Chapter 174: Brucellosis

KEY CLINICAL POINTS

1. Brucellosis is a bacterial zoonosis transmitted directly or indirectly to humans from infected animals, predominantly domesticated ruminants and swine.
2. The disease is known colloquially as undulant fever because of its remittent character.
3. B. melitensis is the most common cause of symptomatic disease in humans, acquired from sheep, goats, and camels.
4. Fever of brucellosis shows an undulating pattern that persists for weeks before the commencement of an afebrile period that may be followed by relapse.
5. Musculoskeletal symptoms are present in about one-half of all patients; osteomyelitis more commonly involves the lumbar and low thoracic vertebrae.
6. Diagnosis requires isolation of brucellae from blood, CSF, bone marrow, or joint fluid (definitive) or serologic evidence (IgM followed by IgG/IgA).
7. Standard treatment for adults is dual therapy: IM streptomycin (0.75–1 g daily for 14–21 days) plus doxycycline (100 mg twice daily for 6 weeks).
8. Alternative regimen: Rifampin (600–900 mg/d) plus doxycycline (100 mg twice daily) for 6 weeks.
9. Relapse follows standard treatment in 5–10% of cases; adherence is critical as poor adherence underlies almost all cases of apparent treatment failure.
10. Tuberculosis must always be excluded in patients with vertebral osteomyelitis as several antimicrobial agents used to treat brucellosis are also used to treat tuberculosis.

FIGURES IN THIS CHAPTER

No figures extracted.

1. DEFINITION & OVERVIEW

• Brucellosis is a bacterial zoonosis transmitted directly or indirectly to humans from infected animals, predominantly domesticated ruminants and swine.

• The disease is known colloquially as undulant fever because of its remittent character.

• Although brucellosis commonly presents as an acute febrile illness, its clinical manifestations vary widely, and definitive signs indicative of the diagnosis may be lacking.

• Thus, the clinical diagnosis usually must be supported by the results of bacteriologic and/or serologic tests.

• Human brucellosis is caused by strains of the genus Brucella, with several species groups defined by differences in chromosomal structure, host preference, and epidemiologic patterns of infection.

• B. melitensis and B. suis have historically been developed as biological weapons by several countries and could be exploited for bioterrorism.

• This possibility should be borne in mind in the event of sudden unexplained outbreaks.

1.1 Etiologic Agents

• All brucellae are small, gram-negative, unencapsulated, nonsporulating rods or coccobacilli.

• They grow aerobically on peptone-based medium incubated at 37°C; the growth of some types is improved by supplementary CO2.

• In vivo, brucellae behave as facultative intracellular parasites.

• The 2 organisms are sensitive to sunlight, ionizing radiation, and moderate heat; they are killed by boiling and pasteurization but are resistant to freezing and drying.

• Their resistance to drying renders brucellae stable in aerosol form, facilitating airborne transmission.

• The organisms can survive for up to 2 months in soft cheeses made from goat's or sheep's milk; for at least 6 weeks in dry soil contaminated with infected urine, vaginal discharge, or placental or fetal tissues; and for at least 6 months in damp soil or liquid manure kept in cool dark conditions.

• Brucellae are easily killed by a wide range of common disinfectants used under optimal conditions but are likely to be much more resistant at low temperatures or in the presence of heavy organic contamination.

• B. melitensis is the most common cause of symptomatic disease in humans, for which the main sources are sheep, goats, and camels.

• B. abortus is acquired from cattle or buffalo.

• B. suis is generally acquired from swine but has one variant that is enzootic in reindeer and caribou and another in rodents.

• B. canis is acquired from dogs.

• B. ovis causes reproductive disease in sheep but has not been clearly implicated in the human disease.

• Rare human infections have been reported with B. neotomae, which is found in desert rodents.

• Two species, B. ceti and B. pinnipedialis, have been identified in marine mammals, including seals and dolphins.

• At least one case of laboratory-acquired human disease due to one of these species has been described, and several cases of natural human infection have been reported.

• Other reported species include B. microti (isolated from field voles), B. papionis (from baboons), B. vulpis (from foxes), and B. inopinata (from a patient with a breast implant).

• Additional novel strains have been described in diverse species, including frogs, bats, and various rodents, and the genus likely will expand further in forthcoming years.

• The genus Brucella is closely related to the genus Ochrobactrum, which includes free-living environmental bacteria that can occasionally cause opportunistic infections.

• Recent changes in taxonomy now place Ochrobactrum spp. as subspecies of Brucella on genetic grounds, although the ecology, physiology, clinical niche, and antimicrobial sensitivity of these organisms are completely different.

2. EPIDEMIOLOGY

• Brucellosis is a zoonosis whose occurrence and control are closely related to its prevalence in domesticated animals.

• Its distribution is worldwide apart from the few countries where it has been eradicated from the animal reservoir.

• The true global prevalence of human brucellosis is unknown because of the imprecision of diagnosis and the inadequacy of reporting and surveillance systems in many countries.

