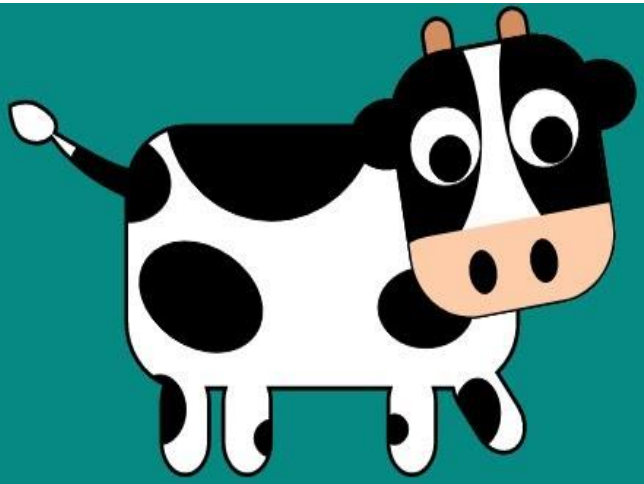
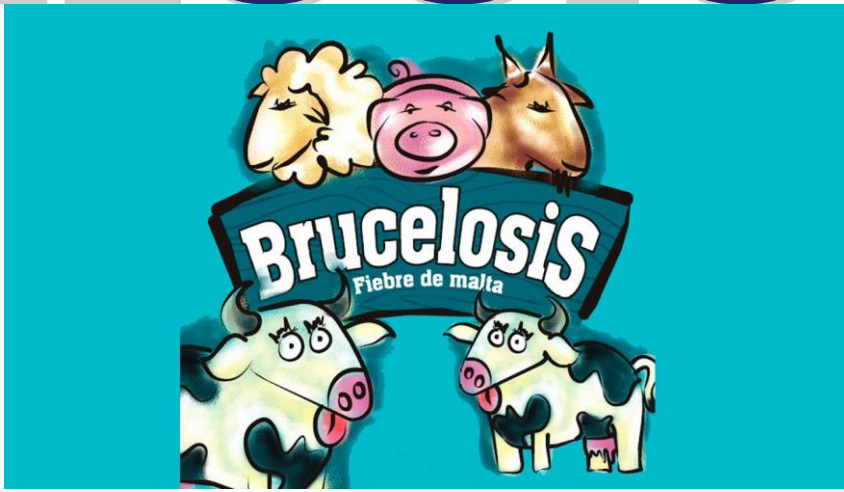


Brucellosis

BRUCELLOSIS



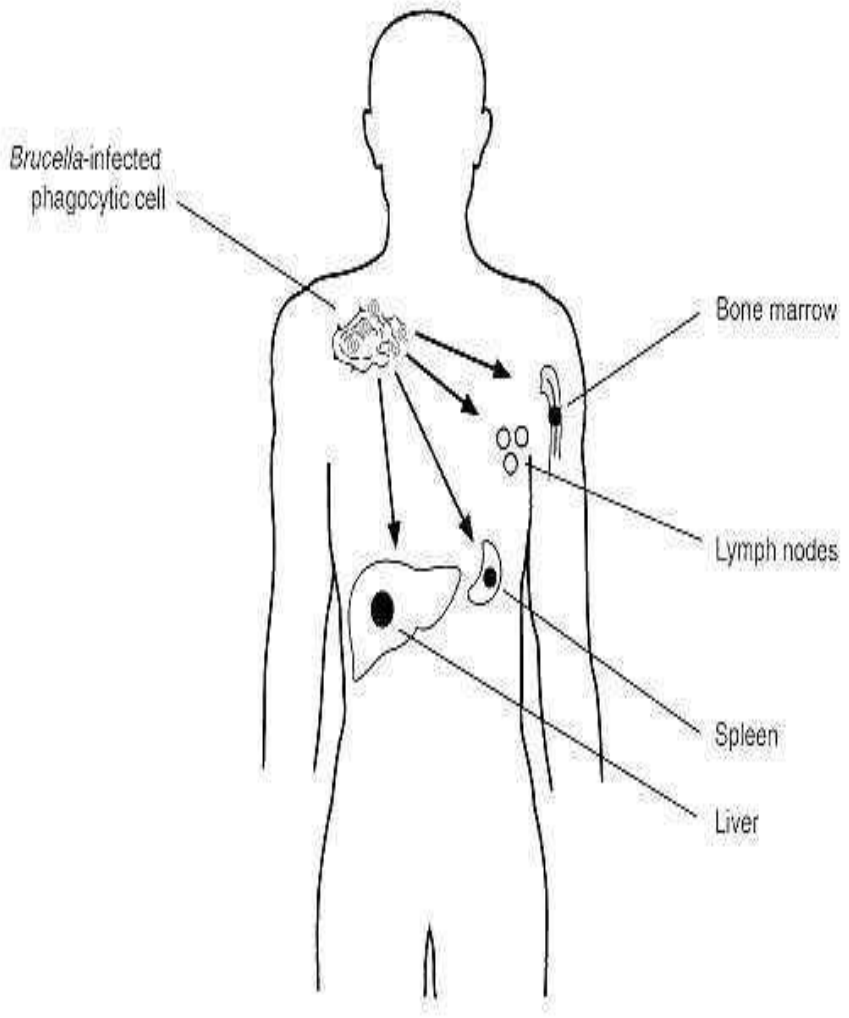
Brucellosis, also called

- **Bangs disease,**
- **Crimean fever,**
- **Gibraltar fever,**
- **Malta fever,**
- **Maltese fever,**
- **Mediterranean fever,**
- **rock fever, or**
- **undulant fever,**

is a highly contagious zoonosis caused by ingestion of unsterilized milk or meat from infected animals or close contact with their secretions

Brucellosis is a zoonotic infectious-allergic disease prone to chronicity, characterized by:

LONG FEVER
INJURIES OF THE SUPPORT-MOTOR, NERVOUS, CARDIOVASCULAR, UROGENITAL AND OTHER SYSTEMS OF THE BODY



HISTORICAL INFORMATION:

In his book Epidemics, Hippocrates first described a condition of recurring fever and death with a duration of 4 months in 450 B.C.

