## Summary


- Gram-negative coccobacilli (*Brucella* spp.) with a tropism for the reticulo-endothelial system
- Zoonosis, through infected dairy products and animal contact (goats, sheep, cattle)
- Chronic granulomatous infectious disease
- Chronic fever and wide range of symptoms
- Diagnosis by serology and culture
- Treatment by rifampicin, doxycycline, aminoglycoside for at least 6 weeks


# General

Brucellosis is a **chronic granulomatous infectious disease** caused by small, facultative intracellular, Gram-negative coccobacilli. *Brucella melitensis* (goats, sheep, camels, chamois, ibex), *B. abortus* (cattle, buffalo, bison, zebra, impala, waterbuck, hippopotamus), *B. suis* (pigs) and *B. canis* (dogs) are the causative agents of this **zoonosis**, in descending order of importance. There are several biovars. For example; pigs are infected by *B. suis* biovars 1, 2 and 3, European wild rabbits by biovar 2. Biovar 4 is found in caribou and reindeer. Humans are accidentally infected and play no role in the survival of these organisms in nature. Animals are the only source of infection and **there are no known vectors**. *B. ovis* (sheep) and *B. neotomae* (desert rats) are not known to cause disease in man. Other species (*Brucella pinnipediae*, *B. maris*, *B. cetaceae*) infect marine mammals, such as seals, dolphins, porpoises, minke whales, etc. There have been rare cases of human infection with some of these marine strains.

### Historical

The condition was known as **Malta fever** as a result of a persistent epidemic at the end of the 19th-century in British soldiers on the island. The disease was studied intensively by David Bruce of *Trypanosoma* fame. He studied 91 cases and found two features: **splenomegaly and undulating fever**. In 1887 he isolated the organism from splenic tissue of dead soldiers and named it "*Micrococcus melitensis*". This organism was capable of infecting healthy chimpanzees. In 1897, Wright described a serum agglutination test for

the diagnosis of this disease. In 1904 the Brucella Committee was established, as a result of which it was possible to undertake large-scale epidemiological research. In 1905, Themistocles Zammit discovered that the blood of many, apparently healthy goats agglutinated *Brucella* organisms. Bruce identified the organism in goat blood and milk and as such discovered the reservoir of the organism. Up to 10% of animals had *Brucella* in their milk. Monkeys which received infected goat's milk to drink developed the disease.

After some hesitation, specific measures were implemented. **Pasteurization** was introduced as a legal requirement in Malta in 1938. The transport of goats was restricted, infected goats had to be killed and milk had to be boiled or pasteurised, including the milk used for the preparation of cheese. The ban on using fresh milk resulted in a dramatic fall in the number of cases in the British Army, but the reduction of cases in the island population was much less spectacular because the indigenous population did not accept the idea of boiling milk. The last documented outbreak of brucellosis on the island occurred in 1995.

In 1895-1897 the Danish doctor/veterinarian Bernhard Bang (1848-1932) identified *Brucella abortus* in cows, the pathogen of infectious abortion in these animals. A previous name for brucellosis was "Bang's disease". In 1921, a substantial problem of brucellosis was seen in Rhodesia in people who had had no contact with goats. However, there was often infectious abortions seen in livestock. Apparently *Brucella abortus* could also infect humans. So, there appeared to be more than one organism that caused undulating fever.

In 1914 Traum identified *B. suis* in pigs. Carmichael and Bruner discovered *B. canis* in 1968 in dogs. *B. pinnipediae* and *B. cetaceae* were only discovered in 1994 by Ewalt and Ross.

## Transmission

Transmission of brucellosis occurs mainly through **eating or drinking contaminated unpasteurized animal-milk products** such as raw milk, soft cheese (cottage cheese), butter and ice cream. Hard cheese, yogurt and sour milk are less dangerous because of the fermentation which has taken place. Eating undercooked infected animal products (spleen, liver) are occasionally responsible for infection. A low pH in the stomach is partially protective (importance of antacids, ranitidine, omeprazole, etc.). **Direct contact** (inoculation through

skin wound, conjunctiva) with secretions and excretions of infected animals (e.g. placenta, aborted foetuses) can also cause disease. Pregnant infected animals usually develop placentitis. Inhalation of **infected aerosolized particles** can occur (personnel working in microbiology labs!). This has been studied in the context of biowarfare. Brucellosis is an **occupational disease** in farmers, livestock producers, herdsmen, butchers, veterinarians, shepherds, abattoir workers, dairy-industry professionals and lab workers. There is almost no human-to-human transmission although in rare cases sexual transmission has been suspected. The organism has been isolated from human breast milk and from sperm. In animals the disease is commonly transmitted sexually.