• Recent estimates suggest there may be more than 2 million cases of human infection a year worldwide.

• There has been increased recognition of brucellosis in India, Pakistan, Sri Lanka, and China, and importations to countries in Oceania, such as Fiji, and in Asia, such as Thailand and Vietnam.

• In Europe, the incidence of brucellosis in a country is inversely related to gross domestic product, and in both developed and less well-resourced settings, human brucellosis is related to rural poverty and inadequate access to medical care.

• Failure of veterinary control programs due to conflicts or for economic reasons contributes further to the emergence and re-emergence of disease, as seen currently in some eastern Mediterranean countries.

• Even in well-resourced settings, the true incidence of brucellosis in domesticated animals may be 10–20 times higher than the reported figures.

• Bovine brucellosis has been the target of control programs in many parts of the world and has been eradicated from the cattle populations of much of northern Europe, Australia, New Zealand, and Canada, among other nations.

• Its incidence has been reduced to a low level in the United States and most western European countries, with a varied picture in other parts of the world.

• Efforts to eradicate B. melitensis infection from sheep and goat populations have been much less successful.

• These efforts have relied heavily on vaccination programs, which have tended to fluctuate with changing economic and political conditions.

• In some countries (e.g., Israel), B. melitensis has caused serious outbreaks in cattle.

• Infections with B. melitensis still pose a major public health problem in Mediterranean countries; in western, central, and southern Asia; and in parts of Africa and South and Central America.

• Infections with B. abortus are common in cattle-rearing communities in African countries such as Kenya and Uganda.

• Canine infection with B. canis is present on most continents—the incidence appears to be increasing in North America and in several European countries, often associated with importation of dogs from an endemic area.

• Human brucellosis is usually associated with occupational or domestic exposure to infected animals or their products.

• Farmers, shepherds, goatherds, veterinarians, and employees in slaughterhouses and meat-processing plants in endemic areas are occupationally exposed to infection.

• Feral pig hunters are at risk of infection with B. suis in several countries, including Australia.

• Family members of individuals involved in animal husbandry may be at risk, although it is often difficult to differentiate food-borne infection from environmental contamination under these circumstances.

• Laboratory workers who handle cultures or infected samples also are at risk.

• Travelers and urban residents usually acquire the infection through consumption of contaminated foods.

• In countries that have eradicated the disease, new cases are most commonly acquired abroad.

• Dairy products, especially soft cheeses, unpasteurized milk, and ice cream, are the most frequently implicated sources of infection; raw meat and bone marrow and may be sources under exceptional

circumstances.

• Infections acquired through cosmetic treatments using materials of fetal origin have been reported.

• Person-to-person transmission is extremely rare, as is transfer of infection by blood or tissue donation.

• Although brucellosis is a chronic intracellular infection, there is no evidence for increased prevalence or severity among individuals with HIV infection or with immunodeficiency or immunosuppression of other etiologies.

3. ETIOLOGY & PATHOGENESIS

• Exposure to brucellosis elicits both humoral and cell-mediated immune responses.

• The mechanisms of protective immunity against human brucellosis are presumed to be similar to those documented in laboratory animals, but such generalizations must be interpreted with caution.

• The response to infection and its outcome are influenced by the virulence, phase, and species of the infecting strain.

• Differences have been reported between B. abortus and B. suis in modes of cellular entry and subsequent compartmentalization and processing.

• Antibodies promote clearance of extracellular brucellae by bactericidal action and by facilitation of phagocytosis by polymorphonuclear and mononuclear phagocytes; however, antibodies alone cannot eradicate infection.

• Organisms taken up by macrophages and other cells can establish persistent intracellular infections.

• The key target cell is the macrophage, and bacterial mechanisms for suppressing intracellular killing and apoptosis result in very large intracellular populations.

• Opsonized bacteria are actively phagocytosed by neutrophilic granulocytes and by monocytes.

• In these and other cells, initial attachment takes place via specific receptors, including Fc, C3, fibronectin, and mannose-binding proteins.

• Opsonized—but not unopsonized—bacteria trigger an oxidative burst inside phagocytes.

• Unopsonized bacteria are internalized via similar receptors but at much lower efficiency.

• Smooth strains enter host cells via lipid rafts.

• Smooth lipopolysaccharide (LPS), β-cyclic glucan, and possibly an invasion–attachment protein (Alb) are involved in this process.

• Tumor necrosis factor α (TNF-α) produced early in the course of infection stimulates cytotoxic lymphocytes and activates macrophages, which can kill intracellular brucellae (probably mainly through production of reactive oxygen and nitrogen intermediates) and may clear infection.

• However, virulent Brucella cells can suppress the TNF-α response, and control of infection in this situation depends on macrophage activation and interferon γ (IFN-γ) responses.

• Cytokines such as interleukin (IL) 12 promote production of IFN-γ, which drives T 1-type responses and stimulates macrophage activation.

• Inflammatory cytokines, including IL-4, IL-6, and IL-10, downregulate the protective response.