Brucellosis **first came to the attention of British medical officers in the 1850s in Malta during the Crimean War, and was referred to as** ***Malta Fever.***

Jeffery Allen Marston (1831–1911) described his own case of the disease in 1861. The causal relationship between organism and disease was first established in 1887 by David Bruce. The agent that Bruce identified was classed as a coccus.

In 1897, Danish veterinarian Bernhard Bang isolated a bacillus as the agent of heightened spontaneous abortion in cows, and the name "Bang's disease" was assigned to this condition. At the time, no one knew that this bacillus had anything to do with the causative agent in Malta fever. Maltese scientist and archaeologist Themistocles Zammit identified unpasteurized goat milk as the major etiologic factor of undulant fever in June 1905.

HISTORICAL INFORMATION:

Undulant fever did not enter into the United States until 1905 through the shipping of 65 Maltese goats on the *S.S. Joshua Nicholson.*

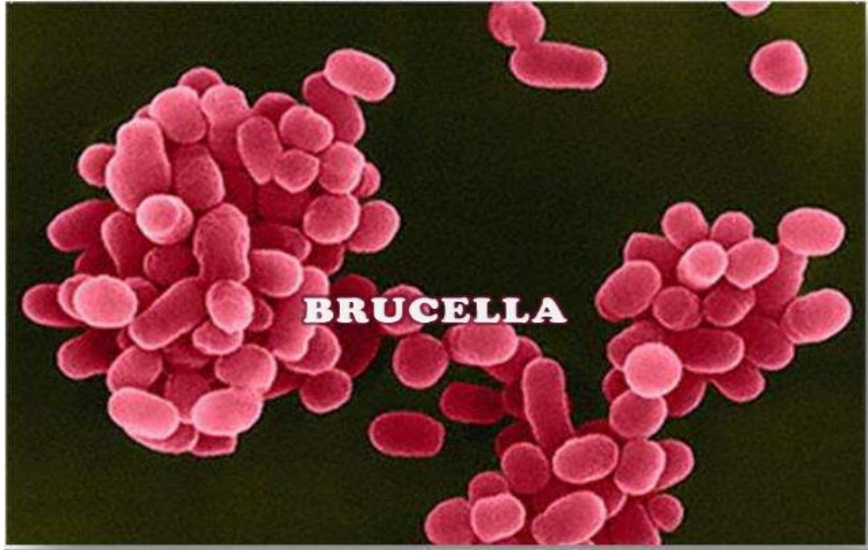
In 1920, bacteria are united into one genus, named after D. Bruce Brucella, and the disease they cause is called Brucellosis

