Summary

- Environmental bacterium (soil, water): *Burkholderia pseudomallei*
- Southeast Asia and Northern Australia are hotspots
- Infection is through skin and inhalation
- Diabetes and other immune depressed at risk
- Acute or chronic disease
- Skin infection – pneumonia – blood stream infection – deep abscesses, high mortality
- Treatment: ceftazidime or meropenem followed by co-trimoxazole or co-amoxiclav (at least 3 months)

General

Burkholderia pseudomallei (formerly *Pseudomonas pseudomallei*) is a facultative intracellular Gram-negative rod-shaped bacterium also known as Whitmore's bacillus. The organism is responsible for infections in sheep, goats, pigs, cattle, horses, rats, cats and dogs. **Soil and stagnant water (rice fields)** form its natural reservoir. Humans are infected by **contaminated soil via skin** abrasions. **Swallowing and inhalation** of the bacilli can also result in clinical infection. Neonates can be infected on rare occasions (via placental micro-abscesses?). The disease is endemic in **Southeast Asia and northern Australia**. Very rarely cases are diagnosed in Central and South America and also in Africa.

B. pseudomallei has two chromosomes. Together they contain more than 7 megabasepairs, making it a very complex bacterial genome. Genotyping of multiple *B. pseudomallei* colonies from several tissue sites showed substantial genetic diversity within a single patient, illustrating the capacity of the bacterium to evolve rapidly within a host. It can invade and survive in a range of phagocytic and non-phagocytic cells. It replicates in the cytosol after leaving the vacuole.

Historical perspective

Glanders is a chronic disease of horses associated with involvement of the nasal mucosa with mucus production, as well as local lymph node enlargement. Glanders in animals is

caused by the immotile *Burkholderia mallei* (formerly *Pseudomonas mallei*). Human infections are rare.

In 1911, the British pathologist Captain Alfred Whitmore and his assistant C.S. Krishnaswami discovered that ill-nourished and neglected inhabitants of Rangoon, Burma, exhibited the same sort of lesions as horses with glanders. They also performed autopsies on emaciated morphine addicts. About one in every twenty post-mortem examinations in Rangoon Central Hospital was on a case of the disease. The organism which was recovered from the numerous and widespread abscesses observed at post-mortem examination in these cases could be grown on peptone agar or on potato slopes (the bacteriological tools of the day). The organism isolated from humans, however exhibited some differences from the one that caused glanders in animals. The new bacterium was motile (glanders is caused by an immotile bacterium) and caused a slightly different reaction after inoculation in guinea pigs. The bacterium was initially called *Bacillus pseudomallei*. The term “pseudoglanders” is sometimes used in English. In 1913 there was an outbreak of an unusual “distemper-like” disease in the veterinary department of the Institute for Medical Research in Kuala Lumpur, Federated Malay States. Dr Fletcher isolated the organism during this outbreak, but he was unable to identify it. In 1917 Stanton isolated the bacterium during an outbreak among Tamil rubber tappers, and saw it was identical to Whitmore’s bacillus. In the following years Stanton and Fletcher conducted research on this organism and named the disease meioidosis (Gr. “melis”, referring to glanders-like disease of asses).

The occurrence of infections in Vietnam in French colonial soldiers involved in a car accident led to the hypothesis that the organism could enter the body via mud-soiled wounds or via aspiration of muddy water. Guinea pigs with a scarified abdomen could be infected by immersion in muddy water. Finally, the organism was cultured in vitro from soil. It was shown that the organism produced a heat-labile exotoxin. During the Vietnam War several cases occurred in wounded soldiers, but there were also abnormally large numbers of cases among helicopter pilots, which suggested that aerogenic transmission was possible. Several American veterans developed active melioidosis up to 26 years after their stay in Vietnam. An 82-year-old U.S. veteran held as a Japanese prisoner of war in Indochina during World War II developed an infected ulcer on his right hand as symptom of melioidosis. This was 62 years after his exposure. No-one knows the anatomical site where the bacterium survives or how the immune system is evaded. All in all, our knowledge about melioidosis is clearly

inadequate. There is a strong association between **melioidosis and rainfall** (80% of cases occur in the wet season). Heavy rain and wind, such as in monsoon season seems to cause a shift from inoculation towards inhalation of *Burkholderia pseudomallei*.