After entering the human body and being taken up by local tissue lymphocytes the bacteria migrate via the regional lymph nodes into the general circulation. They display a tropism for the **reticuloendothelial system**. *Brucella* bacteria **replicate intracellularly** without affecting cellular viability. They switch off cellular apoptosis rendering the host cell immortal.

## Clinical aspects

The clinical features are **very varied and often non-specific**. The incubation period is usually **two to four weeks** but can be as short as one week or as long as several months. The temperature is often only raised in the evening. General malaise, various symptoms such as sweating, headache, muscle pain, abdominal pain, tiredness, depression, etc., may occur. Sometimes the clinical presentation is that of **fever of unknown origin**. Chronic febrile arthritis should point to brucellosis (and tuberculosis). Some patients try to explain their joint or bone lesions as being due to local trauma, whereas the real cause is a *Brucella* infection. Osteomyelitis of the vertebrae can resemble tuberculosis (Pott's disease). Sacroiliitis, arthritis of the sternoclavicular joints and involvement of the large joints (hip, knee) is not unusual. The fever can occur in waves ("**undulant fever**"). Uveitis, both posterior and anterior, can be found. Brucellosis can mimic various other diseases and is one of the great "imitators" in the world of infectious diseases. Rarely peripheral neuritis, orchitis, meningitis, cholecystitis, aortitis or endocarditis can be seen as a consequence. Neurobrucellosis is a feared complication. The risk of abortion in women is thought to be much lower than in animals.

On physical examination, **splenomegaly is observed in 25%** sometimes with enlarged lymph nodes in the groin and neck. Skin abnormalities (papules, erythema nodosum, fine

erythematous rash) can occur, but is found only in a minority of cases (5%). There can be signs of arthritis in general large joints (hip, knee, or the sarcoiliac joints). The clinical findings in neurobrucellosis depend on the localisation of the lesions. A slitlamp eye examination and ophthalmoscopy should always be included in any physical examination.

Physical examination usually does not provide pathognomonic findings. Above all the **possibility of brucellosis should be considered** in the differential diagnosis. With the cluster of orchitis arthralgia-eye problems, consideration should first be given to Reiter's syndrome rather than to brucellosis, although brucellosis can lead to such symptoms.

## Diagnosis

**Leukopenia** or a normal white blood cell count is more common than leukocytosis. Normocytic **anaemia** is frequently present. Sometimes there is thrombocytopenia. Liver tests may be abnormal and a liver biopsy or bone marrow specimen can often (± 75%) show **granulomatous lesions**. If granuloma are large enough, they can display fibrinoid necrosis. The cerebrospinal fluid can be abnormal with an **increased lymphocyte count**, raised CSF protein and normal glucose concentration.

Brucellosis can be suspected **serologically**, but the antibodies cross-react with, for example, *Yersinia enterocolitica, Francisella tularensis, Salmonella* and other organisms. Serologically, *B. canis* infections can be detected only with difficulty. False negative results are common early in the course of infection. A prozone effect can also occur (negative serology at low dilutions becoming positive at higher dilutions). There are rare cases of active Brucella infections in which the standard serology is negative ("blocking antibodies"?). Many laboratories use the so-called "**Rose Bengal**" test, an agglutination test which gives results within 5 minutes. If positive, a **Wright** serological test can be performed but this test needs a longer time (serum agglutination test with overnight incubation). After successful therapy, the IgG titre falls.

**Isolation of the organism** from blood, tissue, urine, bone marrow, cerebrospinal fluid, require specific culture media. It is a **slow-growing organism**. It is best to notify the laboratory beforehand. Bone marrow cultures have a higher sensitivity than blood cultures. With some rapid automated commercial methods, misidentification of the organism as

*Moraxella phenylpyruvica* is possible. Because the organism is a coccobacillus, a laboratory can wrongly describe the organism as a coccus on one occasion and as a rod-shaped bacterium on another.

Radiographs, bone scans, computerized tomography (CT), magnetic resonance imaging (MRI), and echocardiography may be helpful in evaluating focal disease but do not provide a definitive diagnosis. Localized snowflake calcification in chronic hepatosplenic brucellosis is the only specific radiographic finding that may be used to distinguish brucellosis from other diseases. PCR is a promising tool for rapid and accurate diagnosis of human brucellosis.

