GLANDERS (*Burkholderia mallei*) and MELIOIDOSIS (*Burholderia pseudomallei*)

1. Clinical and Laboratory Features
   a. Bacterium: Size: 0.8 x 1.5 µm

b. Mode of Transmission
   i. Inoculation of environmental organisms through penetrating wounds or into existing skin lesions, the aspiration of contaminated water during near-drowning episodes and iatrogenic (due to the doctor) inoculation.  
   ii. The precise mode of infection with *B. pseudomallei* is often unknown, although most cases are assumed to be acquired by inoculation. However, cases can occur in tourists with no obvious soil or water contact.  
   iii. Experimental animals have been infected by inhalation and this mode of acquisition was thought to account for the predominance of helicopter crews with pulmonary melioidosis during the Vietnam War.  

c. Virulence
   i. The LD$_{50}$ (50% lethal dose) for *B. pseudomallei* in the Syrian hamster model of acute melioidosis is less than ten organisms.  
   ii. Animal-to-human transmission has rarely been documented but can result in fatalities as *B. pseudomallei* has an extremely broad host range.  

d. Spectrum of Disease
   i. *Burkholderia mallei* infections can have two forms: the nasal-pulmonary form (glanders) and the cutaneous form (farcy). These two forms may be present simultaneously and are usually accompanied by systemic disease. The route of infection, dose and virulence determine the severity of the disease.  
   ii. “Humans are most often afflicted with the acute form of the disease characterized by a rapid onset of pneumonia, bacteremia, pustules and death occurring within days. In contrast, the chronic form of the disease is characterized by intermittent recrudescence, milder signs and symptoms, and may last up to 25 years.”  
   iii. Molecular pathogenesis: “*B. pseudomallei* survives inside several eukaryotic cell lines and is seen within phagocytic cells in pathological specimens. After internalisation, it escapes from endocytic vacuoles into the infected cell cytoplasm and then forms membrane protrusions by inducing actin polymerisation at one pole. The actin protrusions from the infected cell membrane mediate spread of the organism from cell to cell. The role of exotoxins in the pathogenesis of melioidosis is unresolved. The high mortality of *B. pseudomallei* infections is related to an increased propensity to develop high bacteraemias (more than 1 cfu/mL), but the relation between bacterial counts in blood and mortality is similar to that of other gram-negative pathogens. This finding suggests that exotoxins do not contribute directly to outcome. The cell wall lipopolysaccharide (LPS), which is the immunodominant antigen, is highly conserved. High concentrations of antibodies to LPS 2 are associated with improved survival in severe
melioidosis. B. pseudomallei produces a highly hydrated glycocalyx polysaccharide capsule, an important virulence determinant that helps to form a slime. This capsule facilitates formation of microcolonies in which the organism is both protected from antibiotic penetration and phenotypically altered, resulting in reduced susceptibility to antibiotics (small colony variants). Passive immunisation with antibody to this exopolysaccharide reduces the lethality of infection in mice. To date, the organisms which cause invasive disease are indistinguishable from those found in the environment.”

iv. Incubation period from defined inoculating events was previously ascertained as 1-21 (mean 9) days. “In endemic areas, seroepidemiological surveys showed that infection, mostly latent, occurred fairly commonly since childhood as 80% of children had antibodies by the age of four years. However, clinical melioidosis is more common in the elderly which in some cases are due to reactivation of primary latent infection. Since the incubation period of the reactivation can vary from weeks to many years.”

v. “Melioidosis should be suspected in any severely ill febrile patient with an underlying predisposing condition who lives in, or has travelled from, an endemic area. In northeast Thailand, B. pseudomallei is the most common cause of septicemic illness during the rainy season in adult diabetics. Evidence of abscess formation is often noted either in the lungs on the chest radiograph, or in the liver and spleen on ultrasound examination. Whereas liver abscess can be caused by Entamoeba histolytica or by enteric bacteria, splenic abscess is much less common, and is more likely than liver abscess to suggest melioidosis in endemic areas; in northeast Thailand 95% of splenic abscesses are caused by B pseudomallei. Up to 13% of patients with septicemia have subcutaneous abscesses in which gram-negative rods can be detected. Haematological and biochemical findings are similar to those in patients with other causes of bacterial sepsis, although evidence of the underlying predisposing condition (hyperglycaemia or renal impairment) is often noted.”