• As in other types of intracellular infection, it is assumed that initial replication of brucellae takes place within cells of the lymph nodes draining the point of entry.

• Subsequent hematogenous spread may result in chronic localizing infection at almost any site, although the reticuloendothelial system, musculoskeletal tissues, and genitourinary system are most frequently targeted.

• Both acute and chronic inflammatory responses develop in brucellosis, and the local tissue response may include granuloma formation with or without necrosis and caseation.

• Abscesses may also develop, especially in chronic localized infection.

• The determinants of pathogenicity of Brucella have not been fully characterized, and the mechanisms underlying the manifestations of brucellosis are incompletely understood.

• The organism is a 'stealth' pathogen whose survival strategy is centered on several processes that avoid triggering innate immune responses and that permit survival within monocytic cells.

• These processes include evasion of intracellular destruction by restricting the fusion of type IV secretion system–dependent Brucella-containing vacuoles with lysosomal compartments, inhibition of apoptosis of infected mononuclear cells, and prevention of dendritic cell maturation, antigen presentation, and activation of naïve T cells.

• The smooth Brucella LPS, which has an unusual O-chain and core-lipid composition, has relatively low endotoxin activity and plays a key role in pyrogenicity and in resistance to phagocytosis and serum killing in the nonimmune host.

• In addition, LPS is believed to play a role in suppressing phagosome–lysosome fusion and diverting the internalized bacteria into vacuoles located in endoplasmic reticulum, where intracellular replication takes place.

• Specific exotoxins have not been isolated, but a type IV secretion system (Vir) that regulates intracellular survival and trafficking has been identified.

• In B. abortus, this system can be activated extracellularly, but in B. suis, it is activated (by low pH) only during intracellular growth.

• Brucellae then produce acid-stable proteins that facilitate the organisms' survival in phagosomes and may enhance their resistance to reactive oxygen intermediates.

• A type III secretion system based on modified flagellar structures also has been inferred, although not yet confirmed.

• Virulent brucellae are resistant to defensins and produce a Cu-Zn superoxide dismutase that increases their resistance to reactive oxygen intermediates.

• A hemolysin-like protein may trigger the release of brucellae from infected cells.

4. CLINICAL FEATURES

• Brucellosis almost invariably causes fever, which may be associated with profuse sweats, especially at night.

• In endemic areas, brucellosis may be difficult to distinguish from other causes of fever.

• However, two features recognized in the nineteenth century distinguish brucellosis from other tropical fevers, such as typhoid and malaria:

• Left untreated, the fever of brucellosis shows an undulating pattern that persists for weeks before the commencement of an afebrile period that may be followed by relapse.

• The fever of brucellosis is associated with musculoskeletal symptoms and signs in about one-half of all patients.

• The incubation period varies from 1 week to several months, and the onset of fever and other symptoms may be abrupt or insidious.

• In addition to experiencing fever and sweats, patients become increasingly apathetic and fatigued; lose appetite and weight; and have nonspecific myalgia, headache, and chills.

• Overall, the presentation of brucellosis often fits one of three patterns: febrile illness that resembles typhoid but is less severe; fever and acute monoarthritis, typically of the hip or knee, in a young child; and long-lasting fever, misery, and low-back or hip pain in an older person (especially men).

• In an endemic area (e.g., much of the Middle East), a patient with fever and difficulty walking into the clinic would be suspected to have brucellosis until it was proven otherwise.

• Diagnostic clues in the patient's history include travel to an endemic area, employment in a diagnostic microbiology laboratory, consumption of unpasteurized milk products (including soft cheeses), contact with animals, accidental inoculation with veterinary Brucella vaccines, and—in an endemic setting—a history of similar illness in the family (documented in almost 50% of cases).

• Focal features are present in the majority of patients.

• The most common are musculoskeletal pain and physical findings in the peripheral and axial skeleton (~40% of cases).

• Osteomyelitis more commonly involves the lumbar and low thoracic vertebrae than the cervical and high thoracic spine.

• Individual joints that are most commonly affected by septic arthritis are the knee, hip, sacroiliac, shoulder, and sternoclavicular joints; the pattern may be one of monoarthritis or polyarthritis.

• Osteomyelitis may also accompany septic arthritis.

• In addition to the usual causes of vertebral osteomyelitis or septic arthritis, the most important disease in the differential diagnosis is tuberculosis.

• This point influences the therapeutic approach as well as the prognosis, given that several antimicrobial agents used to treat brucellosis are also used to treat tuberculosis.

• Septic arthritis in brucellosis progresses slowly, starting with small pericapsular erosions.

• In the vertebrae, anterior erosions of the superior end plate are typically the first features to become evident, with eventual involvement and sclerosis of the whole vertebra.

• Anterior osteophytes eventually develop, but vertebral destruction or impingement on the spinal cord is rare and usually suggests tuberculosis.

• Other systems may be involved in a manner that resembles typhoid.

• About one-quarter of patients have a dry cough, usually with few changes visible on the chest x-ray, although pneumonia, empyema, intrathoracic adenopathy, or lung abscess can occur.

