**Melioidosis** is an infectious disease caused by a gram-negative bacterium called *Burkholderia pseudomallei*. Most people infected with this organism do not experience any 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 lungs 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."[1]

Humans are infected with *B. pseudomallei* by contact with an infected water or by breathing dust containing the bacteria, which can enter the body through the nose or mouth. Person-to-person or animal-to-human transmission is extremely rare.[2] The infection is constantly present in Southeast Asia particularly in northeast Thailand and northern Australia.[3] Other countries such as Europe and the United States, melioidosis cases are usually imported from countries where melioidosis is endemic.[1] The signs and symptoms of melioidosis resemble tuberculosis and misdiagnosis is common.[3] Diagnosis is usually made by finding bacteria from an infected person's blood or other body fluids.[3] Those with melioidosis are treated first with an "intensive phase" course of intravenous antibiotics (most commonly ceftazidime) followed by a several-months treatment course of oral trimethoprim.[1] Even if the disease is properly treated, approximately 10% of people with melioidosis die from the disease.[3] If disease is improperly treated, the death rate could reach 40%.[1]

Efforts to prevent melioidosis include: wearing protective gear while handling contaminated soil, avoiding direct contact with soil, water, or heavy rain, and decontaminating non-porous objects with a representative only for individuals at risk for getting the disease after being exposed to the bacteria.[1] There is no approved vaccine for melioidosis.[3]

Approximately 165,000 people are infected by melioidosis per year, resulting in about 89,000 deaths.[4] Melioidosis is an important cause of severe illness and death in high risk populations.[5] This is an open access article distributed under the Creative Commons Attribution-ShareAlike License and will also be used to update that article after peer review.

You can follow its progress through the peer review process at this tracking page.

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**Signs and symptoms**

**Acute**

Most people exposed to *B. pseudomallei* experience no symptoms.[1] However, 5% of the people experience acute melioidosis.[3] The mean incubation time of acute melioidosis is 9 days (range 1–21 days).[3] Nevertheless, 85% of the people experience acute melioidosis. The mean incubation time of acute melioidosis is 9 days (range 1–21 days).[3] Nevertheless, 85% of the people experience acute melioidosis.[3] The mean incubation time of acute melioidosis is 9 days (range 1–21 days).[3] Nevertheless, 85% of the people experience acute melioidosis.[3]

People with melioidosis are at increased risk of developing melioidosis. The disease should be considered in anyone with a history of travel or exposure to the bacteria.[1] In northern Australia, 60% of the infected children presented with only skin lesions, while 20% presented with pneumonia.[2] In northern Australia, 60% of the infected children presented with only skin lesions, while 20% presented with pneumonia.[2] In northern Australia, 60% of the infected children presented with only skin lesions, while 20% presented with pneumonia.[2] In northern Australia, 60% of the infected children presented with only skin lesions, while 20% presented with pneumonia.[2] The clinical manifestations of the disease can range from simple skin changes to severe organ problems.[1] Skin changes can be non-specific abscesses or ulcers.[1] The clinical manifestations of the disease can range from simple skin changes to severe organ problems.[1] Skin changes can be non-specific abscesses or ulcers.[1] The clinical manifestations of the disease can range from simple skin changes to severe organ problems.[1] Skin changes can be non-specific abscesses or ulcers.[1] The clinical manifestations of the disease can range from simple skin changes to severe organ problems.[1] Skin changes can be non-specific abscesses or ulcers.[1] The clinical manifestations of the disease can range from simple skin changes to severe organ problems.[1] Skin changes can be non-specific abscesses or ulcers.[1]

Depending on the course of infection, other severe manifestations develop. About 1% to 5% of those infected develop inflammation of the brain and brain covering (meninges), kidney abscess or prostatic abscesses, 0 to 30% develop urticarial skin lesions, 20% to 33% develop liver, spleen, or other intramuscular abscesses, 4 to 14% develop septic arthritis and osteomyelitis.[3] Rare manifestations include involvement of the heart (encephalitis), diaheresia, and in children, pneumonia may have minimal coughing.[5] Rare manifestations include involvement of the heart (encephalitis), diaheresia, and in children, pneumonia may have minimal coughing.[5] Rare manifestations include involvement of the heart (encephalitis), diaheresia, and in children, pneumonia may have minimal coughing.[5] Rare manifestations include involvement of the heart (encephalitis), diaheresia, and in children, pneumonia may have minimal coughing.[5]

