Brucellosis

Synonyms: Bang’s disease (after a Danish vet), Mediterranean gastric remittent fever, Malta fever, Mediterranean fever, undulant fever, rock fever, Cyprus fever, Gibraltar fever.

This disease is notifiable in the UK, see NOIDs article for more details.

The disease was first described in Hippocrates’ time, although the organism was not isolated until 1887 when a British Army physician, David Bruce, isolated the organism from the spleens of five patients with fatal cases on Malta. The disease gets its names from both its course (undulant fever) and location (Malta fever, Crimean fever).

Pathogenesis

A Gram-negative, aerobic bacillus (facultative intracellular) which is endemic worldwide, causing disease mainly in domestic animals and subsequently transmitted to man.

Species affected include:

- Goats, sheep, camels, foxes, some deer species (Brucella melitensis).
- Pigs, reindeer, cattle, bison, hares, rodents and various species of deer (B. suis).
- Cattle, bison, elk, buffalo, foxes and various deer species (B. abortus).
- Dogs, coyote (B. canis).

There are many other strains and species, including B. ovis and the newly discovered B. maris, affecting cetaceans and seals - a possible source of a new occupational disease.

The majority of human infections result from B. melitensis, the most pathogenic species in man, although B. suis is emerging as an agent in cattle and may become increasingly important.

Epidemiology

- It is very common worldwide and believed to be greatly under-reported (in Western Nigeria over 55% of the population were found to be seropositive). \[1\]
- Frequency of brucellosis is higher in more agrarian societies. Central Asia is seeing a large increase in cases. \[2\]
- The reported frequency in the USA is 0.02 per 100,000 people. \[3\]
- It is rare in UK residents. \[4\]
- However, a high index of suspicion should be maintained for people travelling from endemic areas. \[5\]
- The Middle East is also particularly high-risk. \[6\]
- In countries where adequate animal control measures (surveillance and vaccination programmes) exist, it is largely an occupational disease.
- However, areas considered high-risk include: \[7\]
  - Portugal.
  - Spain.
  - Greece.
  - Turkey.
  - North Africa (just considering the European area). \[2\]

Mode of transmission

- **Inhalation**: the most common mode in endemic areas, affecting farmers, herdsmen (and particularly families where the animals share the same accommodation), laboratory technicians and abattoir workers.
- **Skin (intact or broken) or mucous membrane (conjunctival) contact**: abattoir workers/meat packers, veterinarians (particularly accidental needlestick injury or eye splashes with live vaccines), laboratory technicians and hunters.
- **Consumption of infected/contaminated food**: untreated milk/dairy products (particularly unpasteurised cheeses), raw meat or liver.
- **Person-to-person (rare)**: by sexual transmission (has never been well documented), breast-feeding, blood transfusion, bone marrow transplant.
- **Bioterrorism**: although weaponised by the former Soviet Union, brucellosis is less likely to be used as an agent due to its low mortality, although the prolonged morbidity might hold attractions. The organism can be freeze-dried enhancing its infectivity and can survive in the environment for up to two years under conditions of darkness, coldness, and high CO₂. It is likely to be distributed by aerosol or contamination of food. \[8\]
Presentation

The key point is to think of the diagnosis and then take a travel and occupational history. Most cases involve exposure to an infected animal. The incubation period is typically 5-30 days but can be up to six months or possibly longer.\[^9\]

Symptoms

Brucellosis may be asymptomatic.\[^10\] Symptoms are generally nonspecific. Symptoms may appear suddenly over 1-2 days or gradually over seven days or more. In a study of 84 patients:\[^11\]

- Fever was observed in 73% of patients. It is a differential in pyrexia of unknown origin (PUO). Classically undulant but other patterns occur.
- Arthritis/arthralgia (in 64%).

Other symptoms can include malaise, back pain, headaches, loss of appetite, weight loss (in chronic infection), constipation, abdominal pain, sleep disturbances, cough, testicular pain, and skin rash (less common).\[^11, 2\]

It may be apyrexial in the chronic form, with myalgia, fatigue and depression (differential: chronic fatigue syndrome).\[^12\]

Signs

- In around half of patients: arthritis, spinal tenderness.\[^13\]
- In around a quarter of patients: looks ill, pallor, lymphadenopathy, splenomegaly, hepatomegaly, epididymo-orchitis, skin rash.
- Less than 5%; jaundice, central nervous system (CNS) abnormalities, cardiac murmur, pneumonia.

Investigations\[^14\]

Presumptive diagnosis is supported by rose Bengal test (RBT) or serum agglutination test but further confirmatory tests are required for screening; positive tests to be confirmed by one of the tests mentioned below:

- Isolation of *Brucella* spp. from the clinical specimen is considered to be the gold standard. This involves inoculating a blood sample into Castaneda's medium, a brain heart infusion agar and broth with Brucella selective supplement.
- If direct isolation is not available (a common circumstance in resource-poor areas), antibody testing can be used, although at best it gives indirect evidence of contact.\[^15, 16\]
  - The best test is the tube agglutination method, which tests for anti-O-polysaccharide antibody.
  - Titres of 1:160 or higher are diagnostic.
  - Raised immunoglobulin G (IgG) antibodies indicate recent infection; raised IgM antibodies indicate active disease.