• Sputum or pleural effusion cultures are rarely positive in such cases, which respond well to standard brucellosis treatment.

• One-quarter of patients have hepatosplenomegaly, and 10–20% have significant lymphadenopathy; the differential diagnosis includes glandular fever–like illness such as that caused by Epstein-Barr virus, Toxoplasma, cytomegalovirus, HIV, or Mycobacterium tuberculosis.

• Up to 10% of men have acute epididymo-orchitis, which must be distinguished from mumps and from surgical problems such as torsion.

• Prostatitis, inflammation of the seminal vesicles, salpingitis, and pyelonephritis all occur.

• There is an increased incidence of fetal loss among infected pregnant women, although teratogenicity has not been described and the tendency toward abortion is much less pronounced in humans than in animals.

• Neurologic involvement is common, with depression and lethargy whose severity may not be fully appreciated by either the patient or the physician until after treatment.

• A small proportion of patients develop intracerebral abscess, a variety of cranial nerve deficits, or ruptured mycotic aneurysms.

• Endocarditis occurs in ~1% of cases, most often affecting the aortic valve (natural or prosthetic).

• Any site in the body may be involved in metastatic abscess formation or inflammation; the female breast and the thyroid gland are affected particularly often.

• Nonspecific maculopapular rashes and other skin manifestations are uncommon and are rarely noticed by the patient even if they develop.

4.1 Radiology of the Spine

• Osteomyelitis more commonly involves the lumbar and low thoracic vertebrae than the cervical and high thoracic spine.

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Table 1 Table 174-1 Radiology of the Spine: Differentiation of Brucellosis from Tuberculosis

Site	BRUCELLOSIS	TUBERCULOSIS
Vertebrae	Multiple or contiguous	Contiguous
Diskitis	Late	Early
Body	Intact until late	Morphology lost early
Canal compression	Rare	Common

Site	BRUCELLOSIS	TUBERCULOSIS
Osteophyte	Anterolateral (parrot beak)	Unusual
Deformity	Wedging uncommon	Anterior wedge, gibbus
Recovery	Sclerosis, whole-body	Variable
Psoas abscess	Rare	More likely

5. DIFFERENTIAL DIAGNOSIS

• The clinical picture of brucellosis is not distinctive, the diagnosis must be based on a history of potential exposure, a presentation consistent with the disease, and supporting laboratory findings.

• Results of routine biochemical assays are usually within normal limits, although serum levels of hepatic enzymes and bilirubin may be elevated.

• Peripheral leukocyte counts are usually normal or low, with relative lymphocytosis.

• Mild anemia may be documented.

• Thrombocytopenia and disseminated intravascular coagulation with raised levels of fibrinogen degradation products can develop.

• The erythrocyte sedimentation rate and C-reactive protein levels are often normal but may be raised.

• In body fluids such as cerebrospinal fluid (CSF) or joint fluid, lymphocytosis and low glucose levels are the norm.

• Elevated CSF levels of adenosine deaminase cannot be used to distinguish tubercular meningitis, as they may also be found in brucellosis.

• Biopsied samples of tissues such as lymph node or liver may show noncaseating granulomas without acid-fast bacilli.

• The radiologic features of bony disease develop late and are much more subtle than those of tuberculosis or septic arthritis of other etiologies, with less bone and joint destruction.

• Isotope scanning is more sensitive than plain x-ray and continues to give positive results long after successful treatment.

• Isolation of brucellae from blood, CSF, bone marrow, or joint fluid or from a tissue aspirate or biopsy sample is definitive, and attempts at isolation are usually successful in 50–70% of cases.

• Blood culture using modern nonradiometric or similar signaling systems (e.g., Bactec) usually become positive within 7 days.

• Clinicians should alert the laboratory to the possibility of brucellosis if suspected, as all cultures should be handled under containment conditions appropriate for dangerous pathogens.

• Brucella species may be misidentified as Agrobacterium, Ochrobactrum, or Psychrobacter (Moraxella) phenylpyruvicus by the gallery identification strips that may still be used in the diagnostic laboratory.

• In recent years, matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) has emerged as a powerful tool for bacterial identification in well-resourced laboratories.

• Earlier implementations of MALDI-TOF often failed to identify Brucella species correctly as a genus or at species level.

• Following recent changes in taxonomy, Ochrobactrum isolates may now be reported as a subspecies of Brucella.

• This can lead to confusion and have important clinical and public health consequences, as management differs completely.

• Clinicians should confirm the meaning of any culture report suggestive of brucellosis with laboratory colleagues before making therapeutic decisions.

• The peripheral blood–based polymerase chain reaction (PCR) has enormous potential to detect bacteremia, to predict relapse, and to exclude 'chronic brucellosis.'

• This method is more sensitive and quicker than blood culture, and it does not carry the attendant biohazard risk posed by culture.

• However, it is not perfect, and false-negative results are sometimes observed in patients with positive blood cultures.