vi. “The clinical spectrum of melioidosis in Australia is similar to that in Thailand, but there are also some differences. Similarities include the high proportion (50%) of cases presenting as pneumonia, with skin (13%) and soft tissue (4%) abscesses, osteomyelitis or septic arthritis (4%) are also seen frequently. Differences include the frequency of both prostatic abscesses (18% of male cases) and neurological melioidosis (4%) in Australia. Neurological manifestations were also present in two out of six pediatric cases seen recently in northern Australia. Prostatic abscesses have also been reported from Singapore, and pelvic imaging is probably warranted in any male with melioidosis, particularly if their response to treatment is slow. Furthermore, the overall mortality in Australia is considerably lower (19%) than that reported elsewhere. This may partly reflect the earlier presentation of patients in Darwin (only 46% were bacteremic compared with 62% in north-east Thailand).”

vii. “Melioidosis acute suppurative parotitis is a unique syndrome. In about 10% of cases, parotitis is bilateral. In advanced cases rupture can arise, either to the
skin or through the external ear. Management is with antibiotics (initially ceftazidime, followed by oral amoxicillin-clavulanate) and with incision and drainage. Great care should be taken to avoid damaging the facial nerve. Delay in drainage can result in permanent Bell's palsy. The optimum duration of maintenance treatment for suppurative parotitis has not been determined, but generally 8 weeks of treatment is sufficient. These patients do not relapse and the overall outlook is good.” 7

viii. “It is now evident that at least some of the cases presenting with classical neurological melioidosis with involvement of brainstem, cerebellum and spinal cord have direct invasion of the CNS.” 7

ix. Pulmonary melioidosis: This form develops usually after inhalation or through haematogenous spread of the bacteria. This could be the major form of the disease in a bioterrorist attack. When bacteria are aerosolised, they enter the respiratory tract and pulmonary infection may develop, manifested by pneumonia, pulmonary abscesses and pleural effusion. In cases of inhalational melioidosis, cutaneous abscesses may also develop and take months to appear. Without specific treatment, the disease progresses and results in bacteraemia and septicaemia. 10

x. “Acute melioidosis pneumonia has a spectrum from fulminant septic shock (mortality 84% in the Darwin study) to mild undifferentiated pneumonia, which can be acute or subacute in nature, both with little mortality. Septicaemic patients present as acutely unwell with high fevers and prostration and often little initial cough or pleuritic pain. There may also be multiple abscesses in abdominal organs. On chestradiography they often have diffuse nodular infiltrates throughout both lungs, which coalesce, cavitate and progress rapidly, consistent with the caseous necrosis and multiple metastatic abscess formation seen at autopsy. However, some septicaemic pneumonia patients have a more predominant cough with productive sputum, dyspnoea and chest radiography showing discrete but progressive consolidation in one or more lobes. Acute pneumonia with upper lobe consolidation in endemic regions warrants consideration of melioidosis. While such upper lobe disease has predominated in some reports, lower lobe infiltrates were more common overall in non-septicaemic acute and subacute melioidosis from one study. Pleural effusions have generally been uncommon in acute melioidosis, but effusions and empyema can still occur, especially with lower lobe disease. Patients with chronic pulmonary melioidosis have fevers, weight loss and a productive cough, sometimes with haemoptysis. Pleuritic chest pain occurs in half. Disease is often slowly progressive over months. It can also be remitting and relapsing over many years, but acute deterioration with septicaemia may also occur. Classically upper lobe changes with infiltrates and/or cavitation are seen on chest radiography, being present in 37 out of 39 (95%) chronic cases in one study. Initial chest radiography showed cavitary disease with or without infiltrates in 27 out of 39 (69%) and infiltrates in 12 out of 39 (31%). Pleural effusions were present in two out of 39, hilar adenopathy in only one out of 39 and only three out of 39 had bilateral disease. The cavities are usually single and thin walled and rarely contain an air-fluid level. Computed
tomography (CT) scan may show small cavities not evident on chest radiography. There are numerous reports of chronic melioidosis being initially misdiagnosed as tuberculosis.\textsuperscript{10} The incubation period is 10-14 days. Ulcerative lesions and nodules of the nasal cavity may be present, where in some cases, the septum may perforate. Chest radiography may show a bilateral bronchopneumonia, miliary nodules (0.5 -1 cm), small multiple lung abscesses involving upper lungs, segmental or lobar infiltrates and cavitating lesions, which are often mistaken for tuberculosis.\textsuperscript{11}

2. Bacterial Load

Hamster

The change in bacterial counts in the blood, spleen, liver and lung of hamsters after intraperitoneal inoculation with \textit{Burholderia mallei}. Approximate values after Figure 1 from Fritz et al.\textsuperscript{6}

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<th>Day postinoculation</th>
<th>Blood (log10 CFU/ml)</th>
<th>Spleen (log10 CFU/g)</th>
<th>Liver (log10 CFU/g)</th>
<th>Lung (log10 CFU/g)</th>
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References