

CD Alert

National Centre for Disease Control,
Directorate General of Health Services, Government of India

April 2019

MELIOIDOSIS

INTRODUCTION

Melioidosis is an infectious disease caused by a Gram negative bacterium, *Burkholderia pseudomallei*. It is seasonal, with 75–85% of cases occurring during the rainy season. The clinical spectrum of illness is diverse and ranges from pulmonary consolidation and localized abscesses to rapidly fatal septicemia. Melioidosis has a high case fatality rate (CFR) ranging from 16% to 50% in known endemic regions. Several risk factors are associated with melioidosis including immunosuppressive conditions such as diabetes and other diseases like chronic kidney disease, and certain drug treatments. Diabetes mellitus is the most common risk factor and increases the relative risk of melioidosis. The disease is endemic in Southeast Asia and Northern Australia. It is classified as category B bioterrorism agent.

HISTORICAL BACKGROUND

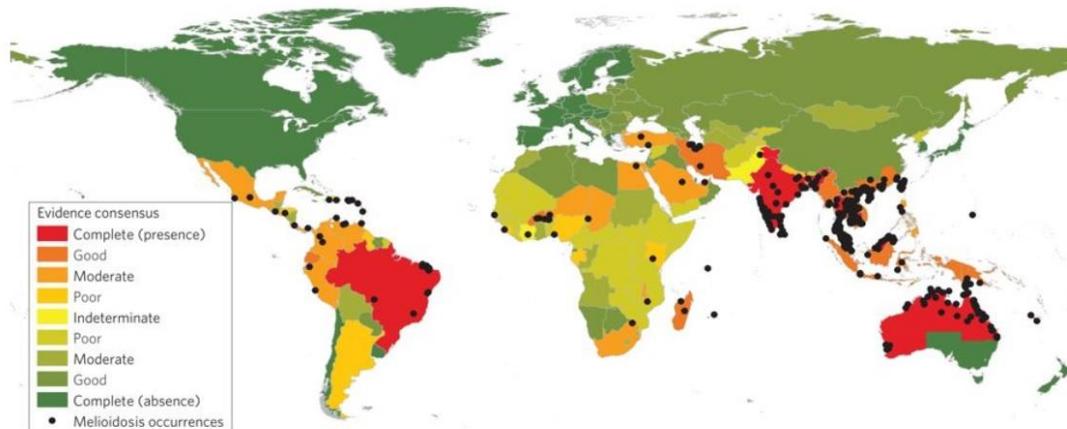
Alfred Whitmore and CS Krishnaswami first described melioidosis as a “Glanders-like disease” among morphine addicts in Rangoon in 1911. Stanton and Fletcher in 1932 proposed the name “melioidosis”, derived from the Greek melis meaning “a distemper of asses” and suffixes -oid (similar to) and -osis (a condition).

EPIDEMIOLOGY

Burden Worldwide

Melioidosis is an infectious disease endemic in Southeast Asia, northern Australia, much of the Indian subcontinent, southern China, Hong Kong, and Taiwan (Figure 1). In northern Australia and northeast Thailand, it accounts for 20% of all community-acquired septicemias. It is the most common cause of severe community-acquired pneumonia in northern Australia.

Figure 1: Global distribution of *Burkholderia pseudomallei* and burden of melioidosis



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Burden in India

Melioidosis is prevalent in many parts of India, but is under-diagnosed and under-reported. The first indigenous case from India was detected in Mumbai in 1991. Improvement in diagnostic facilities has led to identification of more cases of melioidosis, along the coastal regions from the states of Karnataka, Kerala, and Tamil Nadu. Suitable environment, huge magnitude of diabetes mellitus and big rural setting make India vulnerable for melioidosis. India was predicted to have the highest burden for the disease (20,000-52,000 new cases/year with an estimated mortality of 32,000 per year).

Asymptomatic sero-conversion to the extent of 29% among adults 18-65 years was found in sero-surveillance studies in Udupi, South India. This suggests that exposure to *Burkholderia pseudomallei* is relatively common, although cross-reaction with closely related organisms cannot be excluded.

Epidemiology

Agent

Burkholderia pseudomallei is a saprophytic, oxidase-positive, Gram-negative, motile bacillus, showing bipolar staining. *Burkholderia pseudomallei* is an environmental saprophyte found in soil and water, and can infect humans or animals.

Host

The highest risk for melioidosis exists in military personnel, adventure travellers, eco-tourists and workers in construction, rice farming, fishing, and forestry whose contact with contaminated soil or water may expose them to the bacteria. High risk groups categories are:

1. Diabetes mellitus
2. Chronic Kidney disease
3. Alcohol abuse
4. Liver disease
5. Thalassemia
6. Chronic lung diseases, including cystic fibrosis, chronic obstructive pulmonary disease (COPD), and bronchiectasis

7. Cancer or another condition that affects immune system function but not HIV
8. People older than age 40 years

Modes of Transmission

Percutaneous inoculation, aerosol inhalation and ingestion are important routes of transmission. Some activities that increase the risk of acquiring melioidosis infection are:

1. Touching contaminated soil with the hands or feet, especially if there are small cuts in the skin.
2. Drinking contaminated water that has not been chlorinated
3. Breathing in contaminated dust or water droplets
4. Exposure to severe weather events such as tropical monsoon storms, cyclones, hurricanes and typhoons

Person to person transmission is very rare. Animal to human or insect to human transmissions are not documented. The bacteria can live for years in contaminated soil and water.

