

Melioidosis

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Melioidosis
Pseudoglanders
Whitmore Disease

Melioidosis is also known as Pseudoglanders or Whitmore Disease.

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Overview

- Organism
- History
- Epidemiology
- Transmission
- Disease in Humans
- Disease in Animals
- Prevention and Control

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In today's presentation we will cover information regarding the organism that causes Melioidosis and its epidemiology. We will also talk about the history of the disease, how it is transmitted, and the clinical signs in humans and animals. Finally, we will address prevention and control measures for Melioidosis.


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The Organism

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Organism

- *Burkholderia pseudomallei*
 - Aerobic, gram-negative motile bacillus
 - Found in water and moist soil
 - Opportunistic pathogen
 - Produces exotoxins
 - Can survive in phagocytic cells
 - Latent infections common



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“Melioidosis” is derived from the Greek word meaning glanders-like illness or distemper of the asses. It is caused by the bacterium *Burkholderia pseudomallei* (previously called *Pseudomonas pseudomallei*). It is an aerobic, gram-negative motile bacillus found in water and moist soil and is endemic in tropical and subtropical countries. It is an opportunistic pathogen that produces exotoxins. Because it can survive in phagocytic cells, latent infections are a common disease manifestation.

[Image from: CDC/ Courtesy of Larry Stauffer, Oregon State Public Health Laboratory.]

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History

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History

- 1912, Burma
- Alfred Whitmore
- Organism isolated in humans
 - Glanders-like disease
 - Colony growth differed
 - No equine exposure
 - “Whitmore” disease



Alfred Whitmore 1876-1941

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In 1912, Captain Alfred Whitmore (a pathologist) and his assistant C. S. Krishnaswami noted a disease similar to glanders in emaciated morphine addicts in Rangoon, Burma. However, the patients had no history of equine exposure and the colony morphology of the organism differed from that of glanders (*Burkholderia mallei*). This led to the discovery of a new organism and disease, *Burkholderia pseudomallei* and melioidosis, respectively. Melioidosis is also called “Whitmore” disease, in his honor. Whitmore further documented the pathology of the disease from subsequent cases, most of whom were morphine addicts. He determined that the disease was a consequence of the general debility and wasting found in these patients, rather than from the direct inoculation of the organism.

[Image from: illustrated history of tropical diseases, the Wellcome Trust. Edited by FEG Cox.]


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History

- 1913, Malaysia
- Stanton and Fletcher
- “Distemper-like” outbreak in animals
 - Isolated *B. pseudomallei*
- Pioneered serological tests for diagnosis



Ambrose Thomas Stanton



William Fletcher

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In 1913, in Malaysia, a fatal ‘distemper-like’ outbreak occurred in animals at the Institute for Medical Research. Although the bacterium was isolated, it was not until 1917 that it was identified as *B. pseudomallei* (then called *Bacillus pseudomallei* or Whitmore’s bacillus). This was discovered by Ambrose Thomas Stanton, a bacteriologist, and William Fletcher, a pathologist. Over the next decade, they documented 39 human cases and several cases in wild and domesticated animals. They also pioneered the serological tests used for diagnosing the disease. During this time the disease was also found in Vietnam, Sri Lanka and Indonesia. Stanton and Fletcher originally associated rodent excreta to the zoonotic transmission. This has since been disproved.

[Image from: illustrated history of tropical diseases, the Wellcome Trust. Edited by FEG Cox.]