Consequences of melioidosis include fever, weight loss, productive cough with or without bloody sputum which may mimic tuberculosis.[1] Consequences of melioidosis include fever, weight loss, productive cough with or without bloody sputum which may mimic tuberculosis.[1] Consequences of melioidosis include fever, weight loss, productive cough with or without bloody sputum which may mimic tuberculosis.[1] Consequences of melioidosis include fever, weight loss, productive cough with or without bloody sputum which may mimic tuberculosis.[1]

Clinical signs include: unilateral upper motor neuron limb weakness, cerebellar signs, and cranial nerve palsies (V, VII, nerve palsy and bulbar palsy). Some cases presented with facial paralysis alone.[1] In northern Australia, all melioidosis with encephalomyelitis cases had elevated white cells in the cerebrospinal fluid (CSF), mostly mononuclear cells with elevated CSF protein.[3]

**Chronic**

Chronic melioidosis is usually defined by symptoms lasting greater than two months and occurs in about 10% of patients.[1] Clinical presentations include fever, weight loss, prodigious cough with or without bloody sputum which may mimic tuberculosis. Additionally, long-standing abscesses at multiple body sites may also present.[3] Tuberculosis should be considered if there are lymph nodes enlargement at the root of the lungs and/or, pneumonia caused by melioidosis rarely causes scarring and calcification of the lungs.[1]

**Bacteria**

Melioidosis is caused by *Burkholderia pseudomallei*, a gram-negative bacterium. It is isolated from the blood of patients with melioidosis and from soil in infected areas.[1] It is adapted from the Wikipedia article "Melioidosis". It is adapted from the Wikipedia article "Melioidosis". It is adapted from the Wikipedia article "Melioidosis". It is adapted from the Wikipedia article "Melioidosis".
Melioidosis is caused by gram-negative, motile, saprophytic bacteria named *Burkholderia pseudomallei*. The bacteria are facultative intracellular pathogens. It is also aerobic and oxidase test positive. A mass of the bacteria at the centre of the bacterium makes a safety pin when Gram stained. The bacteria emit a strong soil smell after 24 to 48 hours of incubation in culture. *B. pseudomallei* produces a glyco-oligosaccharide capsule that is resistant to hydrolysis by many types of antibiotics. It is generally resistant to most antibiotics but sensitive to polymyxin, chloramphenicol, amikacin, and colistin.

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 genotypes in *B. pseudomallei*. Australia has been suggested as the reservoir for *B. pseudomallei* because of the high variability of the bacteria, and the bacteria are transmitted from livestock to human by a common source. Melioidosis is transmitted to the human body through exposure to contaminated water or mud.

Serological tests in people with melioidosis show low white blood cell counts (indicates infection), raised liver enzymes, increased biochemical tests in laboratories.

**Biochemical tests**

**Gastroduodenal fluid (cecal)** or Ashdown’s broth (containing 29% of the CSF cultures are positive. The broth contains 29% of normal CSF and 71% of broth. The broth contains 29% of normal CSF and 71% of broth. The broth is inoculated with the bacteria and used for growth and identification of the bacteria. Such as throat, rectal swabs, pus from abscesses, and sputum can also be used for culture.

Transmission

*B. pseudomallei* is normally found in soil and surface water, and is most abundant at soil depths of 10 cm to 50 cm. It is found in soils, ponds, streams, pools, stagnant water, and rice fields. *B. pseudomallei* can survive in nutrient-poor conditions such as distilled water, desert soil, and nutrient-depleted soil. 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 (89.6 °F). However, the bacteria do not survive in the presence of ultraviolet light.

Bacteria can enter the body through skin or mucous membranes by the ingestion of contaminated water or mud. Inadequate chlorination of water supply is associated with *B. pseudomallei* outbreak in Northern and Western Australia. The bacteria have also been found in an unchlorinated water supply in rural Thailand. Irrigation fluid contaminated with *B. pseudomallei* has caused outbreaks of melioidosis despite their constant exposure to mud. Birds are also resistant to melioidosis.

