinical suspicion for *B. canis* infection



- ELISA is preferred for diagnosis of neurobrucellosis, and may be used to distinguish from other infections that give false positive serologic results due to cross reaction

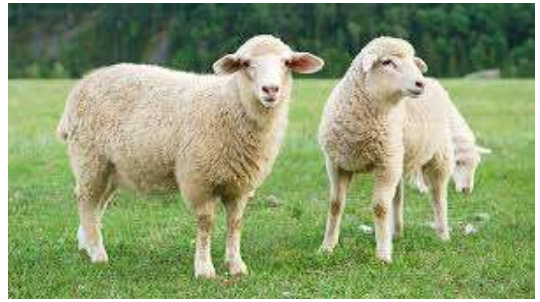
- Serologic tests with short turnaround time that may be used as screening tools, the Rose Bengal agglutination test (, respectively, in one study)



- Serologic tests that may be useful for patients with complicated and/or chronic infection: the ٢-ME agglutination test, and the indirect Coombs test

Disadvantages associated with serologic tests

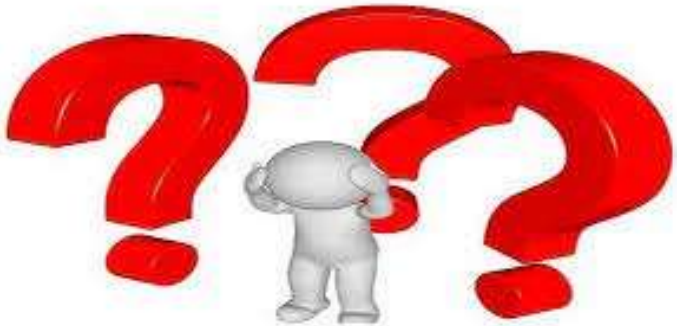
- False Positive standard agglutination tube; cross-reacting organisms: *Francisella tularensis*, *Yersinia enterocolitica*, *Escherichia coli, Salmonella urbana*, *Vibrio cholerae*, and others
- False-negative results, early in the course of infection, in the setting of immunosuppression, and in the presence of incomplete/blocking antibodies (serum agglutination)
- In addition, a "prozone" phenomenon (inhibition of agglutination at low dilutions due to an excess of antibodies/to nonspecific serum factors



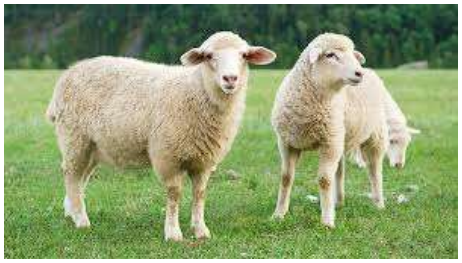
- ✓ The interpretation of serologic tests can be difficult in the setting of chronic infection, reinfection, relapse, and in endemic areas where a high proportion of the population has antibodies against brucellosis

- ✓ Positive serologic test results can persist long after recovery in treated individuals, so it is not always possible to distinguish serologically between active and past infection

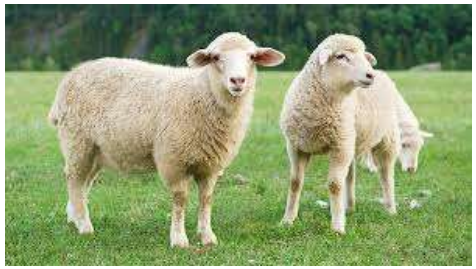
- ✓ A multiplex PCR, can identify and differentiate between *Brucella* species and vaccine strains; it can be used in epidemiologic analysis and for confirmation of relapse and laboratory-acquired infection.