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History

- 1948-1954, Indo-China
 - Over 100 French soldiers
- 1973, Vietnam
 - Over 300 American soldiers
 - “Vietnamese time bomb”
 - Infections reoccurred after latent period
 - Military dogs in Vietnam also affected
 - Fever, myalgia, dermal abscesses



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Melioidosis has been recognized in soldiers stationed in endemic areas. At least 100 cases among French forces in Indochina were reported from 1948 through 1954 during the war of Vietnamese independence from French colonial rule. As American troops replaced the French, they were also affected. By 1973, over 300 cases of melioidosis had been diagnosed among American soldiers stationed in Vietnam. Most cases were acquired by direct contact of wounds with mud and water. However, an unusual number of cases among helicopter crews suggested that inhalation of the organism could also cause infection. Military dogs stationed in Vietnam were also affected and developed fever, myalgia and dermal abscesses from the organism. The latent nature of melioidosis was discovered as many soldiers had reoccurrence, often fatal, of infection after returning to

the States. For this reason, melioidosis has been called the “Vietnamese time bomb”. The current record for the latent period is 26 years, and cases are still occurring in Vietnam veterans today. An estimated 225,000 Americans were potentially exposed while in Vietnam. Unfortunately, a good test to determine latent infection is not currently available.

[Image from: <http://commons.wikimedia.org>]

S l i d e 9	<p style="text-align: center;">History</p> <ul style="list-style-type: none"> • 1970s, France <ul style="list-style-type: none"> – Numerous horses and zoo animals affected – Melioidosis in temperate climates • 1989 <ul style="list-style-type: none"> – Effective antibiotic treatment identified <p style="font-size: small; text-align: center;">Center for Food Security and Public Health, Iowa State University, 2011</p>	<p>Since its discovery, <i>Burkholderia pseudomallei</i> has been found worldwide. It is most prevalent in tropical and subtropical regions. However in the mid-1970’s an outbreak occurred in France. It was first discovered during a necropsy of a horse. Samples from the liver and spleen grew the organism. Later the soil was found to be contaminated with the organism. An intensive disinfection and animal slaughter program was initiated. This outbreak shows that melioidosis can be established and transmitted within temperate regions. Acute melioidosis was highly fatal prior to antibiotic therapy. In 1989, the use of ceftazidime for treatment of melioidosis was found to decrease mortality in these cases by 50%.</p>
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S l i d e 1 0	<p style="text-align: center;">Transmission</p>	
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S l i d e 1 1	<p style="text-align: center;">Transmission</p> <ul style="list-style-type: none"> • Wound infection <ul style="list-style-type: none"> – Contact with contaminated soil or water • Ingestion <ul style="list-style-type: none"> – Contaminated water • Inhalation <ul style="list-style-type: none"> – Dust from contaminated soil • Rarely <ul style="list-style-type: none"> – Person-to-person – Animal-to-person <p style="font-size: small; text-align: center;">Center for Food Security and Public Health, Iowa State University, 2011</p>	<p>Transmission of <i>Burkholderia pseudomallei</i> can occur in several ways. The most common way is through contact of skin wounds with contaminated soil or water. Additional routes of infection include aspiration or ingestion of contaminated water and inhalation of dust from soil. Transmission between infected animals and/or infected people is very rare. Person-to-person transmission has been described rarely, generally to family members in close contact (e.g. family members who nursed patients). Sexual transmission has also been suggested in some cases. Vertical transmission has rarely been proven, although a few cases were described in newborns. One infant may have contracted the bacteria by nursing culture-positive breast milk.</p>
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Epidemiology

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Epidemiology

- Endemic in tropics and subtropics
 - Southeast Asia, China, India, parts of Australia
- Also reported in:
 - Caribbean, Middle East, South America, Singapore, Taiwan
 - May be present in Africa
- U.S. cases linked with travel abroad


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Melioidosis occurs in several areas in the tropics and subtropics. Most endemic regions are between the latitudes of 20 °N and 20 °S. Melioidosis is endemic in Southeast Asia, China, the Indian subcontinent and parts of Australia. It has also been reported from the Caribbean, the Middle East, South America, Singapore and Taiwan. The situation in Africa is uncertain. Although isolated cases were reported from some African countries in the past, melioidosis is not a commonly reported disease in Africa. In the U.S., isolated cases have also been reported in Hawaii and Georgia, however, most were associated with travel abroad.

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Distribution of Melioidosis



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On the map, the orange areas indicate endemic areas while the light blue areas indicate intermittent cases.