Pathogenesis

*B. pseudomallei* has the ability to infect various types of cells and to evade human immune responses. Bacteria first enter at a break in the skin or mucous membrane and replicate in the phagocytic cells. As the bacteria spread and infect various cell types, they are able to interact with both phagocytes and non-phagocytes. For example, *B. pseudomallei* can use its motility to move near host cells, then attach to the cells using various adhesion proteins, such as outer membrane protein A (OMPA). Additionally, adhesion of the bacteria partially depends on the presence of the host protein FimH-activated receptor which is present on the surface of endothelial cells, platelets, and monocytes. Once bound, the bacteria enter host endosomes and endo wounds, ending up inside an endothelial vesicle. As the vesicle acidifies, *B. pseudomallei* uses its Type 3 secretion system (T3SS) to inject effector proteins into the vesicle. The effector proteins then enable the bacteria to escape into the host cytoplasm. Within host host cytoplasm, the bacteria evade killing by the host autophagy using various T3SS effector proteins. The bacteria replicate in the host cytoplasm.

Inside the host cell, the bacteria move by inducing the polarising mechanism of the host actin, facilitating the bacteria forward. This actin-mediated motility is accomplished by the actinotransporter BimA which interacts with actin in the tail-end of the bacterium. Propelled by actin, the bacteria push against the actin network, creating protrusions that extend into neighbouring cells. These protrusions cause neighboring cells to fuse, leading to the formation of multinucleated giant cells (MNGCs). 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. In some process in infected neutrophils can allow bacteria to travel to the lymph nodes or the lymph nodes.

While *B. pseudomallei* can survive in phagocytic cells, these cells can kill *B. pseudomallei* by several mechanisms. Macrophages activated by interferon gamma (IFN-γ) are fully resistant to *B. pseudomallei* via induction 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, which induces death of the host cell by pyroptosis and further activation of the immune system. Several systemic host defenses also contribute to the immune response. *B. pseudomallei* triggers both the complement system and egulation cascade, however, the complement sensitive bacterium cannot activate the complement membrane attack complex.

Additional elements of the immune system are activated by the host toll-like receptors such as TLR2, TLR4, and TLR9 which recognize the conserved pieces of the bacteria such as LPS and flagella. This activation produces the cytokines such as interleukin 1 beta (IL-1b) and interleukin 6 (IL-6). IL-6 increases IFN production through natural killer cells while IL-1beta reduces the IFN production. These immune molecules drive the recruitment of other immune cells such as neutrophils, dendritic cells, B cells, and T cells to the site of infection. T cells are particularly important for controlling *B. pseudomallei*; T cell numbers may fall by up to 90% during infection. When bacteria die in the host, their LPS and core lipopolysaccharides stimulate the release of pro-inflammatory cytokines.

*B. pseudomallei* can remain latent in the human body from 19 to 29 years until it is reactivated during human immunosuppression or stress response. However, the site of bacteria during latent infection and the mechanisms by which they avoid immune recognition for years are both unclear. Amongst mechanisms suggested are: residing in the nucleus of the cell to prevent being digested, entering a stage of slower growth, antibiotic resistance, and genetic adaption to the host environment. Graminomannan (containing neurophils, macrophages, lymphocytes, and multinucleated giant cells) formed at the infection site in melioidosis have been associated with latent infection in humans.

**Diagnosis**

**Culture**

Gastroduodenal fluid (cecal) is the definitive diagnostic of melioidosis. *B. pseudomallei* is not part of human flora. Therefore, any growth of the bacteria is diagnostic of the disease. Blood cultures are the most common samples for diagnosis, as bacteria can be detected in the blood in 80% of melioidosis cases. Other samples include throat, rectal swabs, pus from abscesses, and sputum. Blood agar is used for culture. However, from a patient difficult because in one case series, only 10% of blood cultures were positive. When bacteria do not grow from people strongly suspected of having melioidosis, repeated cultures should be taken as *B. pseudomallei* grows slowly.