• Nucleic acid amplification techniques are now quite widely used, although no single standardized procedure has been adopted.

• Primers for the spacer region between the genes encoding the 16S and 23S ribosomal RNAs (rrs-rrl), various outer-membrane protein–encoding genes, the insertion sequence IS711, and the protein BCSP31 are sensitive and specific.

• Blood and other tissues are the most suitable samples for analysis.

• The clinical significance of prolonged PCR positivity, commonly seen in blood after successful treatment, remains controversial.

• Serologic examination often provides the only positive laboratory findings in brucellosis.

• In acute infection, IgM antibodies appear early and are followed by IgG and IgA.

• All these antibodies are active in agglutination tests, whether performed by tube, plate, or microagglutination methods.

• The majority of patients have detectable agglutinins at this stage.

• As the disease progresses, IgM levels decline, and the avidity and subclass distribution of IgG and IgA change.

• The result is reduced or undetectable agglutinin titers.

• However, the antibodies are detectable by alternative tests, including the complement fixation test, Coomb's antiglobulin test, and enzyme-linked immunosorbent assays.

• There is no clear cutoff value for a diagnostic titer.

• Rather, serology results must be interpreted in the context of exposure history and clinical presentation.

• In endemic areas or in settings of potential occupational exposure, agglutinin titers of 1:320–1:640 or higher are considered diagnostic; in nonendemic areas, a titer of ≥1:160 is considered significant.

• Repetition of tests after 2–4 weeks may demonstrate a rising titer.

• In most centers, the standard agglutination test (or a derivative such as the microagglutination test) is still the mainstay of serologic diagnosis.

• In an endemic setting, >90% of patients with acute bacteremia have standard agglutination titers of at least 1:320 at the time of clinical presentation.

• Some centers rely on the Rose Bengal test, particularly for screening, but it has been only partially validated for human diagnostic use.

• A variety of near-patient or point-of-care tests are still in developmental stages.

• Good evidence supports the use of an aminoglycoside such as gentamicin (5–6 mg/kg per day for 1–2 weeks) instead of streptomycin, and this is recommended in U.S. and U.K. guidelines.

• Shorter courses of gentamicin have been associated with high failure rates in adults.

• Early experience with fluoroquinolone monotherapy was disappointing, but it has been suggested that ofloxacin or ciprofloxacin, given together with rifampin for 6 weeks, might be an acceptable alternative to the other 6-week regimens for adults.

• A substantial meta-analysis did not support the use of fluoroquinolones in first-line treatment regimens, and these drugs were not recommended by an expert consensus group (the Ioannina Recommendations)

except in the context of well-designed clinical trials.

• However, a more recent meta-analysis is more supportive of the efficacy of these drugs, and adequately powered prospective studies will be needed to resolve their role in standard combination therapy.

• Although triple-drug regimens are superior to double-drug regimens in meta-analyses, they are not indicated for uncomplicated brucellosis.

• A triple-drug regimen such as doxycycline and rifampin, enhanced by initial aminoglycoside, should be considered for all patients with complicated disease and for those for whom treatment adherence is likely to be a problem.

• Focal neurologic disease due to Brucella species requires prolonged treatment (i.e., for 3–6 months), usually with ceftriaxone supplementation of a standard regimen.

• Brucella endocarditis is treated with at least three drugs (an aminoglycoside, a tetracycline, and rifampin), and many experts add ceftriaxone and/or a fluoroquinolone.

• Focal presentations may require specific intervention in addition to more prolonged and tailored antibiotic therapy.

• In addition, tuberculosis must always be excluded, or—to prevent the emergence of resistance—therapy should be tailored to specifically exclude drugs active against tuberculosis (e.g., rifampin used alone) or to include a full antituberculous regimen.

• Early experience with streptomycin or tetracycline monotherapy showed that relapse was common; thus dual therapy with both agents became the norm.

• This is still the most effective combination, but alternatives may be used, with the options depending on local or national policy about the use of rifampin for the treatment of nonmycobacterial infection.

• For the several antimicrobial agents that are active in vivo, efficacy can usually be predicted by in vitro testing.

• However, numerous Brucella strains show in vitro sensitivity to a whole range of antimicrobials that are therapeutically ineffective, including assorted β-lactams.

• The use of fluoroquinolones remains controversial despite the good in vitro activity and white-cell penetration of most agents of this class.

• Low intravacuolar pH is probably a factor in the poor performance of these drugs.

• For adults with acute nonfocal brucellosis (duration <1–2 months), a 6-week course of therapy incorporating at least two antimicrobial agents is required.

• Complex or focal disease may necessitate ≥3 months of therapy.

• Adherence to the therapeutic regimen is very important, and poor adherence underlies almost all cases of apparent treatment failure; such failure is rarely due to the emergence of drug resistance, although increasing resistance to trimethoprim-sulfamethoxazole (TMP-SMX) is being reported.

• The gold standard for the treatment of brucellosis in adults is IM streptomycin (0.75–1 g daily for 14–21 days) together with doxycycline (100 mg twice daily for 6 weeks).