Differential Diagnosis



- Malaria Fever, malaise, nausea, vomiting, abdominal pain, diarrhea, myalgia, and anemia. Transmission, via mosquito; The diagnosis, by visualization of parasites on peripheral smear
- Tuberculosis Cough, lymphadenopathy, fevers, night sweats, and weight loss, may present with extrapulmonary manifestations, musculoskeletal and central nervous system involvement.Transmission is human to human, and infection occurs worldwide. Diagnostic evaluation, CXR, sputum microbiology
- Visceral leishmaniasis Malaise, fever, weight loss, and splenomegaly (with /without hepatomegaly).Transmission, via sand fly bites, and endemic areas, the Mediterranean, the Middle East, Afghanistan, Iran, Pakistan, East Africa, India, Nepal, Bangladesh, and Brazil. The diagnosis, by histopathology, culture, serology



- Endocarditis Fever, often associated with chills, anorexia, and weight loss, malaise, headache, myalgias, arthralgias, night sweats, abdominal pain, and dyspnea. The diagnosis, on clinical manifestations, blood cultures, and echocardiography
- HIV infection Fever, lymphadenopathy, sore throat, rash, myalgia/arthralgia, and headache, The diagnosis is established via immunoassay and viral load
- Enteric fever By *Salmonella enterica* serotype Typhi. Abdominal pain, fever, and chills. Classic manifestations, relative bradycardia, pulse-temperature dissociation, and "rose spots" (faint macules on the trunk and abdomen). Hepatosplenomegaly, intestinal bleeding, and perforation, secondary bacteremia and peritonitis. Transmission is fecal-oral. The diagnosis, culture
- Malignancy The most common malignancies presenting with FUO, lymphoma, leukemia, renal cell carcinoma and hepatocellular carcinoma, other tumors metastatic to the liver

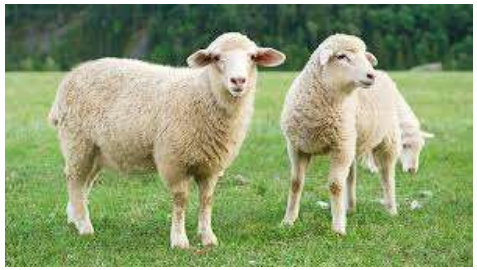
In patients with osteoarticular manifestations, additional diagnostic considerations:

- ✓ Spondyloarthritis, a group of diseases, chronic low back pain, heel enthesitis, dactylitis, and oligoarthritis. The diagnosis, on clinical manifestations, radiographic findings, and laboratory tests
- ✓ Reactive arthritis,a form of arthritis associated with a coexisting or recent antecedent extra-articular infection
- ✓ Enteric and genitourinary pathogens capable of causing reactive arthritis include *Chlamydia trachomatis*, *Yersinia*, *Salmonella*, *Shigella*, *Campylobacter*, *Clostridioides difficile*, and *Chlamydia pneumoniae*. Synovial fluid findings are similar to those seen in patients with arthritis associated with brucellosis. The diagnosis, on clinical presentation and exclusion of other causes
- ✓ Septic arthritis, infection in a joint; it is usually caused by bacteria, via hematogenous seeding; it may also develop as a result of direct inoculation of bacteria into the joint. Rarely, septic arthritis develops via extension of infection into the joint space from adjacent tissues. The diagnosis, on synovial fluid analysis and culture

- Viral infections May cause arthritis, fever, and other constitutional manifestations; rubella, parvovirus B١٩, hepatitis B virus, and others. The diagnosis, via serology and PCR
- Systemic lupus erythematosus By fever, rash, and inflammatory polyarthritis or arthralgias. The diagnosis, via presence of ANA and other characteristic systemic manifestations
- Rheumatoid arthritis,a symmetric, inflammatory, peripheral polyarthritis involving peripheral joints; extra-articular features, anemia, fatigue, subcutaneous nodules, pleuropericarditis, parenchymal lung diseases, neuropathy, and renal involvement The diagnosis, via clinical criteria and laboratory and serologic tests

Treatment

General Approach



- To control the illness and prevent complications, relapses, sequelae, and mortality

General principles of brucellosis treatment:

- Use of antibiotics with activity in acidic intracellular environments (doxycycline and rifampin)
- Use of combination therapy (given high relapse rates with monotherapy)
- Prolonged duration of treatment

- The preferred regimen is doxycycline combined with an aminoglycoside

- However, many favor doxycycline-rifampin since it is more convenient than parenteral therapy, may be better tolerated than aminoglycosides (which are associated with nephrotoxicity and ototoxicity) and is less costly

- Monotherapy regimens and regimens shorter than six weeks are not accepted treatment strategies for brucellosis, given high relapse rates with these approaches

Alternative agents, fluoroquinolones and TMP-SMX, used in combination regimens:

- Fluoroquinolones as alternative second or third agents in combination regimens containing doxycycline or rifampinThey are not appropriate first-line agents (given decreased activity in acidic environments, as well as cost), but may be beneficial in the setting of drug resistance, antimicrobial toxicity, and some cases of relapse
- TMP-SMX, as an alternative second or third agent in combination regimens containing doxycycline or rifampin for treatment of patients with relapse or refractory disease
- The efficacy of doxycycline-TMP-SMX is similar to that of doxycycline-rifampin
- In addition, TMP-SMX should be used with caution for prolonged treatment of brucellosis given its broad spectrum of activity and potential for development of antimicrobial resistance

Children

Regimens for treatment of children ≥٨ years with brucellosis (in the absence of spondylitis, neurobrucellosis/endocarditis) include (table ١):

- Doxycycline(oral) PLUS rifampin(oral), both for ٦ weeks
- Doxycycline (oral) for ٦ weeks PLUS streptomycin (parenteral) for the first ١٤-٢١ days
- Doxycycline (oral) for ٦ weeks PLUS gentamicin (parenteral) for the first ٧-١٠ days
- Many favor doxycycline-rifampin for treatment of children ≥٨ years with brucellosis since it is more convenient than parenteral therapy

Treatment of children <٨ years with uncomplicated brucellosis:

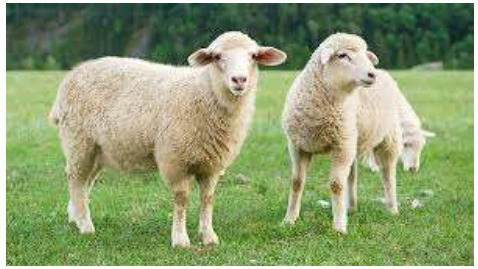
- Trimethoprim-sulfamethoxazole(TMP-SMX) PLUS rifampin, both for ٦ weeks (table ١)
- TMP-SMX or rifampin, in combination with an aminoglycoside
- Doxycycline is not recommended for children <٨ years of age given risk for dental staining with prolonged duration of therapy

Kidney or liver failure

- In patients with hepatic failure,an aminoglycoside in combination with either doxycycline /fluoroquinolone
- In patients with kidney failure, doxycycline plus rifamp

- For adults and children ≥۸ with neurobrucellosis, ceftriaxone for the first ۴ to ۶ weeks, PLUS rifampin and doxycycline, both for at least ۱۲ weeks; the duration of therapy is often extended to ۴ to ۶ months (table ۳)
- For children <۸ years, we substitute TMP-SMX for doxycycline
- An alternative regimen, doxycycline-rifampin-TMP-SMX, all administered for at least ۱۲ weeks
- The total duration of treatment is at least three months and may be up to six months or longer
- The duration of therapy should be tailored to individual patient circumstances including clinical assessment, cerebrospinal fluid findings, and follow-up radiographic imaging
- There is no role for routine use of corticosteroids for treatment of neurobrucellosis
- Use of steroids may be appropriate in the setting of neurobrucellosis complicated by iritis, papilledema, myelopathy, polyneuropathy, radiculopathy, encephalitis, and/or cranial nerve palsies

- ✓ Endocarditis, most patients with *Brucella* endocarditis require a combination of antimicrobial therapy and surgery for the best chance of cure Surgical consultation is warranted for all patients with *Brucella* endocarditis
- ✓ For adults and children ≥٨ years with *Brucella* endocarditis, a triple-combination antibiotic regimen including an aminoglycoside (streptomycin/gentamicin) for the first month, PLUS rifampin and doxycycline both for at least ١٢ weeks
- ✓ An alternative approach, a third-generation cephalosporin for the aminoglycoside For children <٨ years, we substitute TMP-SMX for doxycycline
- ✓ The minimum duration of therapy is ١٢ weeks; the duration of therapy is often extended for four to six months
- ✓ For patients with a prosthetic valve or abscess who do not undergo surgery, a prolonged duration of therapy is warranted

