Melioidosis is an infectious disease caused by a gram-negative bacterium called *Burkholderia pseudomallei*. Most people infected with *B. pseudomallei* experience no symptoms; however, those who do experience symptoms have signs and symptoms that range from mild such as skin changes, pneumonia, and abscesses to severe with inflammation of the brain, inflammation of the joints, and dangerously low blood pressure that causes death. Approximately 10% of people with melioidosis develop symptoms that last longer than two months, termed “chronic melioidosis.”

Humans are infected with *B. pseudomallei* by contact with water. The bacteria enter the body through wounds, inhalation, or ingestion. Person-to-person or animal-to-human transmission is rare. The infection is constantly present in Southeast Asia, particularly in northern Thailand and northern Australia. The signs and symptoms of melioidosis resemble tuberculosis and misdiagnosis is common. Diagnosis is usually confirmed by the growth of *B. pseudomallei* from an infected person’s blood or other body fluids. Those with melioidosis are treated first with an “invasion” course of intravenous antibiotics (most commonly ceftazidime) followed by a several-months treatment course of co-trimoxazole. Even if the disease is properly treated, approximately 1% of people with melioidosis die from the disease. Disease is improperly treated, the death rate could reach 40%.

Efforts to prevent melioidosis include: wearing protective gear while handling contaminated soil, preventing hand hygiene, drinking boiled water, avoiding direct contact with soil, water, or heavy rain, and seeking treatment only for individuals at risk for getting the disease after being exposed to the bacteria. There is no approved vaccine for melioidosis.

In endemic areas, approximately 165,000 people are infected by melioidosis per year, resulting in about 89,000 deaths. Diabetes is a major risk factor for melioidosis; over half of melioidosis cases are in people with diabetes. Sepsis with pneumonia is associated with increased number of melioidosis cases in endemic areas.

### Signs and symptoms

#### Acute

Most people exposed to *B. pseudomallei* experience no symptoms. The mean incubation period of acute melioidosis is 9 days (range 1–21 days). Nevertheless, 18% of the people experience acute melioidosis. The mean incubation period of melioidosis can appear in 24 hours for those experiencing near drowning in water. Those affected present with symptoms of sepsis and pneumonia or acute respiratory distress syndrome. The infection is progressive as fluid accumulates in the pleural cavity and gathering of pus in the brain can lead to increased intracranial pressure.

People with melioidosis often experience a fever, which can be accompanied by chills, sweating, headache, and muscle pain. Red or purple rash can appear on the skin of those with melioidosis only. Those with melioidosis may have a progressive cough with sputum and shortness of breath. However, a cough can also be a reaction from diffuse nodular infiltrates in those without melioidosis that develop secondary pneumonia caused by other bacteria after the primary illness.

### Chronic

Chronic melioidosis is usually defined by symptoms lasting greater than two months and occurs in about 10% of patients. Clinical presentations include fever, weight loss, productive cough with or without bloody sputum which may mimic tuberculosis. Additionally, long-standing abscesses at multiple body sites may also present. Tuberculosis should be considered.

### Bacteria

*Burkholderia pseudomallei* is a bacterium found in rice fields, water, and soil in Southeast Asia. In Australia, the longest recorded latency period is 24 years. The potential for long incubation was recognized in US service members involved in the Vietnam War, and was referred to as the “Vietnam time-bomb.” In Australia, the longest recorded latency period is 24 years. Various comorbidities such as diabetes, renal failure, and alcoholism can predispose to reactivation of melioidosis.
Melioidosis is caused by gram-negative, motile, saprophytic bacteria named Burkholderia pseudomallei. The bacteria can be opportunistic, facultative intracellular pathogens. It is also aerobic and oxidases test positive. The bacteria at the centre of the bacterium makes a safety pin when Gram stained. This elicits a strong soil smell after 24 to 48 hours of growth in culture. B. pseudomallei produces a cytochrome-p-450 oxidase that is a major type of antibiotic (E. coli). It is generally resistant to ampicillin and chloramphenicol but sensitive to cotrimoxazole and amoxicillin-clavulanic acid (co-amoxiclav). B. pseudomallei is a causative agent of the disease melioidosis. B. pseudomallei can be differentiated from other species of Burkholderia by its ability to assimilate arabinose. B. pseudomallei is highly adaptable to various environments, and it is capable of adapting to the human body.

The genome of B. pseudomallei consists of two replicons: chromosome 1 encodes housekeeping functions of the bacteria such as cell wall synthesis, mobility, and metabolism; chromosome 2 encodes functions that allow the bacteria to adapt to various environments. Horizontal gene transfer among B. pseudomallei has resulted in highly variable genomes in B. pseudomallei. Australia has been suggested as the reservoir for B. pseudomallei because of the high variability of the bacteria and the ability of B. pseudomallei to have a cosmopolitan distribution in the 19th century. B. mallei is a clone of B. pseudomallei that has lost substantial portions of its genetic material. It is a highly virulent pathogen and can live exclusively in mammals.