***B. suis* was isolated in 1914 by Traum in the U.S. from aborting swine in Indiana.**

***B. ovis* was isolated in 1953 from sheep with ram epididymitis in New Zealand and Australia.**

***B. canis* was discovered in 1966 from dogs, caribou, and reindeer.**

Etiology

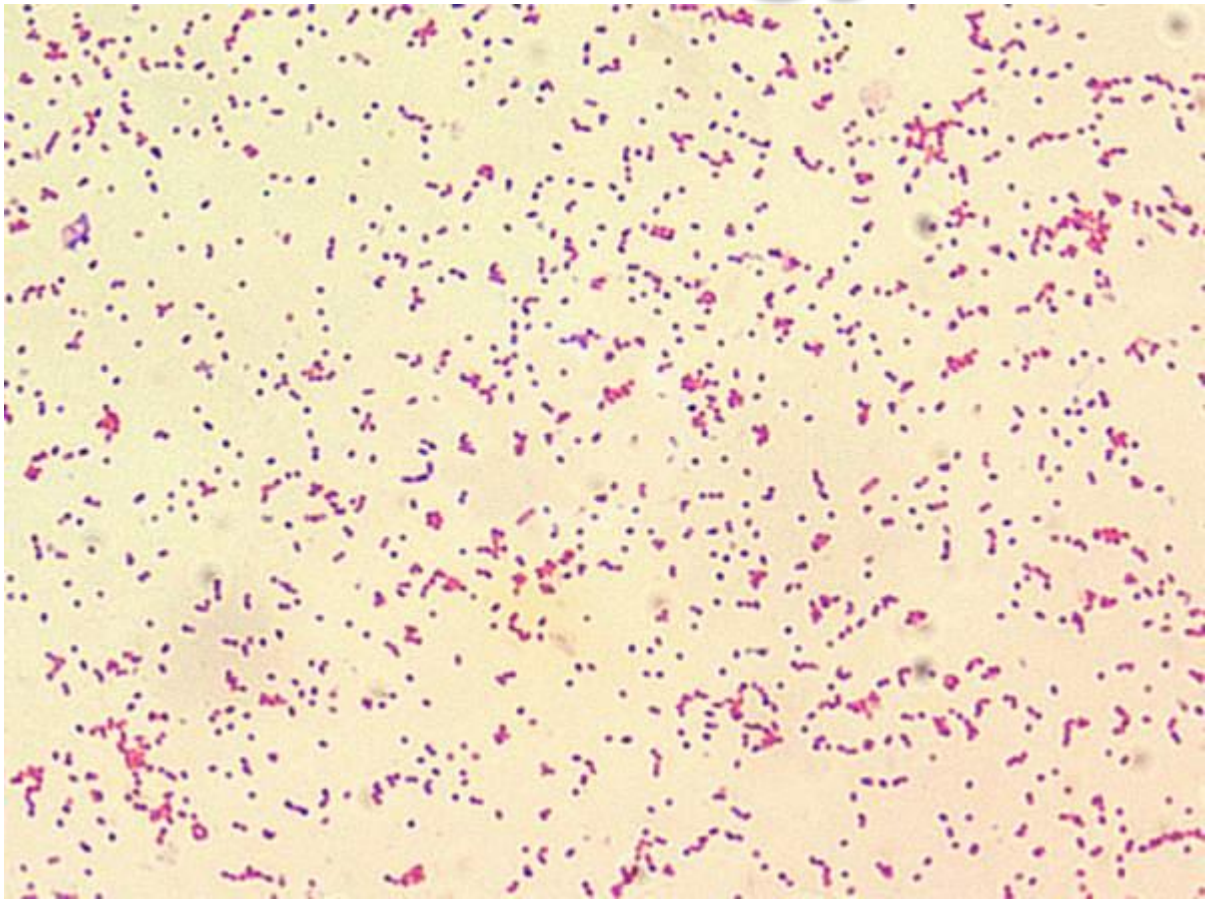


Human brucellosis is caused by strains of Brucella,

- **aerobic,**
- **small,**
- **gram-negative,**
- **unencapsulated,**
- **nonsporulating rods or coccobacilli.**

In vivo, brucellae behave as facultative intracellular parasites

Etiology



Brucella can be oval, spherical, and rod-shaped.
In addition to shapes, they come in different sizes:
Coccal - 0.3-0.6 microns and rod-shaped 0.6-2.5 microns.

Each Brucella species is associated most often with certain mammalian hosts. The organism is able to withstand drying, particularly when organic material is present and can survive in dust and soil. In conditions of high humidity, low temperatures, and no sunlight, these organisms can remain viable for several months in water, aborted fetuses, manure, wool, hay, equipment and clothing. Brucella spp. can survive even longer at lower temperatures, particularly when it is below freezing.

In a liquid medium at a temperature of 60^0C, they die after
30 minutes, when boiled - instantly.
In a dry environment at a temperature of 90-95^0C, brucella die within an hour.
They remain viable for up to 76 days in tap water, for up to 40 days in raw milk, for up to 60 days in cheese made from raw sheep's milk, and for the entire period of nutritional value in butter, cream, yogurt.
They can be stored in raw meat for up to three months,
in salted meat for up to 30 days,
and in wool for up to 4 months.

Brucella is sensitive to all disinfectants:
0.2-1% chlorine solution,
0.5% lysol solution,
0.2% formalin solution,
0.1% chloramine solution,
2% solution of carbolic acid and
1% creolin solution.
When processing the soil with these solutions, brucella die within 1-3 hours.
Direct sunlight kills brucella

MAIN TYPES OF BROCELLOSIS AGENTS

Br. melitensis- affects sheep and goats

Br. abortus bovis- cattle

Br. abortus suis – pigs

Br. canis – dogs

Br. ovis – sheep

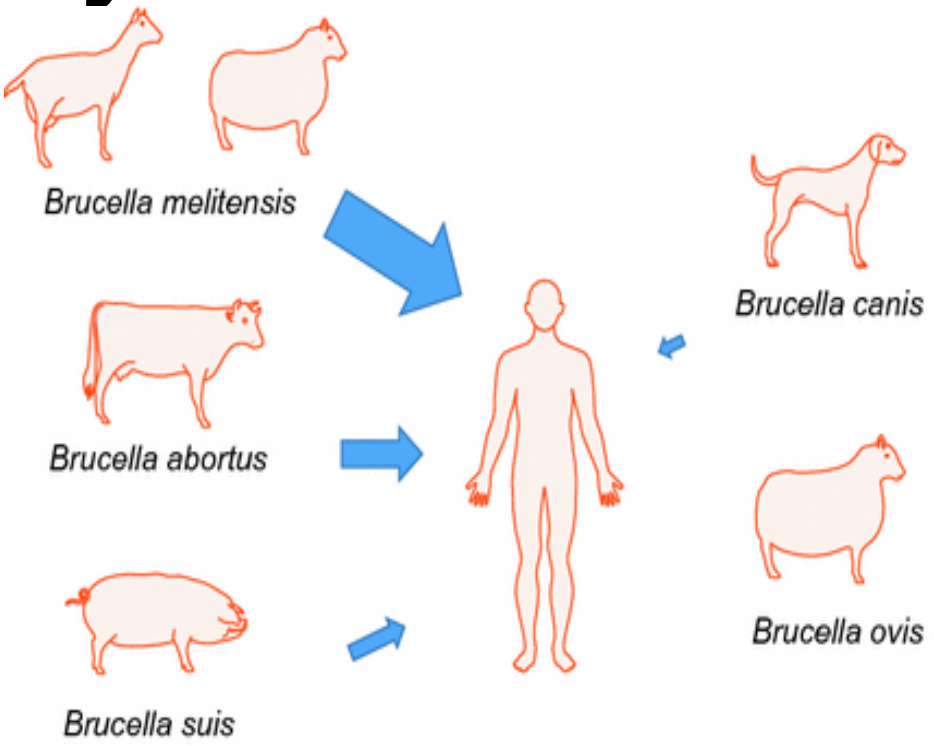
Br. neotomae - desert bush rats

The virulence and pathogenicity of brucella are determined by their species. The main role in human infection is played by

Br. melitensis,

Br. abortus,

Br. suis.



FEATURES OF THE AGENT

1. high contagiousness or infectivity of brucella;
2. their resistance to nonspecific factors of protection;
3. resistance of the microbe to the action of enzymes of the lysosomal apparatus of leukocytes, which makes it possible to multiply intracellularly;
4. destructively small inactivating role of anti-brucellosis antibodies.

Routes of transmission from animal to human include:

- ✓ 1) direct contact with infected animals or their secretions through cuts or abrasions in the skin or conjunctiva,
- ✓ 2) inhalation of contaminated aerosols, and
- ✓ 3) ingestion of unpasteurized dairy products.

In areas where drinking animal blood or ingesting raw liver are traditions, foodborne infection from other than dairy products is possible.

- ➢ **Person-to-person transmission of brucellosis is unusual; however, rare cases in which sexual and vertical transmission was suspected have been reported.**

In addition, blood transfusions and bone marrow transplants can be sources of brucellosis.