In 1950 there was an epidemic in Aruba – an island off the coast of Venezuela. In 1970 an outbreak in France was linked to the zoo in the Jardin des Plantes near the Musée National d'Histoire Naturelle. It was assumed that the epidemic was caused either by an infected giant panda imported from China or an infected horse introduced from Iran.

Clinical aspects

The incubation period can last **weeks, months or years**. Subclinical infections can occur. The disease can be latent for years. Often the clinical presentation is that of an acute febrile respiratory infection (**pneumonia**), **but acute localized skin infection** (skin abscess with or without drainage sinus, necrotizing fasciitis, lymphangitis), **blood stream infection** with or without a clear focus, genitourinary infection, synovitis with or without septic arthritis, osteomyelitis, neurological involvement (myelitis, brain-stem encephalitis with cranial-nerve palsies) and chronic disease with **disseminated organ abscesses** also occur. Suppurative parotitis seems to be common in Thailand and Cambodia but is very rare elsewhere. **Pure cutaneous** forms without systemic features exist, from a primary solitary lesion to multiple lesions (secondary spread). Pustular rash can be found during septicaemia. Respiratory tract infection is sometimes difficult to distinguish from tuberculosis (both classical and miliary). Pulmonary cavities can appear. Splenomegaly is regularly present. During pulmonary melioidosis, urticaria, flushing and/or cyanosis can occur. In some areas, such as northern Thailand, it is the most important cause of community-acquired bloodstream infection.

Meloidosis is one of the "**great imitators**" due to its wide -ranging clinical presentation

Melioidosis tends to have a **protracted course** and cure is difficult without a **prolonged course** of appropriate antibiotics.

Risk factors include alcoholism, malnutrition, renal failure, chronic pulmonary disease, corticosteroid use, cancer and especially diabetes. There is insufficient data about a possible

interactions with HIV. Mortality in active disseminated disease is high, about **40-80%,** especially when additional risk factors are present. With early diagnosis and institution of therapy with ceftazidime or meropenem and access to state-of-the-art intensive care therapy, the overall mortality from melioidosis can now be as low as 10 percent.

Diagnosis

Patients tend to be from Southeast Asia (esp Northeast Thailand, Cambodia) or Northern Australia. The infection can be suspected from a chest X-ray. The diagnosis is established by **culture** (blood, urine, skin, sputum). The organism grows on several media but should be distinguished from *Pseudomonas* species. Growth can be quite slow, as compared with other bacteria that cause blood stream infection. In view of the risk which this organism presents, culture and isolation is best left to well-equipped laboratories. Gram stain of sputum and abscess pus may reveal gram-negative bacilli of B. pseudomallei. The organisms often have a characteristic bipolar staining with a “safety pin” appearance.

Antibodies can be detected serologically. A positive serology can point to an active infection or a previous (including subclinical) melioidosis. Most seropositive patients have no overt clinical disease. A latex agglutination test which can be used with urine has been developed. The main differential diagnoses are tuberculosis, disseminated fungal infections and chronic pyogenic osteomyelitis but melioidosis is one of the “great imitators”. It is clear that more research is needed.

Treatment

Burkholderia pseudomallei is **intrinsically resistant to numerous antibiotics**, including aminoglycosides, penicillin, ampicillin, first- and second-generation cephalosporins, chloramphenicol and fluoroquinolones. First line treatment for severe cases is IV **ceftazidime** (Glazidim®, a beta-lactam belonging to the third generation cephalosporins) combined with cotrimoxazole. Dosage is ceftazidime 2 grams TDS for a minimum of 2 weeks. Beta-lactams belonging to the carbapenems such as imipenem in combination with cilastatin (Tienam®) or meropenem (Meronem®) are (expensive and often difficult-to-access) alternatives.

For mild ambulatory cases, amoxicillin with clavulanic acid (co-**amoxiclav**, Augmentin), also in combination with high dose **cotrimoxazole** forte 3 to 4 tablets per day for an adult (one tablet containing trimethoprim 160 mg + sulfamethoxazole 800 mg) is often used.

The optimal duration of maintenance treatment (cotrimoxazole or doxycycline) is not known but **3-6 months** is often recommended.

Relapse can occur after several years, especially during immunosuppression. This means that lifelong follow-up is indicated.

There is currently no vaccine available.