[Image from: illustrated history of tropical diseases, the Wellcome Trust. Edited by FEG Cox.]

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Epidemiology

- Clinical disease uncommon
 - In endemic areas
 - Antibodies in 5 to 20% agricultural workers
 - No history of clinical disease
- Wet season
 - Heavy rainfall
 - High humidity or temperature



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Clinical disease is relatively uncommon. In certain endemic areas, 5 to 20% of agricultural workers have antibodies to *B. pseudomallei*; however, they have not shown overt disease. Outbreaks and cases typically occur during the wet season or after periods of heavy rainfall in areas with high humidity or temperature.

[Bottom image from: illustrated history of tropical diseases, the Wellcome Trust. Edited by FEG Cox.]

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Disease in Humans

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Human Disease

- Incubation period: <1 day to years
 - Latent infection
- Most infections asymptomatic
- Clinical forms
 - Acute pulmonary infection
 - Most common
 - Focal infection
 - Septicemia
 - Neurological (rare)


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Melioidosis in humans has a variable incubation period from less than 1 day (after very high exposure) to several months to many years. Due to the ability of *B. pseudomallei* to survive in phagocytic cells, many cases of melioidosis occur after a latent period. Immunosuppressive events or chronic diseases, such as diabetes mellitus or renal disease, have been reported to be a risk factor for disease reoccurrence. Based on serologic studies, most infections are asymptomatic. When clinical disease develops, many manifestations can occur. The most common form is acute pulmonary infection. Additionally, melioidosis can be limited to a focal infection. Localized lesions may occur in the skin (as a result of infected wounds) or various internal organs (as a result of septicemic spread). Many times focal infections become chronic conditions. The disease can also occur in a severe septicemic form. This can either be nondisseminated (only involving one organ) or disseminated. Finally, on rare occasions, melioidosis can produce neurological disease.

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Acute Pulmonary Infection

- Most common form
- High fever, headache
- Dull aching chest pain
- Cough, tachypnea, rales
- Chest X-rays
 - Upper lobe consolidation
 - Nodular lesions
 - Pleural effusion


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As previously mentioned, most infections of melioidosis are usually asymptomatic. However of clinical infections, pulmonary infection is the most common form seen. Infection may occur either through inhalation or by septicemic spread of the organism to the lungs. It is demonstrated by a high fever, headache and pneumonia with caseous lesions. A dull aching chest pain, cough, tachypnea, and rales can also occur. Chest x-rays may show upper lobe consolidation, nodular lesions or pleural effusion.

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Focal Infection

- Abscess or granuloma formation
 - Skin
 - Bone and/or muscle
 - Joints
 - Internal organs
 - Genitourinary
 - Nervous system (infrequent)

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Focal melioidosis involves abscess formation in various tissues or organs. The lesions can be either acute (abscess) or chronic (granulomatous). Infection typically occurs from a contaminated wound or trauma. Skin, bone, muscle and joints may be affected this way. Hematogenous spread from wounds may then further infect internal organs such as the liver, spleen, heart, and genitourinary tract. Infrequently infection of the nervous system may occur, resulting in meningitis, encephalitis and motor paralysis.

[Image from: illustrated history of tropical diseases, the Wellcome Trust. Edited by FEG Cox.]

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Septicemic Melioidosis

- Acute onset
 - High fever, tachypnea, dyspnea, myalgia, hepatosplenomegaly, septic shock
- Concurrent disease
- Mortality
 - 90% without treatment
 - 50% with treatment

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Septicemic melioidosis is acute in onset and fatal without treatment. Clinical signs for this form of melioidosis include high fever, tachypnea and dyspnea, myalgia, hepatosplenomegaly, and septic shock. Additionally, disorientation, severe headache, pharyngitis, diarrhea and pustular skin lesions may be noted. This form of melioidosis is rapidly progressive with a mortality of 90% without treatment and 50% with treatment. It has been reported that the onset of septicemic or chronic melioidosis is much more common in persons suffering from a debilitating illness, such as diabetes mellitus. In one study conducted in Thailand, 17 of 29 patients with disseminated melioidosis were found to be suffering from concurrent diabetes mellitus.