- ❖ **Brucellae are potential airborne biologic weapon**

Pathogenesis.

Exposure to brucellosis elicits both humoral and cellmediated immune responses.
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 multiply within them and establish persistent intracellular infections.
Brucellae within macrophages and monocytes become localized in organs of the reticuloendothelial system, such as the lymph nodes, liver, spleen, and bone marrow

Pathogenesis.

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.

Pathogenesis.

- **The first phase is lymphogenous drift with fixation of brucella in the lymph nodes, which turn into primary foci of infection. This phase corresponds to the incubation period of the disease and lasts from 3 to 10 days.**
- **The second phase, the phase of hematogenous drift, or primary generalization, is characterized by the breakthrough of brucella into the blood and their spread with the blood flow throughout the body.**
  It corresponds to the clinic of acute brucellosis.
- **The third phase includes the process of formation of metastatic hematogenous foci (the so-called phase of polyfocal localization), which is clinically manifested by the development of specific (brucellosis) sepsis.**
- **The fourth phase - exofocal seeding - its development is associated with repeated generalization, often multiple, and corresponds to the chronic period of the disease, which occurs with relapses and exacerbations.**
- **The fifth phase of residual metamorphosis corresponds to the outcomes of the disease - fibrosis, cirrhosis, scar tissue changes and resorption of specific granulomas.**

The leading factor in the pathogenesis of brucellosis is allergic lesions, which are detected from the 2-3rd week, and sometimes from the very onset of the disease and persist indefinitely.

Allergy with brucellosis is characterized by delayed-type hypersensitivity.

Allergic background largely determines both the originality of the pathomorphological changes and the features of the clinical course.

The degree of allergic remodeling in patients with brucellosis can vary significantly.Inadequate nutrition, hypothermia, overheating, concomitant diseases inhibit allergic reactivity.

Clinical features

The duration of the incubation period has not been precisely established, in most patientsit is 2-3 weeks, but can increase up to 4-7 weeks, sometimes more.

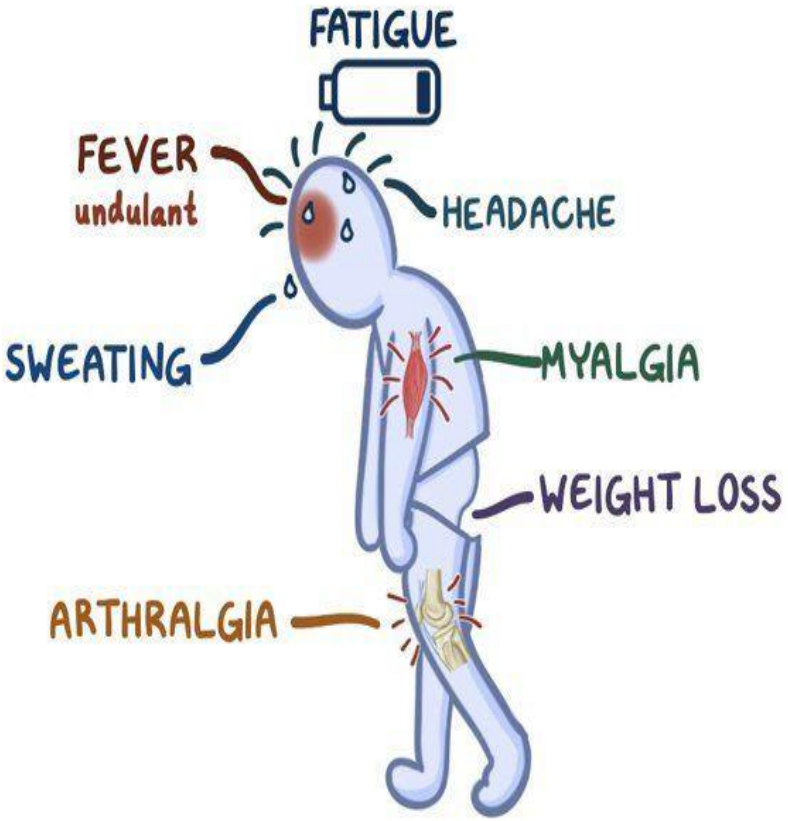
The incubation period for infection and disease with brucellosis in vaccinated people is longer than in unvaccinated people, and is 2-2.5 months.

The disease often begins gradually, and in 40% of cases - **acute.**

Asymptomatic forms of the disease have also been described.