- Raised serum brucella agglutinins.
- Cerebrospinal fluid cultures are positive for brucellosis less than 50% of the time but enhanced polymerase chain reaction tests can detect relatively small amounts of brucella DNA.\[^16\]
- White cell count is usually normal. Leukocytosis is rare and a significant number of patients are neutropenic.
- Plain X-rays of joints and spine are usually normal. Occasionally there is bone destruction at the discovertebral junction with anterior osteophytes and reduced disc space. CT and bone scintigraphy have limited value because of their inadequate soft tissue resolution and MRI is more sensitive. Arthrocentesis may be necessary to exclude septic arthritis.\[^17\]
- MRI scanning is the investigation of choice for brucellar spondylodiscitis. Diffusion weighting imaging can help to differentiate between acute and chronic infection.\[^18\]
- Liver or bone marrow biopsy may be appropriate in certain cases.

Differential diagnosis

This is quite broad, given that symptoms of brucellosis are nonspecific. Conditions to be considered include:

- Mechanical back pain.
- Bronchitis.
- Illnesses caused by use of biological warfare agents.
- Endocarditis.
- Gastroenteritis.
- Meningitis.
- Osteomyelitis.
- Pneumonia.
- Subarachnoid haemorrhage.
- Thrombocytopenic purpura.\[^19\]
- Tuberculosis.
- Urinary tract infection.

Management
Of the currently existing alternative regimens, only the combination of doxycycline with gentamicin can be considered therapeutically adequate and cost-effective, the latter factor being a major obstacle in using quinolones for brucellosis.\cite{20,21} Doxycycline-rifampicin-aminoglycoside (triple drug regimen) and longer treatment regimes (>6 weeks) have the lowest rates of failure.\cite{22} One study of the treatment of brucellar spondylitis reported that six months of triple therapy were required to prevent recurrences.\cite{23}

**Adults**

- Doxycycline (100 mg PO bd for six weeks) is the most appropriate monotherapy in simple infection; however, relapse rates approach 40% for monotherapy treatment. **NB**: emphasise the need to complete the full six-week course of antibiotics, as failure to do so increases the risk of relapse.
- Rifampicin (600-900 mg/day) is usually added to doxycycline for a full six-week course. A Cochrane review found that doxycycline (six weeks) plus streptomycin (two or three weeks) was a more effective regimen than doxycycline plus rifampicin (six weeks). However, streptomycin involves daily intramuscular injections and is more expensive than rifampicin.\cite{24}
- In patients with spondylitis or sacroiliitis, doxycycline plus streptomycin (1 g/day IM for three weeks) was found to be more effective than the doxycycline/rifampicin combination.\cite{12}
- The Cochrane review found that quinolone plus rifampicin (six weeks) regimen is slightly better tolerated than doxycycline plus rifampicin but there was no difference in effectiveness.\cite{24}

**Children**\cite{12}

- In paediatric patients older than 12 years, doxycycline (5 mg/kg/day for three weeks) plus gentamicin (5 mg/kg/day IM for the first five days) is the recommended therapy.
- For children younger than 12 years, trimethoprim/sulfamethoxazole (TMP-SMZ) for three weeks and a five-day course of gentamicin are most effective.

**Pregnant women**\cite{12}

- The optimal treatment during pregnancy has not been determined. The teratogenic potential of many drugs is unknown. Co-trimoxazole has been used in individual cases with reported success. Another alternative is rifampicin therapy for at least 45 days, depending on the clinical outcome.

**Potential problems**

- Quinolones have a high relapse rate when used as monotherapy.
- No uniform recommendation exists for treatment of endocarditis. However, TMP-SMZ, rifampicin and doxycycline are commonly used in various combinations. Early replacement of the infected valve is recommended, along with medical therapy.\cite{25}
- Likewise, there are no consensus guidelines for the treatment of meningitis. One case study reported the successful use of TMP-SMZ, rifampicin and ceftriaxone in a child aged under 8.\cite{26} In adults, the quinolone can be replaced by doxycycline or tetracycline.\cite{27}
- Corticosteroids may be indicated in CNS infection, particularly if symptoms worsen due to extreme output of brucella antigens and immune response but evidence to support their efficacy is lacking.\cite{28}

**Prognosis**\cite{29}

- Most patients recover completely without complications, if they receive appropriate antibiotic treatment.
- The relapse rate is approximately 10%, even with treatment.
- Mortality is rare, one review quoting a figure of <0.4%. Death is usually associated with endocarditis.

**Complications**

Complications are rare in the patient who is treated appropriately:

- Cardiovascular: the primary complication is the need for valve replacement in the patient with endocarditis.
- Bone: residual musculoskeletal complaints may be present in the patient with long-term infection, sacroiliitis and osteomyelitis.
- Genitourinary: especially epididymo-orchitis.
- Blood: immune thrombocytopenic purpura has been described as a consequence of brucellosis infection.
- Neurological: mental state, visual, hearing changes (may be the most common cause of acquired hearing loss in endemic areas), cranial and peripheral nerve dysfunction, cerebellar ataxia, spinal syndromes, etc.
- Abscess formation: most commonly hepatic but also elsewhere.
- Chronic fatigue syndrome may be seen.
- Infection in pregnancy may result in abortion, congenital and neonatal infections and infection of the delivery team.\cite{30}

**Prevention**

- This relies on control of the disease in animals, by a combination of surveillance, slaughtering and vaccination.
- Pasteurisation of milk and avoidance of consumption of unpasteurised milk products, raw or undercooked meat.
- Education, protective clothing, adequate ventilation and disinfection of premises and safe disposal of offal, for those exposed occupationally.
- There is no human vaccine available.
Further reading & references

- Brucellosis; World Health Organization

4. Brucella Reference Unit; Frequently Asked Questions; GOV.UK, 2013
7. Eradicating, control and monitoring programmes; European Commission, 2014
10. Akhvediani T et al; The changing pattern of human brucellosis: clinical manifestations, epidemiology, and treatment outcomes over three decades in Georgia, BMC Infectious Diseases, 2010.
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