**Transmission**

B. pseudomallei is normally found in soil and water, and is most abundant at soil depths of 10 cm to 100 cm. It has been found in soils, ponds, streams, pools, stagnant water, and rice fields. B. pseudomallei can survive in nutrient-poor conditions such as dried water, desert soil, and nutrient-depleted soil for more than 16 years. The bacteria can also survive in antiseptic and detergent solutions, acidic environments (pH 4.5 for 70 days), and in environments at temperatures ranging from 24 °C (75.2 °F) to 32 °C (90.4 °F). However, the bacteria do not survive in the presence of ultraviolet light.

Bacteria can enter the body through wounds, ingestion, inhalation of contaminated water, or through aerosol particles. Person-to-person transmission is extremely rare. Melioidosis is a recognized disease in animals including dogs, goats, sheep, and cattle, water buffalo, and crocodiles are considered to be relatively resistant to melioidosis despite their constant exposure to the bacteria and are also resistant to melioidosis. Transmission from animals to humans is rare.

Inadequate chlorination of water supplies has been associated with B. pseudomallei outbreaks in Northern and Western Australia. The bacteria have also been identified in water samples from Thailand. Infection from B. pseudomallei is associated with respiratory infection in Australia and melioidosis. In the whole genome sequencing of the bacteria, humans may play a role in moving B. pseudomallei from place to place.

**Pathogenesis**

B. pseudomallei has the ability to infect various types of cells and to evade human immune responses. Bacteria first enter a break in the skin or mucous membranes and replicate in the infected area to spread and infect various cell types. As the bacteria grow, both phagocytes and non-phagocytes B. pseudomallei can attach to the cells to move near host cells, then attach to the cells using various adhesion proteins, as the bacteria replicate, they are more likely to be killed. Additionally, adherence of the bacteria partially depends on the presence of the host protein FimH via its mannose receptor. When present on the surface of endothelial cells, platelets, and monocytes, once bound, the bacteria enter host cells by endocytosis, ending up inside an endosome. As the vesicle acidifies, B. pseudomallei uses its Type 3 secretion system (T3SS) to inject effector proteins, altering the membrane and allowing the bacteria to escape into the host cytoplasm. Within the host cytoplasm, the bacteria evade being killed by the host autophagy using various T3SS effector proteins. The bacteria replicate inside the host cells.

Inside the host cell, the bacteria use the host repairing processes to help expand the infection in the host cell. The bacteria enter the cell by manipulating the host actin behind them, propelling the bacteria forward.

This actin-mediated motility is accomplished with the autotransporter BimA which interacts with actin at the tail of the bacterium. Propelled by actin, the bacteria push against the surface of the cell, creating protrusions that extend into neighboring cells. These protrusions cause neighboring cells to fuse, leading to the formation of multinucleated giant cells (MNGC). When MNGCs lyse, they form plaques (a central clear area with a ring of fused cells) that provide shelter for the bacteria for further replication or latent infection. This same process in infected neutrophils can allow bacteria to travel through nerve roots in the spinal cord and brain, leading to inflammation of the brain and spinal cord.

The bacteria can survive in antigen-presenting cells and dendritic cells. Thus, these cells act as vehicles that transport the bacteria into the lymphatic system, causing widespread dissemination of the bacteria in the human body.

While B. pseudomallei can survive in phagocytes, these cells can kill B. pseudomallei by several mechanisms. Macrophages activated by interferon gamma (IFN-γ) and activated T cells (CD4+ or CD8+) kill B. pseudomallei via the production of inducible nitric oxide synthase. Acidification of the endosome and degradation of the bacteria is also possible, however, the bacterial capsule and LPS makes B. pseudomallei resistant to lysozyme degradation. Once B. pseudomallei escapes into the host cytoplasm it can be recognized by pattern recognition receptors such as NOD-like receptors, triggering the formation of the inflammasome and activation of caspase-1 (caspase-1p), which induces the release of IL-1β. These processes induce pyroptosis and widespread dissemination of the bacteria in the human body.

Adaptability of the intracellular bacteria to evade the host immune response is an important factor in melioidosis. Although macrophages show deregulated cytokine responses in individuals with HIV infection, bacterial internalization and intracellular killing are still effective. Infection with B. pseudomallei develops antibodies against the bacteria, and people that live in endemic areas tend to have antibodies that recognize the bacteria. However, effectiveness of these antibodies at preventing melioidosis is unclear.