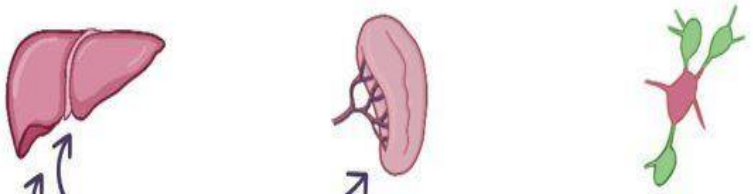
SYMPTOMS

* NON-SPECIFIC & INFLUENZA-LIKE



* PHYSICAL EXAM

HEPATOMEGALY SPLENOMEGALY LYMPHADENOPATHY



- B. abortus
  - GRANULOMAS
- B. suis
  - LIVER ABSCESSES

~ UNTREATED → COMPLICATIONS

- OSTEOMYELITIS
- MENINGITIS
- ENDOCARDITIS

Acute onset of the disease

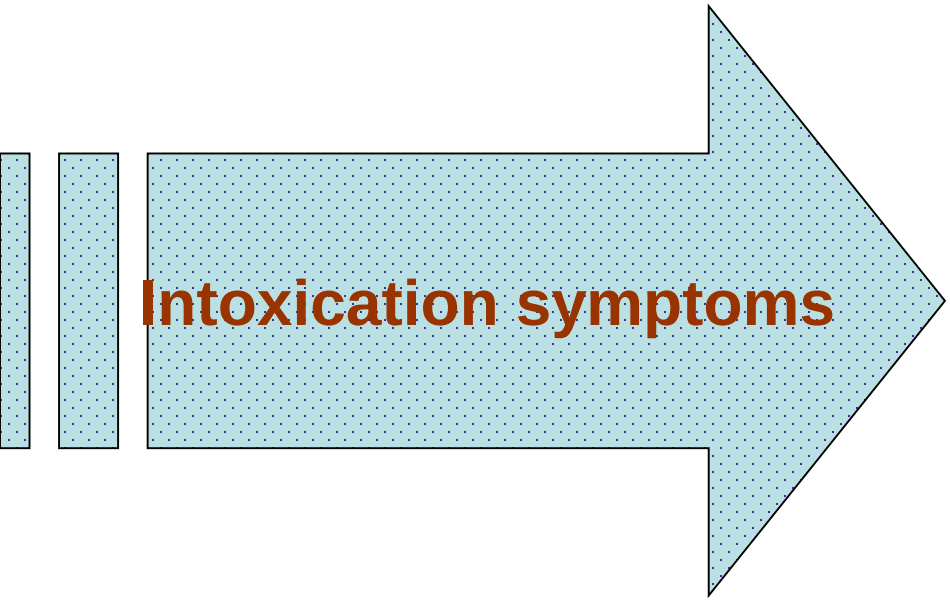
- **temperature increase**
- **chills**
- **profuse sweating**

Subacute onset of the disease

- **low-grade fever in the evenings**
- **chilling**
- **growing weakness**

COMPLAINTS in the prodromal period:

malaise,
feeling overwhelmed
depression of mood,
sleep disorders,
headache,
irritability,
back pain,
pain in different muscle groups, joints,
chills.
During this period, subfebrile condition, enlargement of the liver, spleen and lymph nodes are revealed.