• In both clinical trials and observational studies, relapse follows such treatment in 5–10% of cases.

• The usual alternative regimen favored by the World Health Organization and many national guidelines consists of rifampin (600–900 mg/d) plus doxycycline (100 mg twice daily) for 6 weeks.

• This is easier for the patient and health care provider but requires sustained treatment adherence.

• The relapse/failure rate of this regimen is ~10% in trial conditions but can rise to >20% in many nontrial situations, possibly because doxycycline levels are reduced and clearance rates increased by concomitant rifampin administration.

• Patients who cannot tolerate or receive tetracyclines (children, pregnant women) can be given high-dose TMP-SMX instead (two or three standard-strength tablets twice daily for adults, depending on weight).

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• However, numerous Brucella strains show in vitro sensitivity to a whole range of antimicrobials that are therapeutically ineffective, including assorted β-lactams.

• The use of fluoroquinolones remains controversial despite the good in vitro activity and white-cell penetration of most agents of this class.

• Low intravacuolar pH is probably a factor in the poor performance of these drugs.

• For adults with acute nonfocal brucellosis (duration <1–2 months), a 6-week course of therapy incorporating at least two antimicrobial agents is required.

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• The gold standard for the treatment of brucellosis in adults is IM streptomycin (0.75–1 g daily for 14–21 days) together with doxycycline (100 mg twice daily for 6 weeks).

• In both clinical trials and observational studies, relapse follows such treatment in 5–10% of cases.

• The usual alternative regimen favored by the World Health Organization and many national guidelines consists of rifampin (600–900 mg/d) plus doxycycline (100 mg twice daily) for 6 weeks.

• This is easier for the patient and health care provider but requires sustained treatment adherence.

• The relapse/failure rate of this regimen is ~10% in trial conditions but can rise to >20% in many nontrial situations, possibly because doxycycline levels are reduced and clearance rates increased by concomitant rifampin administration.

• Patients who cannot tolerate or receive tetracyclines (children, pregnant women) can be given high-dose TMP-SMX instead (two or three standard-strength tablets twice daily for adults, depending on weight).

6. INVESTIGATIONS & DIAGNOSIS

• Because the clinical picture of brucellosis is not distinctive, the diagnosis must be based on a history of potential exposure, a presentation consistent with the disease, and supporting laboratory findings.

• Results of routine biochemical assays are usually within normal limits, although serum levels of hepatic enzymes and bilirubin may be elevated.

• Peripheral leukocyte counts are usually normal or low, with relative lymphocytosis.

• Mild anemia may be documented.

• Thrombocytopenia and disseminated intravascular coagulation with raised levels of fibrinogen degradation products can develop.

• The erythrocyte sedimentation rate and C-reactive protein levels are often normal but may be raised.

• In body fluids such as cerebrospinal fluid (CSF) or joint fluid, lymphocytosis and low glucose levels are the norm.

• Elevated CSF levels of adenosine deaminase cannot be used to distinguish tubercular meningitis, as they may also be found in brucellosis.

• Biopsied samples of tissues such as lymph node or liver may show noncaseating granulomas without acid-fast bacilli.

• The radiologic features of bony disease develop late and are much more subtle than those of tuberculosis or septic arthritis of other etiologies, with less bone and joint destruction.

• Isotope scanning is more sensitive than plain x-ray and continues to give positive results long after successful treatment.

• Isolation of brucellae from blood, CSF, bone marrow, or joint fluid or from a tissue aspirate or biopsy sample is definitive, and attempts at isolation are usually successful in 50–70% of cases.

• Blood culture using modern nonradiometric or similar signaling systems (e.g., Bactec) usually become positive within 7 days.

• Clinicians should alert the laboratory to the possibility of brucellosis if suspected, as all cultures should be handled under containment conditions appropriate for dangerous pathogens.

• Brucella species may be misidentified as Agrobacterium, Ochrobactrum, or Psychrobacter (Moraxella) phenylpyruvicus by the gallery identification strips that may still be used in the diagnostic laboratory.

• In recent years, matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) has emerged as a powerful tool for bacterial identification in well-resourced laboratories.

• Earlier implementations of MALDI-TOF often failed to identify Brucella species correctly as a genus or at species level.

• Following recent changes in taxonomy, Ochrobactrum isolates may now be reported as a subspecies of Brucella.

• This can lead to confusion and have important clinical and public health consequences, as management differs completely.

• Clinicians should confirm the meaning of any culture report suggestive of brucellosis with laboratory colleagues before making therapeutic decisions.

• The peripheral blood–based polymerase chain reaction (PCR) has enormous potential to detect bacteremia, to predict relapse, and to exclude 'chronic brucellosis.'

• This method is more sensitive and quicker than blood culture, and it does not carry the attendant biohazard risk posed by culture.

• However, it is not perfect, and false-negative results are sometimes observed in patients with positive blood cultures.