Melioidosis

S 1 i d e 2 1	<h3>Diagnosis and Treatment</h3> <ul style="list-style-type: none">• Diagnosis<ul style="list-style-type: none">– Isolation of organism– Various serological tests• Treatment<ul style="list-style-type: none">– Systemic antibiotics<ul style="list-style-type: none">• Trimethoprim sulfa• Ceftazidime– Surgical drainage of skin wounds• No vaccine available <p style="text-align: right; font-size: small;">Center for Food Security and Public Health, Iowa State University, 2011</p>	<p>Diagnosis of melioidosis is difficult. It has been called the great imitator because there are no pathognomonic lesions. Isolation of the organism from blood, sputum, tissues or wound exudates can help to diagnose the disease. Serological tests for titers may also be used for diagnosis. Serological tests available include agglutination tests, indirect hemagglutination, complement fixation, immunofluorescence and enzyme assays. Improved methods for rapid diagnosis are being evaluated. Cross-reactions may occur in serologic tests with <i>Burkholderia mallei</i> (causative agent for glanders). <i>B. pseudomallei</i> is variably susceptible to antibiotics. Long-term treatment and multiple drugs will be necessary for chronic and severe cases. Relapses, as soon as 6 months after treatment, are common. Surgical drainage of skin wounds can be effective for localized infection. Currently there is no vaccine available, however, experimental vaccines used in dolphins and other cetaceans reduced mortality.</p>
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S 1 i d e 2 2	<h3>Animals and Melioidosis</h3>
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S 1 i d e 2 3	<h3>Species Affected</h3> <ul style="list-style-type: none">• Severe disease in sheep, goats• Pigs (chronic form)• Occasional infection<ul style="list-style-type: none">– Cattle, horses, dogs, cats, buffalo– Monkeys, rodents, camels, alpacas– Birds, tropical fish• Incubation period<ul style="list-style-type: none">– Variable, days to years <p style="text-align: right; font-size: small;">Center for Food Security and Public Health, Iowa State University, 2011</p>	<p>Many animal species are affected by melioidosis; infection generally results from grazing on contaminated soil or drinking contaminated water. Infected animals can excrete the organism in saliva, pus, urine, and feces, leading to contamination of the environment. Severe disease occurs in sheep, goats; pigs tend to develop chronic disease. Cases have occurred in cattle, dogs, cats, horses, buffalo, rodents, camels, alpacas, various nonhuman primates, some species of birds, and tropical fish, just to name a few. The incubation period for animals is variable ranging from a few days to many years. Some abscesses are carried asymptotically.</p>
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S 1 i d e 2 4	<h3>Sheep, Goats, and Pigs</h3> <ul style="list-style-type: none">• Sheep<ul style="list-style-type: none">– Severe respiratory disease– Arthritis, lameness– Neurological disease• Goats<ul style="list-style-type: none">– Moderate respiratory disease– Lameness, mastitis, abortion• Pigs<ul style="list-style-type: none">– Chronic – splenic abscesses <div style="display: flex; justify-content: space-around;"></div> <p style="text-align: right; font-size: small;">Center for Food Security and Public Health, Iowa State University, 2011</p>	<p>Pulmonary melioidosis is common in sheep; typical symptoms are fever, severe coughing, respiratory distress and profuse mucopurulent yellow nasal and ocular discharge. Some sheep become arthritic and lame. In others, the only symptoms may be fever and generalized weakness. Neurological signs including circling, incoordination, blindness, hyperesthesia, nystagmus and spasms have also been reported. Orchitis with testicular nodules can occur in rams. In goats, respiratory disease is less severe than in sheep, and coughing is not a prominent sign. Progressive emaciation, lameness or hindleg paresis, and abortions have also been reported in goats. Mastitis and aortic aneurysms may be particularly common in this species. Pigs may be relatively resistant to melioidosis when husbandry and nutrition are good. Adult pigs tend to develop chronic infections with few symptoms; however, enlarged lymph nodes (particularly the submandibular nodes) may be palpable. Progressive emaciation, neurological signs, incoordination, multiple skin ulcers and diarrhea have also been reported. Young pigs can develop</p>
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acute septicemia with fever, anorexia, coughing and nasal and ocular discharge. Occasional abortions or stillbirths have been seen in sows, and orchitis can occur in boars. In endemic regions, asymptomatic splenic abscesses are often found in pigs at slaughter.