## Treatment

**Rifampicin** (600-900 mg/day) and **doxycycline** (200 mg/day) are often used as first line. If possible an **aminoglycoside** should be added (minimal dual regimen; optimal tritherapy which includes streptomycin or gentamycin). Sometimes combination treatment includes cotrimoxazole (children, pregnant women) or ofloxacin. It is recommended that a specialist with experience in brucellosis be consulted. Treatment lasts **at least six weeks**, but sometimes must be continued for many months. In general, longer courses of therapy (at least 12 weeks) are warranted for treatment of spondylitis, neurobrucellosis, endocarditis or localized suppurative lesions. Clinical relapse sometimes occurs, usually within 6 months of discontinuing the antibiotics. Relapse is usually not a consequence of antibiotic resistance, but due to the persistence of a focus (drainage sometimes necessary). Naturally, patients can still complain of pain following correct treatment due to the consequences of joint involvement, for example.

It was found (with real-time PCR) that in the majority, *Brucella melitensis* **DNA will persist** in the human body for several years despite appropriate treatment and apparent clinical recovery. It has not been formally shown that this DNA is from dead or living bacteria, but it strongly suggests that *B. melitensis* is a noneradicable persisting pathogen.

## Prevention

**Detection and destruction of infected animals** must be implemented. Brucellosis may be prevented via **vaccination**, which is effective for cattle, sheep and goats (not for

humans), but requires a sustained vaccination program over several years. **Proper pasteurisation of milk** and avoidance of cheese made from potentially contaminated milk are important. If for example cottage cheese is used in cooking, it needs to be heated long enough (the centre heats less quickly than the outside; the centre of the lumps needs to be heated above the minimum temperature to destroy *Brucella* bacteria). Gloves are to be used when working with potentially infected animals and their secretions.

**Uveitis**

Uveitis is a general term for inflammatory disorders of the uveal tract. Anterior uveitis is the term which encompasses iritis and iridocyclitis. Posterior uveitis is the preferred term for choroiditis and chorioretinitis. In the non-granulomatous form, the onset is characteristically acute, with pain, injection, photophobia and blurred vision. There is a circumcorneal flush caused by dilated limbal blood vessels. Fine white deposits on the posterior surface of the cornea can be seen with a slitlamp. The pupil is small and there may be a collection of fibrin with cells in the anterior chamber. If posterior synechiae are present, the pupil will be irregular in shape. In granulomatous uveitis, the onset is usually insidious. Vision gradually becomes blurred and the affected eye becomes diffusely red with circumcorneal flush. Pain is minimal and photophobia is less marked than in the non-granulomatous form. Fresh active lesions of the choroid and retina appear as yellowish-white patches seen hazily with the ophthalmoscope through the cloudy vitreous. As healing progresses, the vitreous haze lessens and pigmentation occurs gradually at the edges of the yellowish-white spots. In the healed stage there is usually considerable pigment deposition. If the macula is not involved, recovery of central vision is complete. The patient is usually not aware of the scotoma in the peripheral field corresponding to the scarred area.

There are various causes, including several infectious diseases, but also auto-immune disorders. A wider range of diagnoses must be considered for patients in developing countries. Expert advice from an experienced ophthalmologist and a specialist in internal diseases is essential to save the patient’s sight. If for example toxocariosis of the eye were to be treated with anthelminthics only, the larva would die and release a large quantity of antigen. This would cause the intra-ocular inflammation to increase, resulting in cloudiness of the vitreous humour and total blindness.

**Infectious causes of uveitis include**

1.Parasitic: toxoplasmosis, Toxocara infection (infection by the larva of a canine nematode), cysticercosis (larval Taenia solium), Onchocerca volvulus microfilaria

2.Bacterial: syphilis, tuberculosis (with granulomata on the retina), leprosy, bartonellosis with cat scratch disease, leptospirosis, Q fever, Lyme disease, brucellosis

3.Viral: CMV (think of HIV), herpes simplex, HTLV-1, measles

4.Fungal: Candida (usually panophthalmitis), cryptococcosis, histoplasmosis

**Non-infectious causes include:**

1.Sarcoidosis

2.Systemic lupus erythematosus (i.e vasculitis).

3.Traumatic and sympathetic ophthalmia.

4.Reiter's syndrome. In addition to anterior uveitis, conjunctivitis, urethritis, balanitis, oral ulcers, low fever and joint pain can also be present. There is often a recent history of infected sexual contact (Chlamydia trachomatis) or enteritis. Hyperkeratotic lesions on the palms of the hands and soles of the feet resembling pustular psoriasis can occur.

5.Associated with juvenile rheumatoid arthritis, Still's disease.

6.Associated with ankylosing spondylitis – HLA B27 (Bechterew's disease).

7.Behçet's syndrome.

8.Vogt-Koyanagi-Harada syndrome (uveo-encephalitis) with cutaneous and neurological symptoms in addition to ocular lesions (birdshot retinopathy).

9.Unknown cause, e.g. heterochromic uveitis (Fuch’s cyclitis)