Polymeric antibodies target the bacteria and develop antibodies against the bacteria, and people that live in endemic areas tend to have antibodies that recognize the bacteria. However, effectiveness of these antibodies at preventing melioidosis is unclear.

**Diagnosis**

Culture

The definitive diagnosis of melioidosis is by isolation and identification of B. pseudomallei. B. pseudomallei is not part of human flora. Therefore, any growth of the bacteria is diagnostic of melioidosis. Blood cultures are the most common samples for diagnosis, as bacteria can be detected in the blood in 50 to 60% of melioidosis cases. Other samples include throat, rectal swabs, pus from abscesses, and sputum. B. pseudomallei can be grown on blood agar, MacConkey agar, Ashdown’s medium (containing gentamicin), and chocolate agar. The bacteria are more sensitive to gentamicin and resistant to ampicillin.

Colonies of B. pseudomallei that are grown on Francisci medium are yellow. For laboratories located outside endemic areas, Burkholderia pseudomallei is identified by selective agar containing 10 g/L gentamicin. The bacteria can be detected by various methods, including the API 20NE or API 20K biochemical kit combined with Gram staining.

Serological tests

General blood tests in people with melioidosis show a high white blood cell count (indicates infection), raised liver enzymes, increased bilirubin levels (indicates liver dysfunction), and raised urea and creatinine (indicates kidney dysfunction). Low blood glucose and anuria predicts a poorer prognosis in those with melioidosis. However, other tests such as C-reactive protein and procalcitonin levels are not reliable in predicting the severity of melioidosis infection.
Serological tests such as indirect haemagglutination have been used to detect the presence of antibodies against *B. pseudomallei*. However, different groups of people have widely different levels of antibodies, so interpretation of these tests depends on location. In Australia, less than 5% of people have *B. pseudomallei* antibodies, so the presence of even relatively low amounts of antibody is unusual and could suggest melioidosis. In Thailand, many people have antibodies against *B. pseudomallei* and the same tests are used to screen for teenagers as part of their routine health assessment. If positive, these tests can be repeated up to 2 weeks later. The ELISA test is highly sensitive but has less than 50% specificity. *B. pseudomallei* is naturally present in the soil of Thailand and neighboring countries, so even healthy people in these areas can have some antibodies. In the United States, lab workers can handle clinical specimens of *B. pseudomallei* in BSL-2 conditions, while mass production of such organisms requires BSL-3 precautions.

Microscopy

By microscopy, *B. pseudomallei* is seen as gram-negative and rod-shaped, with a bipolar staining similar in appearance to a safety pin. Bacteria can sometimes be seen directly in clinical samples from infected people; however, identification by light microscopy is neither specific nor sensitive. Immunofluorescence microscopy is highly specific for detecting bacteria directly from clinical specimens, but has less than 50% sensitivity. A lateral flow immunoassay has been developed but not extensively evaluated. An increasing number of laboratories use w-Matrix-assisted laser desorption/ionization (MALDI-TOF) mass spectrometry to identify the bacteria accurately.

Imaging

Various imaging modalities can also help with the diagnosis of melioidosis. In acute melioidosis with the spreading of the bacteria through the bloodstream, the chest X-ray shows multifocal nodular lesions. It may also show perivascular and mediastinal lymphadenopathy, which may be difficult to diagnose when compared with other causes of lymphadenopathy such as tuberculosis or HIV. Liver and spleen abscesses, an ultrasound scan shows "target-like" lesions while CT scan shows "honeycomb" in liver abscesses. For melioidosis involving the brain, MRI has higher sensitivity than CT in scanning the lesion. MRI shows ring-enhancing lesions for brain melioidosis.

Prevention

Postexposure prophylaxis

After exposure to *B. pseudomallei* (particularly following a laboratory accident), treatment with co-trimoxazole is recommended. Alternately, co-amoxiclav and doxycycline can be used for those who are intolerant to co-trimoxazole. Since co-trimoxazole can cause severe side effects in high-risk individuals, they should receive frequent monitoring.

Vaccination

Further information: w:Burkholderia pseudomallei | Vaccine, candidates

Several vaccine candidates have been tested in animal models. Nevertheless, no vaccine candidates have been tried in humans. Major hurdles of the vaccines are limited efficacy in animal models, establishing the best method of vaccine administration in humans and logistical and financial issues in establishing human trials in endemic areas.

**Treatment**

The treatment of melioidosis is divided into two stages: an intravenous intensive phase and an eradication phase to prevent recurrence. The choice of antibiotics depends upon the susceptibility of the bacteria to various antibiotics. *B. pseudomallei* are generally susceptible to cefazidime, meropenem, imipenem, and co-amoxiclav. These drugs are used to treat infections caused by *B. pseudomallei* in Australia. Co-trimoxazole and doxycycline can be used for infections caused by *B. pseudomallei* in Thailand. Alternatively, co-amoxiclav is used for infections caused by *B. pseudomallei* in Thailand.