• Nucleic acid amplification techniques are now quite widely used, although no single standardized procedure has been adopted.

• Primers for the spacer region between the genes encoding the 16S and 23S ribosomal RNAs (rrs-rrl), various outer-membrane protein–encoding genes, the insertion sequence IS711, and the protein BCSP31 are sensitive and specific.

• Blood and other tissues are the most suitable samples for analysis.

• The clinical significance of prolonged PCR positivity, commonly seen in blood after successful treatment, remains controversial.

• Serologic examination often provides the only positive laboratory findings in brucellosis.

• In acute infection, IgM antibodies appear early and are followed by IgG and IgA.

• All these antibodies are active in agglutination tests, whether performed by tube, plate, or microagglutination methods.

• The majority of patients have detectable agglutinins at this stage.

• As the disease progresses, IgM levels decline, and the avidity and subclass distribution of IgG and IgA change.

• The result is reduced or undetectable agglutinin titers.

• However, the antibodies are detectable by alternative tests, including the complement fixation test, Coomb's antiglobulin test, and enzyme-linked immunosorbent assays.

• There is no clear cutoff value for a diagnostic titer.

• Rather, serology results must be interpreted in the context of exposure history and clinical presentation.

• In endemic areas or in settings of potential occupational exposure, agglutinin titers of 1:320–1:640 or higher are considered diagnostic; in nonendemic areas, a titer of ≥1:160 is considered significant.

• Repetition of tests after 2–4 weeks may demonstrate a rising titer.

• In most centers, the standard agglutination test (or a derivative such as the microagglutination test) is still the mainstay of serologic diagnosis.

• In an endemic setting, >90% of patients with acute bacteremia have standard agglutination titers of at least 1:320 at the time of clinical presentation.

• Some centers rely on the Rose Bengal test, particularly for screening, but it has been only partially validated for human diagnostic use.

• A variety of near-patient or point-of-care tests are still in developmental stages.

• Good evidence supports the use of an aminoglycoside such as gentamicin (5–6 mg/kg per day for 1–2 weeks) instead of streptomycin, and this is recommended in U.S. and U.K. guidelines.

• Shorter courses of gentamicin have been associated with high failure rates in adults.

• Early experience with fluoroquinolone monotherapy was disappointing, but it has been suggested that ofloxacin or ciprofloxacin, given together with rifampin for 6 weeks, might be an acceptable alternative to the other 6-week regimens for adults.

• A substantial meta-analysis did not support the use of fluoroquinolones in first-line treatment regimens, and these drugs were not recommended by an expert consensus group (the Ioannina Recommendations) except in the context of well-designed clinical trials.

• However, a more recent meta-analysis is more supportive of the efficacy of these drugs, and adequately powered prospective studies will be needed to resolve their role in standard combination therapy.

• Although triple-drug regimens are superior to double-drug regimens in meta-analyses, they are not indicated for uncomplicated brucellosis.

• A triple-drug regimen such as doxycycline and rifampin, enhanced by initial aminoglycoside, should be considered for all patients with complicated disease and for those for whom treatment adherence is likely to be a problem.

• Focal neurologic disease due to Brucella species requires prolonged treatment (i.e., for 3–6 months), usually with ceftriaxone supplementation of a standard regimen.

• Brucella endocarditis is treated with at least three drugs (an aminoglycoside, a tetracycline, and rifampin), and many experts add ceftriaxone and/or a fluoroquinolone.

• Focal presentations may require specific intervention in addition to more prolonged and tailored antibiotic therapy.

• In addition, tuberculosis must always be excluded, or—to prevent the emergence of resistance—therapy should be tailored to specifically exclude drugs active against tuberculosis (e.g., rifampin used alone) or to include a full antituberculous regimen.

• Early experience with streptomycin or tetracycline monotherapy showed that relapse was common; thus dual therapy with both agents became the norm.

• This is still the most effective combination, but alternatives may be used, with the options depending on local or national policy about the use of rifampin for the treatment of nonmycobacterial infection.

• For the several antimicrobial agents that are active in vivo, efficacy can usually be predicted by in vitro testing.

• However, numerous Brucella strains show in vitro sensitivity to a whole range of antimicrobials that are therapeutically ineffective, including assorted β-lactams.

• The use of fluoroquinolones remains controversial despite the good in vitro activity and white-cell penetration of most agents of this class.

• Low intravacuolar pH is probably a factor in the poor performance of these drugs.

• For adults with acute nonfocal brucellosis (duration <1–2 months), a 6-week course of therapy incorporating at least two antimicrobial agents is required.

• Complex or focal disease may necessitate ≥3 months of therapy.

• Adherence to the therapeutic regimen is very important, and poor adherence underlies almost all cases of apparent treatment failure; such failure is rarely due to the emergence of drug resistance, although increasing resistance to trimethoprim-sulfamethoxazole (TMP-SMX) is being reported.

• The gold standard for the treatment of brucellosis in adults is IM streptomycin (0.75–1 g daily for 14–21 days) together with doxycycline (100 mg twice daily for 6 weeks).