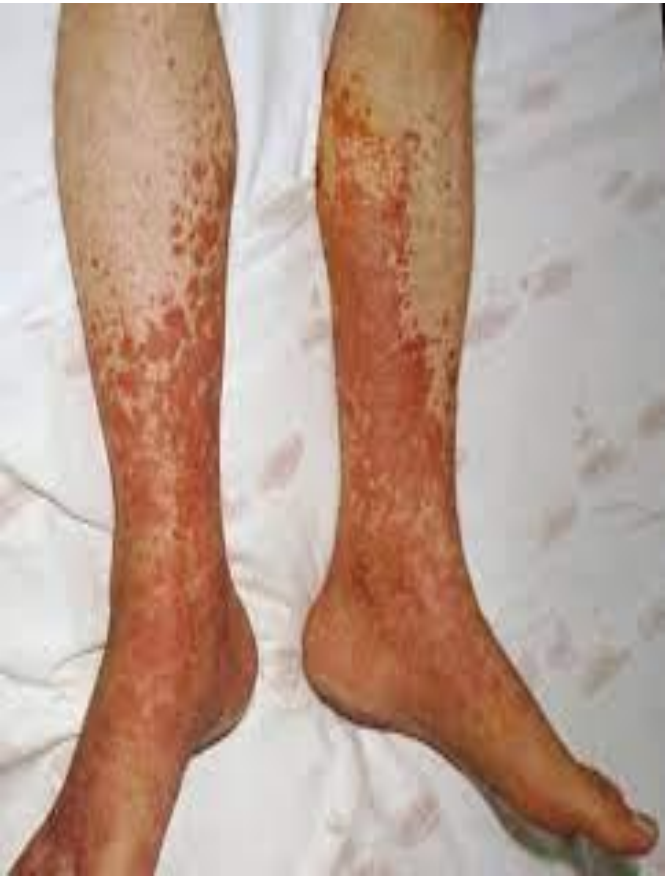
fever,
chills

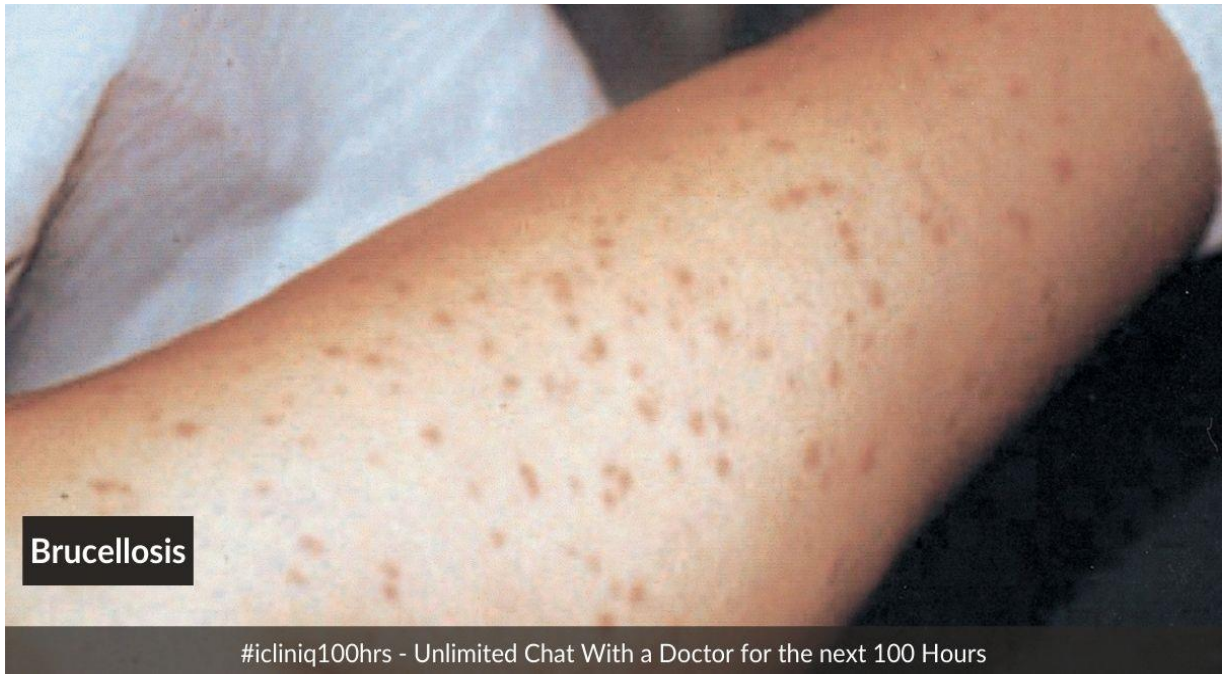
increased sweating

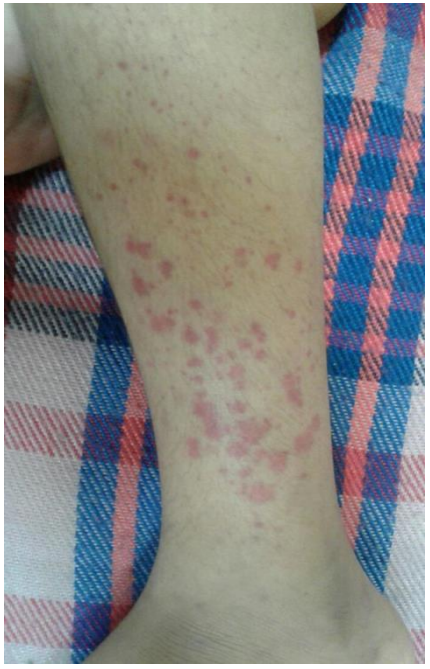
weakness, pain in muscles and joints,

enlargement of the liver, spleen, lymph nodes (neck, axillary inguinal, femoral).

Sometimes there are skin rashes such as urticaria, erythematous, roseola-like and other elements, the appearance of areas of depigmentation, scleroderma.




Brucellosis
#icliniq100hrs - Unlimited Chat With a Doctor for the next 100 Hours



Fever is the most persistent symptom.
The following types of temperature curves are distinguished:

undulating,

intermittent,

remitting,

subfebrile

Feverish waves are accompanied by profuse sweating, a characteristic symptom that manifests itself at normal body temperature.
The intervals between high temperature waves are 3-5 days, weeks, often months.

Palpation of the trunk reveals

painful lumps

fibrositis and

cellulites (nodules or strands).

Complaints about myalgia, arthralgia.

The pains are of a transient, "volatile" nature.

Not only large joints are affected –

shoulder,

elbow,

hip,

knee and ankle,

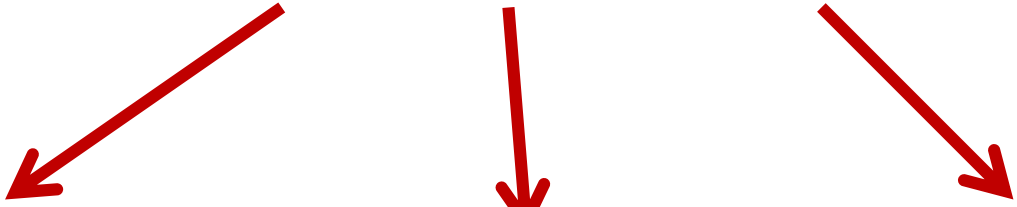
but also small ones.

Brucellosis polyarthritis lasts for a long time, for months.

Subsequently, ankylosis, contractures develop, muscles atrophy.

Frequent bursitis, tendovaginitis.

Course of brucellosis



Acute
up to
3 months

Subacute
more than
3 months

Chronic
more than
6 months

Complications and Brucella

- Endocarditis — 1 percent.Most cases of endocarditis are left-sided, and about two-thirds occur on previously damaged valves.
- Hepatic abscess — 1 percent
- Other less common complications include pneumonitis, pleural effusion, empyema,, or abscess involving the spleen, thyroid, or epidural space, uveitis.
- A few cases of Brucella infection involving prosthetic devices such as pacemaker wires and prosthetic joints have been reported

Chronic Brucellosis

- Patients with undiagnosed and untreated brucellosis can be symptomatic for months. In addition, previously treated patients may present with relapsed infection.

Chronic Brucellosis

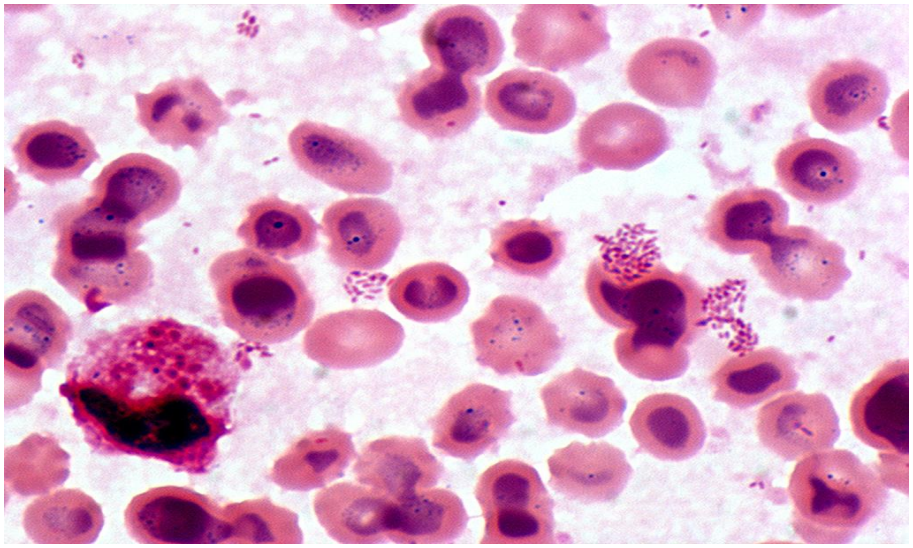
- The presence of granulomatous hepatitis, hepatic micro abscesses, bone marrow granulomas, and/or hemophagocytosis should prompt further diagnostic evaluation for brucellosis.
- Relapse — About 10 percent of patients relapse after therapy