Intensive phase

Intravenous cefazidime is the current drug of choice for treatment of acute melioidosis and should be administered for at least to 14 days. Meropenem, imipenem, and the cephalosporins-sulbactam combination (Sulperazone) are also effective.

Intravenous amoxicillin-clavulanate (co-amoxiclav) may be used if none of the above four drugs is available. Co-amoxiclav prevents death from melioidosis as well as cefazidime.

Intravenous antibiotics are given for a minimum of 7 to 10 days. The median fever clearance time in melioidosis is 9 days.

Intravenous cefazidime is the preferred antibiotic for thermoneutrophils and thermal stress. Cefazidime is an effective agent for introduction of convalescent fluids. In deep-seated infections such as abscesses of internal organs, osteomyelitis, septic arthritis, and neurological melioidosis, the duration of antibiotic given should be longer (up to 4 to 8 weeks).

The dose for intravenous cefazidime in adults (25 mg/kg up to 2 g in children less than 15 years old). The dosage for meropenem is 1g 8-hourly in adults (25 mg/kg up to 1g in children). Resistance to co-trimoxazole is rare in Australia.

Eradication phase

Following the treatment of the acute disease, eradication of the disease is achieved with co-trimoxazole. The drug of choice and should be used for at least 6 months. For those with neurological, ophthalmic, and ophthalmic, antibiotics are recommended for a minimum of 6 months. Co-trimoxazole and doxycycline are drugs of second choice. Co-trimoxazole should not be used in those with glucose-6-phosphate dehydrogenase deficiency as it can cause haemolytic anemia.

Other side effects such as rash, hyperkalemia, renal dysfunction, and gastrointestinal symptoms should prompt the reduction of co-trimoxazole. Cefazidime is an alternative for patients unable to take co-trimoxazole and doxycycline (e.g., pregnant women and children under the age of 12), but is not as effective and has higher relapse rate. Single-agent treatment with fluoroquinolones (e.g., ciprofloxacin) or doxycycline for the eradication phase is ineffective.

In Australia, co-trimoxazole is used in children and pregnant women after the first 12 weeks of pregnancy. Meanwhile, in Thailand, co-amoxiclav is the drug of choice for pregnant women. In children, doxycycline is used.

Surgery

Surgical drainage is indicated for single, large abscesses in the liver, muscle, and prostate. However, for multiple abscesses in the liver, spleen, and kidney, surgical drainage may not be possible or necessary. For septic aneurysms, arteriovenous shunt and drainage is required. Surgical debridement may be necessary. For those with mycotic aneurysm, urgent surgery is required for prosthetic vascular grafts. Other abscesses rarely need to be drained because the majority of them can resolve with antibiotic treatment.
Prognosis

In well-resourced settings, where the disease can be detected and treated early, the risk of death is 10%. In resource-poor settings, the risk of death from the disease is more than 40%.[9]

For those with incomplete treatment, reappearance of symptoms after a period of disease remission, reactivation, recurrence or relapse, can occur due to reactivation or new infection. Risk factors of reactivation include exposure to contaminated dust, repeat exposure to B. pseudomallei, air travel and previous carriage of B. mallei, obesity, diabetes mellitus, human immunodeficiency virus (HIV) infection, use of immunosuppressive drugs or devices, and exposure to contaminated water or soil. Risk factors of new infection are now more common than reactivation. Risk factors of new infection include exposure to contaminated dust, repeat exposure to B. pseudomallei, air travel, and previous carriage of B. mallei, obesity, diabetes mellitus, human immunodeficiency virus (HIV) infection, use of immunosuppressive drugs or devices, and exposure to contaminated water or soil. Risk factors of new infection include exposure to contaminated dust, repeat exposure to B. pseudomallei, air travel, and previous carriage of B. mallei, obesity, diabetes mellitus, human immunodeficiency virus (HIV) infection, use of immunosuppressive drugs or devices, and exposure to contaminated water or soil.

Eradication therapy

The most severe consequence of melioidosis is extrapulmonary. It can cause quadruparesis (muscle weakness in all limbs), partial facial paresis (muscle weakness of both legs), or foot drop. For those with systemic infection, associated bone and joint infections, complications such as abscess formation, bone and joint deforms with limited range of motion can occur.[10]

Epidemiology

Melioidosis is an underdiagnosed disease that remains endemic in developing countries. In 2015, the International Melioidosis Society was formed to raise awareness of melioidosis, by promoting the development and dissemination of evidence-based guidelines for the prevention and management of melioidosis. In 2016, a global monitoring system was established to collect data on melioidosis cases. The system is supported by the World Health Organization (WHO) and the International Organization for Nanosafety (ION).

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