CLINICAL FEATURES

Melioidosis can result in acute or chronic disease, >85% of presentations are acute with less than or equal to 2 months of symptoms. The symptoms of melioidosis vary depending on the type of infection.

Melioidosis may be a localized disease or result in a disseminated disease. Disseminated disease can present with pneumonia, abscesses in liver, spleen, kidney, prostate, skin and subcutaneous tissue, septic arthritis and osteomyelitis, fever of unknown origin or chronic suppurative infection following haematogenous spread. It may also present as suppurative parotitis, submandibular abscesses and lymphadenitis (in children) with fever being the commonest presentation.

Meningoencephalitis, subdural empyema are rare presentations. Sometimes it may result in bacteremia, septic shock and death.

Chronic presentation of melioidosis may mimic tuberculosis, with fever, weight loss, productive cough and upper lobe infiltrate, with or without cavitation.

Burkholderia pseudomallei infection can result in latent infections, capable of reactivation years later or may result in asymptomatic sero-conversion following subclinical infection.

The incubation period is generally 1–21 days, but may extend to months or years; generally symptoms appear 2–4 weeks after exposure. With a high inoculum, symptoms can develop in a few hours. More than 50% of cases present with pneumonia.

Pulmonary infection

The most common presentation is pulmonary infection. It can be mild, like bronchitis, or severe, including pneumonia and leading to acute respiratory distress syndrome (ARDS) and/or septic shock. Other chest manifestations include pleural effusion and mediastinal lymphadenopathy.

Symptoms of pulmonary infection may include:

- Productive cough (with purulent sputum or respiratory secretions)
- Chest pain during breathing
- Breathing difficulty
- High fever
- Headache and general muscle tenderness
- Weight loss
- Shortness of breath
- Hemoptysis

Bloodstream infection/ Septicemic melioidosis

Without timely, appropriate treatment, a pulmonary infection can progress to septicemia. It is the most serious form of melioidosis and can result in septic shock, multi organ dysfunction syndrome (MODS) and death.

Septic-shock usually occurs quickly, though it may develop more gradually in

some. It is characterized by persistent hypotension despite adequate fluid resuscitation and requiring vasopressors to maintain mean blood pressure >65mm Hg. Its symptoms include:

- High grade fever, especially with chills and sweating (rigors)
- Chest pain, breathing difficulty, including shortness of breath (if associated with pneumonia)
- Bone and joint pain, and muscle tenderness
- Local ulcers or sores with pus on the skin (if associated with localized infection)
- Deep-seated abscesses in the liver, spleen, muscle, prostate or salivary glands
- Mental disorientation
- Decreased urine output
- Abnormal bleeding
- Jaundice

Localised infection

This type of melioidosis affects the skin and the organ systems that are the portal of entry of the bacteria. Localised infections can spread to the bloodstream. Symptoms may include:

- Pain or swelling in a contained (localized) area, such as the parotid glands, located below and in front of the ear
- High grade fever
- Ulcerations or abscesses on, or just below, the skin — these may start as firm, grey or white nodules that become soft and inflamed, and then look like wounds caused by flesh-eating bacteria

Disseminated infection

In this type of melioidosis, more than one organ may be affected. Symptoms depend on the involvement of the organs and may include:

- High grade fever
- Weight loss
- Abdominal or chest pain
- Muscle or joint pain
- Headache
- Seizures

The liver, lung, spleen, and prostate are the most common organs affected. Less commonly, infections occur in the joints, bones, lymph nodes, or brain.

Infection in animals

Animals acquire infection directly from contaminated water and soil or through infected animals' milk, urine, faeces, nasal secretions, and wounds.

The most commonly affected animals are: sheep, goats and pigs. Cases have also been reported in horses, cats, dogs, cattle, chickens, marsupials, tropical fish, iguanas, and other animals.

CASE DEFINITIONS

Probable: A case that meets clinical and epidemiological criteria

- **Clinical Criterion:** Presence of fever with acute onset sepsis/ community acquired pneumonia/ skin and soft tissue infections/ deep seated abscesses (liver and spleen, parotid, prostate)/ bone and joint infections (osteomyelitis, septic arthritis).