Diagnosis

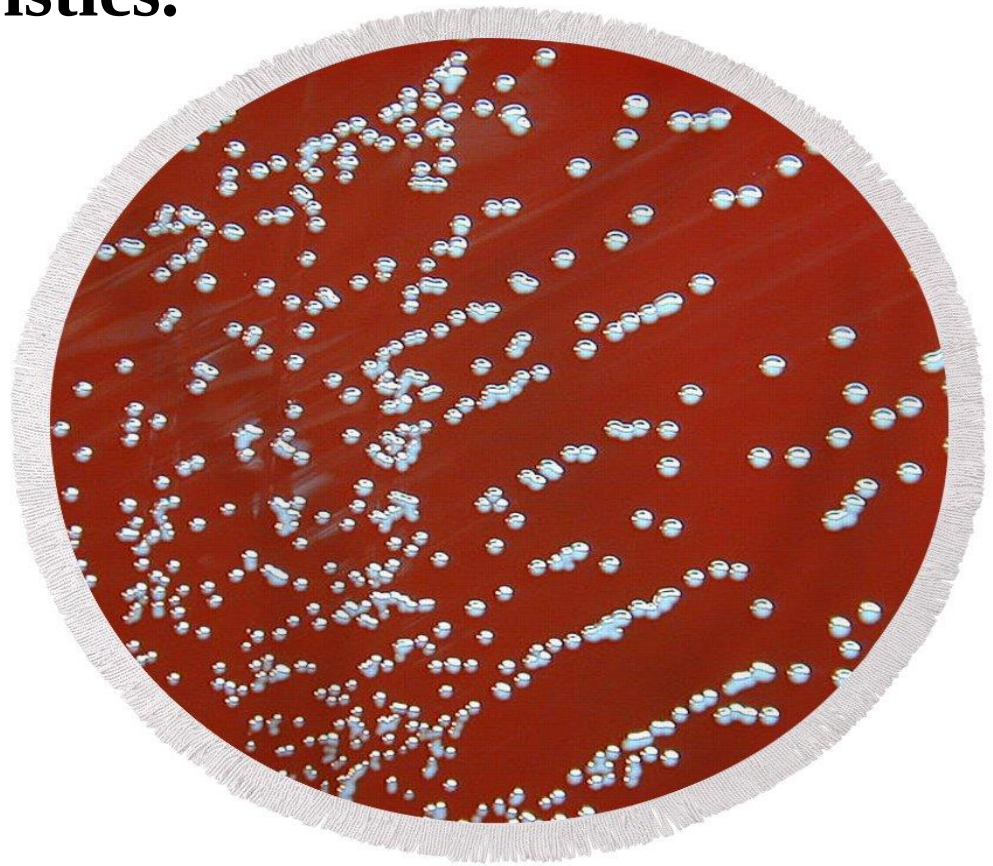
Brucellosis should come to the mind of a physician when he or she sees a patient from an endemic area with a febrile illness of acute or insidious onset, especially if there are manifestations of osteoarticular involvement. Definitive diagnosis of brucellosis is made with the culture of the pathogen from blood, bone marrow, urine or other tissue specimens. Cultures should be kept for at least 4 weeks when brucellosis is a possibility

DIAGNOSIS

Microscopic examination of stained smears can be useful for a presumptive diagnosis, particularly if the direct examination is supported by other tests.
They are not truly acid-fast; however, they are resistant to decolorization by weak acids, and stain red against a blue background with the Stamp's modification of the Ziehl-Neelsen method.



Most Brucella species form colonies within a few days. Brucella isolates can be identified to the species and biovar level by phage typing and cultural, biochemical, and serological characteristics.



In the absence of bacteriologic confirmation confirmation, a presumptive diagnosis can be made by serologic tests.
Raised (1:160) or a rising antibody titre in symptomatic patients suggests the diagnosis of active brucella.
Demonstration of antibodies with various tests including standard tube agglutination test, mercaptoethanol test, classic Huddleson, Wright, and/or Bengal/Rose reactions.
False-negative serologic tests for brucellosis may be due to the prozone phenomenon. False-positive results may be obtained due to cross-reactions (Yersinia enterocolitica, Vibrio cholera, Francisella tularensis).
Attention also should be paid to the fact that IgG antibodies against Brucella species may be found in all forms (acute, recurrent, or chronic) of the infection. An ELISA to detect antibodies against Brucella is more reliable for the diagnosis.

PCR techniques can also be used for diagnosis.
PCR has begun to gain popularity in the diagnosis of brucellosis due to the high specificity and sensitivity of the test, as well as the quick turn around of results.
Chronic brucellosis can be extremely difficult to diagnose if the serologic results are equivocal and the organism cannot be cultured.

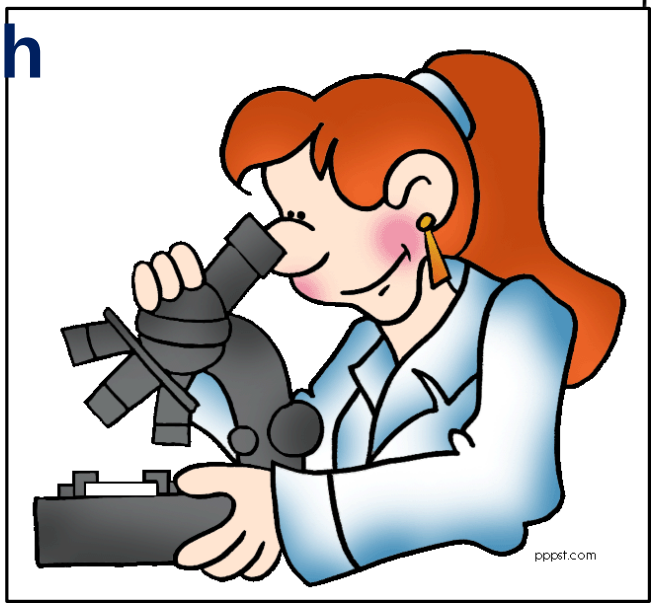
An abdominal ultrasound or CT/MRI of the abdomen will detect enlarge lymph nodes and organomegaly.
Radiological alterations in infected vertebrae – the Pedro Pons sign (preferential erosion of antero-superior corner of lumbar vertebrae) and marked osteophytosis are suspicious of brucellic spondylitis.
A liver biopsy may disclose granulomatous hepatitis

In the blood of patients with brucellosis,be determined:

- **moderate anemia,**
- **leukopenia,**
- **lymphocytosis and monocytosis,**
- **eosinopenia and neutropenia with a moderate shift of the blood count to the left.**

ESR is often not changed, but with complications it increases to 30 mm / hour and higher.