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Other Species

- Horses and cattle
 - Neurologic signs
 - Respiratory disease
- Dogs (rare)
 - Dermal abscesses, epididymitis, lameness, leg swelling
- Rodents
 - Very susceptible



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Melioidosis in other species is sporadic and occurs as isolated cases. Clinical signs for horses include fever, anorexia, dyspnea, mild cough and occasionally, purulent nasal discharge. Cattle are rarely affected but may show similar signs as horses. Canine melioidosis is rarely seen, however, seven cases in U.S. military dogs in Vietnam were reported. Clinical signs may include fever, dermal abscesses, epididymitis, lameness and leg swelling. Postmortem lesions in these dogs consisted of multiple abscesses of the skin, lungs, liver and epididymitis. Rodents are very susceptible to melioidosis. Guinea pigs and hamsters develop fatal disease when as few as 10 organisms are injected intraperitoneally. These animals are frequently used in melioidosis research and for testing soil for contamination by the organism.

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Prevention and Control

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Control and Prevention

- Avoid contact with soil and water in endemic areas
 - Husbandry practices
 - Drinking water
 - Use fresh sources
 - Chlorination effective
- Use care during necropsies
- Thorough cleaning of wounds
- No vaccine available

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Melioidosis is usually acquired from the environment, particularly after contact with soil or water. To minimize contact with dirt, animals can be raised on wooden slats, concrete or paved floors. Providing safe drinking water is important in endemic areas. *B. pseudomallei* is particularly common in muddy water, and it is less likely to be found in fresh or clear water. Although small numbers of bacteria may survive treatment, chlorination of the water supply decreases the risk of infection. Care should also be taken during animal necropsies. This is especially important for immunocompromised persons or anyone with a chronic medical condition such as diabetes mellitus or renal disease. If wounds do become contaminated with soil or water, thorough cleaning of the wound with disinfectant soap and water will help to prevent infection. There is no licensed vaccine for melioidosis available.

Melioidosis

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Melioidosis as a Bioweapon

- CDC Category B Agent
 - Moderately easy to disseminate
 - Moderate morbidity
 - Low mortality
 - Specific diagnostics required
- Very stable in the environment
- Killed very easily by heat

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Melioidosis is listed by the CDC as a Category B potential bioterrorism agent. This indicates agents which are moderately easy to disseminate. Additionally, moderate morbidity and low mortality is noted with these agents. Specific diagnostics will be required in the event of an attack. As an agent, *Burkholderia pseudomallei* can be very stable in the environment, persisting for months. However, it can be killed very easily by heat.

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Additional Resources

- CDC
 - National Center for Zoonotic, Vector-Borne, and Enteric Diseases
 - <http://www.cdc.gov/nczved/divisions/dfbmd/diseases/melioidosis/>

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Additional Resources

- World Organization for Animal Health (OIE)
 - www.oie.int
- U.S. Department of Agriculture (USDA)
 - www.aphis.usda.gov
- Center for Food Security and Public Health
 - www.cfsph.iastate.edu
- USAHA Foreign Animal Diseases ("The Gray Book")
 - www.usaha.org/pubs/fad.pdf

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Authors: Glenda Dvorak, DVM, MS, MPH, DACVPM; Radford Davis, DVM, MPH, DACVPM
Reviewers: Gayle Brown, DVM, PhD, Bindy Sorrsin, BA; Jared Voge, MS; Kerry Leedom Larson, DVM, MPH, PhD

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