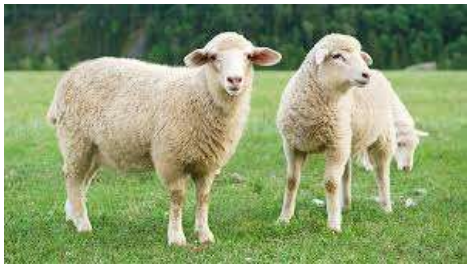


- Relapse, within the first six months following completion of treatment, but may occur up to ١٢ months later
- Relapse of symptoms should prompt assessment for focal disease. Relapse due to antibiotic resistance is rare; nonetheless, antimicrobial susceptibility should be performed on all culture isolates. (Most relapses can be treated successfully with a repeat course of a standard regimen Patients with second or third relapse should be treated with an alternative regimen
- Disease due to vaccine strain RB٥١ — *Brucella* RB٥١ is a live attenuated cattle vaccine strain which can be shed in milk and can cause infection in humans who drink the milk without pasteurization; the strain is resistant to rifampin

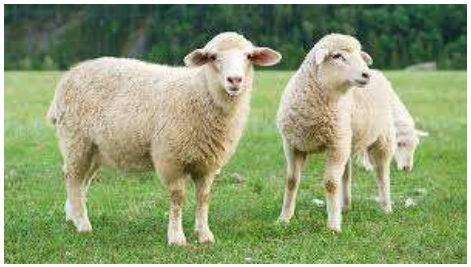
OUTCOME

- Unfavorable outcomes (defined by relapses and therapeutic failures) are usually a result of failure to eradicate intracellular bacteria. Therapeutic failures are usually associated with *Brucella* spondylitis and have been reported in up to ١٥% of cases Rarely, moderate to severe sequelae occur in the setting of spondylitis and neurobrucellosis
- The prognosis of neurobrucellosis is variable
- With appropriate antimicrobial treatment, the mortality rate of brucellosis is <١% endocarditis is the main cause of death attributable to brucellosis

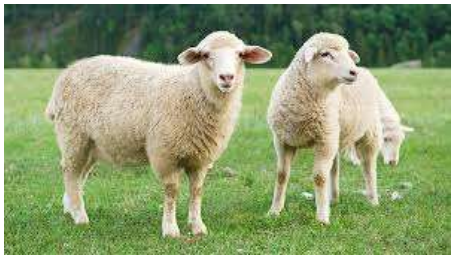
PREVENTION



- General principle, no vaccines for prevention of brucellosis in humans; improved understanding of disease pathogenesis may facilitate identification of vaccine targets
- Treatment of dairy products, precautions for individuals at risk for occupational exposure, precautions to prevent person-to-person transmission, and control of the disease in animals Raw milk should be boiled or pasteurized; consumption of dairy products made from raw milk should be avoided.
- Contact of skin or mucous membranes with infected tissue (such as placenta or miscarriage products) or infected fluids (such as blood, urine, or milk) should be avoided. In addition, inhalation of infected aerosolized particles should be avoided



- Manipulation of *Brucella* cultures should be performed with biosafety level ۳ practices and containment equipment (table ۵)
- In slaughterhouses, protective measures include separation of the killing floor from other processing areas, using designated spaces for known infected animals, use of protective clothing and disinfectants, and control of air circulation.
- To reduce the likelihood of person-to-person transmission, patients should be counseled to wait until completion of treatment before unprotected sexual contact; *Brucella* organisms have been detected in semen and it is unknown how long the risk of sexual transmission persists following initiating of treatment Lactating women with brucellosis should be counseled to discontinue breastfeeding until completion of treatment. In highly endemic regions, we recommend serologic testing for blood and organ donors
- Vaccination of domestic livestock – Available vaccines for prevention of brucellosis in animals include *Brucella abortus* B۱۹ and RB۵۱ (for cattle) and *Brucella melitensis* Rev ۱ (for small ruminants such as sheep and goats). A sustained vaccination program over several years is required. These are live attenuated vaccines that are also known to cause disease in humans during preparation or by accidental inoculation; inadvertent exposure requires careful follow-up [There are no suitable vaccines for prevention of *B. melitensis* in cattle or prevention of *Brucella suis* in swine



- Screening contacts — Screening household members of an index case enables detection of unrecognized cases, facilitating early treatment and prevention of complications
- Household members of an index case should undergo clinical evaluation for signs and symptoms of brucellosis serologic testing (with repeat testing at ۶ and ۱۲ weeks); they should be instructed to seek medical attention if they develop relevant clinical manifestations