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• Patients who cannot tolerate or receive tetracyclines (children, pregnant women) can be given high-dose TMP-SMX instead (two or three standard-strength tablets twice daily for adults, depending on weight).

7. MANAGEMENT & TREATMENT

• The broad aims of antimicrobial therapy are to treat and relieve the symptoms of current infection and to prevent relapse.

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• Early experience with streptomycin or tetracycline monotherapy showed that relapse was common; thus dual therapy with both agents became the norm.

• This is still the most effective combination, but alternatives may be used, with the options depending on local or national policy about the use of rifampin for the treatment of nonmycobacterial infection.

• For the several antimicrobial agents that are active in vivo, efficacy can usually be predicted by in vitro testing.

• However, numerous Brucella strains show in vitro sensitivity to a whole range of antimicrobials that are therapeutically ineffective, including assorted β-lactams.

• The use of fluoroquinolones remains controversial despite the good in vitro activity and white-cell penetration of most agents of this class.

• Low intravacuolar pH is probably a factor in the poor performance of these drugs.

• For adults with acute nonfocal brucellosis (duration <1–2 months), a 6-week course of therapy incorporating at least two antimicrobial agents is required.

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Table 2 Table 174-2: Antimicrobial Regimens for Brucellosis

Regimen	Drugs	Dose	Duration	Indication
Gold Standard	Streptomycin + Doxycycline	Streptomycin 0.75–1 g IM daily; Doxycycline 100 mg PO BID	14–21 days (Streptomycin); 6 weeks (Doxycycline)	Adults with acute nonfocal brucellosis
Alternative WHO Regimen	Rifampin + Doxycycline	Rifampin 600–900 mg/d; Doxycycline 100 mg PO BID	6 weeks	Adults with acute nonfocal brucellosis
Alternative for Tetracycline Intolerance	TMP-SMX	Two or three stan dard-strength tablets PO BID	6 weeks	Children, pregnant women
Focal Neurologic Disease	Standard Regimen + Ceftriaxone	Standard Regimen; Ceftriaxone 2 g IV daily	3–6 months	Focal neurologic disease
Brucella Endocarditis	Aminoglycoside + Tetracycline + Rifampin + Ceftria xone/Fluoroquino lone	Aminoglycoside; Tetracycline; Rifampin; Ceftriax one/Fluoroquinol one	Prolonged (≥3 months)	Endocarditis

8. PROGNOSIS & COMPLICATIONS

• In both clinical trials and observational studies, relapse follows standard treatment in 5–10% of cases.

• The relapse/failure rate of the rifampin/doxycycline regimen is ~10% in trial conditions but can rise to >20% in many nontrial situations, possibly because doxycycline levels are reduced and clearance rates increased by concomitant rifampin administration.

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9. SPECIAL CONSIDERATIONS

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• There is an increased incidence of fetal loss among infected pregnant women, although teratogenicity has not been described and the tendency toward abortion is much less pronounced in humans than in animals.

• Although brucellosis is a chronic intracellular infection, there is no evidence for increased prevalence or severity among individuals with HIV infection or with immunodeficiency or immunosuppression of other etiologies.

• Specific antigen-based tests used in veterinary practice to detect B. canis and B. ovis produce inconsistent results in human diagnosis and are not validated for this purpose.

• Clinicians should consult with the laboratory about the test selection if B. canis infection is suspected.

• Similarly, live B. abortus vaccine strain RB51 does not elicit antibody responses in serologic tests that use smooth antigens, and this fact must be taken into account if serologic tests are employed in attempts to identify or follow the course of infections in persons accidentally exposed to the vaccine.

10. KEY PEARLS & CLINICAL TRAPS

• Brucellosis is a bacterial zoonosis transmitted directly or indirectly to humans from infected animals, predominantly domesticated ruminants and swine.

• The disease is known colloquially as undulant fever because of its remittent character.

• B. melitensis is the most common cause of symptomatic disease in humans, acquired from sheep, goats, and camels.

• Fever of brucellosis shows an undulating pattern that persists for weeks before the commencement of an afebrile period that may be followed by relapse.

• Musculoskeletal symptoms are present in about one-half of all patients; osteomyelitis more commonly involves the lumbar and low thoracic vertebrae.

• Diagnosis requires isolation of brucellae from blood, CSF, bone marrow, or joint fluid (definitive) or serologic evidence (IgM followed by IgG/IgA).

• Standard treatment for adults is dual therapy: IM streptomycin (0.75–1 g daily for 14–21 days) plus doxycycline (100 mg twice daily for 6 weeks).

• Alternative regimen: Rifampin (600–900 mg/d) plus doxycycline (100 mg twice daily) for 6 weeks.

• Relapse follows standard treatment in 5–10% of cases; adherence is critical as poor adherence underlies almost all cases of apparent treatment failure.

• Tuberculosis must always be excluded in patients with vertebral osteomyelitis as several antimicrobial agents used to treat brucellosis are also used to treat tuberculosis.