**Biochemical tests**

General blood tests in people with melioidosis show low white blood cell counts (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* due to repeated exposure to this organism. Later, an antigen is not produced until many years after initial infection. In IFAT, both *B. pseudomallei* antigen and *B. thailandensis* can be used to quantify the amount of antibodies produced against the organism. Therefore, results have to be interpreted with caution as there could be a false-positive reaction if someone is previously exposed to non-pathogenic *B. thailandensis*. Later, agglutination is useful in screening for suspected *B. pseudomallei* colonization. Commercial ELISA kits for melioidosis no longer available in the market due to low sensitivity to human antibodies and detection.

**Microscopy**

By microscopy, *B. pseudomallei* is seen as gram-negative 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. Immuno-fluorescence microscopy is highly specific for detecting bacteria directly from clinical specimens, but has less than 90% sensitivity. A lateral flow immunoassay has been developed but not extensively evaluated. An increasing number of laboratories use w-Matrix-assisted laser desorption/ionisation (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 may show multifocal nodular lesions. It may also show merging nodules or cavitations. For those with acute melioidosis without the spread to the bloodstream, chest X-ray should show lobe consolidation or cavitations. In chronic melioidosis, the slowly progressing of upper lobe consolidation of the lungs resembles osteomyelitis. Other parts of the body apart from the lungs, especially in the liver and spleen, are generally affected. This has a higher sensitivity when compared with an ultrasound scan of the liver and spleen abscesses, an ultrasound scan shows "target-like" lesions while CT scan shows "honeycombing" signs in liver abscesses. For melioidosis involving the brain, MRI have higher sensitivity than the scan in diagnosing the lesion. MRI shows ring-enhancing lesions for brain melioidosis.

**Prevention**

**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 ceftazidime, meropenem, imipenem, and co-amoxiclav. These drugs are used to inhibit the growth of the bacteria. However, the bacteria can also be resistant to penicillin, ampicillin, tetracycline, and macrolides.

**Intensive phase**

Intravenous ceftazidime is the current drug of choice for treatment of melioidosis and should be administered for at least 10 to 14 days. Meropenem, imipenem, and the cephalosporin-ceftazidime combination (Sulperazone) are also effective. Intravenous amoxicillin-clavulanate (co-amoxiclav) may be used if none of the above four drugs are available. If amoxiclav prevents death from melioidosis as well as ceftazidime, intravenous antibiotics are given for a minimum period of 14 days. The median fever clearance time in melioidosis is 9 days.

**Eradication phase**

Following the treatment of the acute disease, eradication (cure) treatment with co-trimoxazole is the drug of choice and should be used for at least 3 months. For those with neurological conditions, eradication (cure) treatment with co-trimoxazole is the drug of choice and should be used for at least 3 months. Co-trimoxazole should not be used in those with glucose-6-phosphate dehydrogenase deficiency as it can cause haemolysis. Other side effects such as rash, hyperkalaemia, renal dysfunction, and gastrointestinal symptoms should prompt the reduction of co-trimoxazole dosage. Chloramphenicol is no longer routinely recommended for this purpose. Co-amoxiclav 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 fluoroquinolone (e.g., ciprofloxacin) or doxycycline for the eradication phase is ineffective.

In Australia, co-trimoxazole is used in children and pregnant mothers after the first 12 weeks of pregnancy. Meanwhile, in Thailand, co-amoxiclav is the drug of choice and should be used for at least 3 months. If co-trimoxazole is required, other co-amoxiclav is used. The dosing regimen for co-trimoxazole (trimethoprim/sulphamethoxazole) in acute phase is 6/30 mg/kg, up to $240\times 1200$ mg in adults and $240\times 1200$ mg in adults weighing 40 to 60 kg, and $420\times 1600$ mg in adults weighing more than 60 kg, taken orally every 12 hours for 3 months. In children, co-trimoxazole is taken with folic acid (e.g., $200\times 1$ mg to $1$ mg in children). There are also cases where melioidosis is successfully treated with co-trimoxazole for 3 months without going through intensive therapy provided there are only skin manifestations without the involvement of internal organs or sepsis. For those with co-trimoxazole resistance in Australia, ciprofloxacin and doxycycline are recommended. In Australia, co-trimoxazole is used in children and pregnant mothers after the first 12 weeks of pregnancy. Meanwhile, in Thailand, co-amoxiclav is the drug of choice and should be used for at least 3 months. If co-trimoxazole is required, other co-amoxiclav is used. The dosing regimen for co-trimoxazole (trimethoprim/sulphamethoxazole) in acute phase is 6/30 mg/kg, up to $240\times 1200$ mg in adults and $240\times 1200$ mg in adults weighing 40 to 60 kg, and $420\times 1600$ mg in adults weighing more than 60 kg, taken orally every 12 hours for 3 months. In children, co-trimoxazole is taken with folic acid (e.g., $200\times 1$ mg to $1$ mg in children). There are also cases where melioidosis is successfully treated with co-trimoxazole for 3 months without going through intensive therapy provided there are only skin manifestations without the involvement of internal organs or sepsis. For those with co-trimoxazole resistance in Australia, ciprofloxacin and doxycycline are recommended.
**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%.