Thrombocytopenia is typical.



Serological Tests

- Most serological studies for diagnosis of Brucellosis are based on antibody detection

These include:

- Serum agglutination (standard tube agglutination)
- ELISA Rose Bengal agglutination
- Complement fixation
- Indirect Coombs
- Immunecapture-agglutination (Brucellacapt

- Serology
  - Main laboratory method of diagnosis
  - Serum agglutination test - most widely used
    - measures agglutination for IgG, IgM, IgA
    - 2ME - break sulf-hydrile bonds in IgM polymer - no agglutination
    - which level is diagnostic ??

      1 : 160 - non endemic area

      1 : 320 - endemic area
    - SAT - false negative
      - Prozone
      - Blocking antibodies
  - Other tests: coombs, ELISA, CFT, FTA

Serum agglutination

- It is generally agreed that a titer of >1:160 in the presence of a compatible illness supports the diagnosis of brucellosis.
- Demonstration of a fourfold or greater increase or decrease in agglutinating antibodies over 4 to 12 weeks provides even stronger evidence for the diagnosis.

ELISA•

ELISA is probably the second most common serologic method.

- **The sensitivity of the ELISA was 100 percent when compared with blood culture but only 44 percent compared with serologic tests other than ELISA**
- **The Specificity was >99 percent**

PCR an Emerging Tool

- Polymerase chain reaction (PCR) shows promise for rapid diagnosis of Brucella spp in human blood specimens
- Positive PCR at the completion of treatment is not predictive of subsequent relapse
- PCR testing for fluid and tissue samples other than blood has also been described

Imaging•

Patients with spine symptoms
MRI examination to rule out spinal cord compromise.
• Plain radiographs, radionuclide bone scintigraphy, CT scanning, and joint sonography

Differential diagnosis is carried out with:

typhoid-paratyphoid diseases,
sepsis,
septic endocarditis,
lymphogranulomatosis,
leishmaniasis,
psittacosis,
tularemia
Q fever,
hemorrhagic fevers,
infectious mononucleosis,
toxoplasmosis,
tuberculosis,
rheumatism
meningitis of various etiologies,
malaria and other diseases of infectious and non-infectious nature.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Treatment.

Although multiple antibiotics display in vitro activity against *Brucella* species, clinical response has been demonstrated with only a limited number of agents. Drugs that display clinical activity with low relapse rates include the following:

- **Doxycycline**
- **Gentamicin**
- **Streptomycin**
- **Rifampin**
- **Trimethoprim-sulfamethoxazole (TMP-SMZ)**

Other agents with potential roles include the following:

- ✓ **Chloramphenicol**
- ✓ **Imipenem-cilastatin**
- ✓ **Tigecycline**
- ✓ **Fluoroquinolones**

In those cases where relapse has occurred, the development of antibiotic resistance does not appear to be the underlying cause.

Optimal antibiotic therapy for brucellosis has been studied to some degree; however, recommendations may differ.

For simple infections,
doxycycline (100 mg PO twice daily for 6 weeks) may be the most appropriate monotherapy;
however, relapse rates with such monotherapy approach 40% and as a result,
rifampin (600-900 mg/day) is usually added.
Fluoroquinolones (eg, ciprofloxacin) have been used as monotherapy as well but also carry a high relapse rate;
adding these agents to doxycycline offers no specific advantages over other combination regimens but may be preferred in areas where resistance to rifampin is high.
At least one study has demonstrated equivalence between 2-drug and 3-drug regimens in treating uncomplicated brucella infection, although it was a small retrospective cohort study.

For acute brucellosis in adults and children older than 8 years, the World Health Organization (WHO) guidelines recommend the following:

Doxycycline 100 mg PO twice daily plus rifampin 600-900 mg/day PO – Both drugs are to be given for 6 weeks; this regimen is more convenient but probably increases the risk of relapse

Doxycycline 100 mg PO twice daily for 6 weeks and streptomycin 1 g/day IM for 2-3 weeks – This regimen is believed to be more effective, mainly in preventing relapse;

gentamicin can be used as a substitute for streptomycin and has shown equal efficacy

Ciprofloxacin-based regimens have shown efficacy equal to that of doxycycline-based regimens

Prevention.

The prevention of human brucellosis depends on the elimination of the disease in animals.
Vaccination of cattle and identification of sick animals are the mainstay of such an approach.
Also human should avoid contact with infected animals.
Good standards of hygiene in the production of raw milk and its products, or pasteurization of all milk, will prevent brucellosis acquired from ingestion of milk.
No safe vaccine is available for professions at risk.

Prevention and control

Prevention of brucellosis is based on surveillance and the prevention of risk factors. The most effective prevention strategy is the elimination of infection in animals. Vaccination of cattle, goats and sheep is recommended in enzootic areas with high prevalence rates. Serological or other testing and culling can also be effective in areas with low prevalence. In countries where eradication in animals through vaccination or elimination of infected animals is not feasible, prevention of human infection is primarily based on raising awareness, food-safety measures, occupational hygiene and laboratory safety.

Pasteurization of milk for direct consumption and for creating derivatives such as cheese is an important step to preventing transmission from animals to humans. Education campaigns about avoiding unpasteurized milk products can be effective, as well as policies on its sale.

In agricultural work and meat-processing, protective barriers and correct handling and disposal of afterbirths, animal carcasses and internal organs is an important prevention strategy.