For those with incomplete treatment, reappearance of symptoms after a period of disease remission can occur. Treatment failures are usually caused by re-infection or re-activation of the latent disease. Risk factors for re-infection include the severity of disease (patients with positive blood cultures or multifocal disease have a higher risk of relapse). An improved understanding of the pathophysiology of the host-parasite relationship and the development of specific diagnostic tests are needed to prevent re-infection and improve patient outcomes.

**Epidemiology**

Melioidosis is an under-recognized disease that remains endemic in many countries. In 2015, the International Melioidosis Society was formed to raise awareness of the disease. In 2016, a statistical model was developed which showed that the number of deaths per year can be estimated from the number of cases occurring in Asia. Melioidosis is endemic in parts of Southeast Asia (including Asia, Thailand, and the Mediterranean basin, the Philippines, and Australia). The true incidence of melioidosis in Africa and Central Europe is more than 0.5% per million population.

Melioidosis is found in all age groups. For Australia and Thailand, the median age of infection is at 50 years; 5 to 10% of the patients are less than 15 years of age. The single most important risk factor for developing melioidosis is diabetes mellitus, followed by hazardous alcohol use, chronic liver disease, and chronic lung disease. Greater than 50% of people with melioidosis have diabetes; diabetes increases the risk of acquiring melioidosis.

In patients with melioidosis, the bacteria colonize the skin or the mucosa, usually through a breach in the skin. The bacteria gain entry into the blood through the cutaneous barrier, leading to dissemination and organ involvement. The bacteria may also enter the body through the respiratory tract, the gastrointestinal tract, or the skin.

**Incubation period**

The incubation period for melioidosis ranges from 6 months to 6 years. Without treatment, the disease progresses from localized skin infection to systemic disease.

**Clinical presentation**

The clinical presentation of melioidosis can vary from a localized skin infection to a life-threatening septicemia. Patients may present with fever, chills, myalgia, and prolonged fever. Other common symptoms include: skin abscesses, pneumonia, and pleural effusion.

**Laboratory diagnosis**

Ceftazidime is the drug of choice for treating melioidosis. Other antibiotics, such as gentamicin or chloramphenicol, are also effective. Supportive care, including intravenous fluids, nutrition, and respiratory support, is essential. Melioidosis is often diagnosed using blood cultures, which are positive in 50% of cases. The bacteria can be grown in the laboratory from positive blood cultures.

**Treatment**

The standard treatment for melioidosis is a three-drug combination of antibiotics. Chloramphenicol (or cephalosporins) is given intravenously, and gentamicin or tobramycin is also used. The treatment duration is typically 8 weeks. A total of 10 to 20% of patients may experience relapse or recurrence after treatment.

**Prognosis**

In 1989, the mortality rate for melioidosis was less than 8%. However, in 2015, the mortality rate increased to 20%. Risk factors include age greater than 45 years, prolonged steroid use, and immunosuppression. Melioidosis is a severe illness, and death can occur within hours to days of hospital admission.

**Prevention**

Prevention of melioidosis includes avoiding exposure to soil, water, and other sources of infection. Personal protective measures, such as wearing gloves and protective clothing, are recommended in endemic areas. The use of antibiotics for prophylaxis is controversial and not recommended by most experts.

**References**