AND

Any of the major risk factors like diabetes, chronic alcoholism, chronic kidney disease

- **Epidemiological criterion:** Resident of or history of travel to a melioidosis-endemic region or exposure to contaminated soil/ water

Confirmed case: Probable case confirmed by culture or PCR

Laboratory Diagnosis of Melioidosis

- Blood
- Pus/ aspirate/tissue
- Sputum/ ET aspirate/ BAL
- CSF
- Urine

Processing: It can grow on routine culture media such as blood agar or MacConkey media usually after 2-4 days of incubation at 37°C. However, selective mediums such as Ashdown's medium/CVC-50 broth can be used for enrichment. Typical colony morphology may be subjected to preliminary identification with gram stain, oxidase test. It is identified as member of non-fermenters. Arginine positive, lysine negative exhibiting resistance to aminoglycosides, colistin and polymyxin but showing sensitivity to amoxicillin clavulanate may be strongly suggestive of *B.pseudomallei*. The commercial rapid automated systems may not be fully reliable. A validated PCR (type III secretion system gene) performed by quality assured laboratory can provide reliable results. The bacteria are usually susceptible to Ceftazidime, Meropenem, Cotrimoxazole and Doxycycline.



Non Hemolytic colonies of *Burkholderia pseudomallei* on Blood Agar



Moist, light pink colonies of *B.pseudomallei* on MacConkey Agar plate with metallic sheen

TREATMENT

B. pseudomallei is intrinsically **resistant** to penicillin, ampicillin, first- and second-generation cephalosporins, gentamicin, tobramycin, streptomycin, macrolides and polymyxins, and **susceptible** to various newer β -lactam antibiotics, especially ceftazidime, imipenem, meropenem, piperacillin, amoxicillin–clavulanate, and doxycycline with various degrees of bactericidal activity.

Considering the growing problem of antimicrobial resistance, the antibiotic susceptibility test should be performed for optimal treatment of melioidosis.

Treatment may vary depending on the type of melioidosis and is divided into two stages, an intravenous high-intensity phase and an eradication phase to prevent recurrence.

Intensive phase (Minimum 2 weeks)

Ceftazidime: 2-3 gm (50mg/kg/dose upto 2 gm in children) 8 hourly iv for minimum 2 weeks (10-14 days)

PLUS Cotrimoxazole: 10/50 mg/kg (upto 320/1600 gm) every 12 hours, in cases of neurological melioidosis, osteomyelitis and septic arthritis, skin, soft tissue and genitourinary infection.

Meropenem (as an alternative to Ceftazidime): 1gm [or 25 mg/kg] every 8 hourly intravenous for minimum 2 weeks, especially in patients with neurological involvement, persistent bacteraemia or in intensive care unit.

Eradication phase

Follow the treatment of the acute disease, eradication (or maintenance) treatment with cotrimoxazole is recommended to be used for 12 to 20 weeks to reduce the rate of recurrence.

Cotrimoxazole:

1	Adult >60 kg:	160 mg/800mg tablets; two tablets every 12 h
2	Adult 40–60 kg:	80 mg/400mg tablets; three tablets every 12 h
3	Adult <40 kg:	160 mg/800mg tablets; one tablet every 12 h OR 80 mg/400mg tablets; two tablets every 12 h
4	Child	8mg/40mg per kg; max. dose 320 mg/1600mg every 12 h

In contraindicated cases, cotrimoxazole is replaced by doxycycline or amoxicillin-clavulanate.

Surgical treatment

Surgical drainage is usually indicated for prostatic abscesses and septic arthritis, may be indicated for parotid abscesses or a large single hepatic abscesses. Other internal abscesses rarely need to be drained as they frequently resolve with medical therapy. Osteomyelitis may need aggressive and often repeated surgical debridement of the necrotic bone, especially when appropriate medical treatment is delayed. Mycotic aneurysms may need lifelong suppressive therapy with cotrimoxazole, especially in patients who have received prosthetic grafts.

PREVENTION

Melioidosis is potentially preventable; efforts should be made towards raising awareness especially in endemic areas.

Recommendations for endemic areas:

1. Educate paddy field workers regarding appropriate personal protective measures like gumboots.

- Educate health care provider for early diagnosis and treatment of melioidosis. Elderly paddy field workers suffering with fever, cough not responding to treatment with diabetes as comorbidity should also be investigated for melioidosis.

VACCINATION

At present, there is no vaccine available for melioidosis.

PROGNOSIS

With appropriate antibiotics, the mortality rate is about 10% for uncomplicated cases but up to 80% for cases with bacteraemia or severe sepsis.

Without access to appropriate antibiotics, the septicemic form of melioidosis exceeds 90% mortality rate. Recurrence occurs in 10 to 20% of patients, but with cotrimoxazole eradication therapy, this can be reduced to 4%.

CONCLUSION

Clinicians and microbiologists should be made aware about this pathogen and its frequent misdiagnosis. Availability of validated diagnostic reagents for immunological and molecular tests and expansion of databases of commercial identification systems will likely remove the major hurdles in correct identification of *Burkholderia pseudomallei*.

Development of rapid point of care tests such as lateral flow immunoassay would also prove to be helpful in rapid identification of isolates and direct detection from clinical specimens, especially in low-resource settings.

EXPERT GROUP MEETING

The expert group meeting for the preparation of Guidelines for melioidosis was held on 23 April 2019 at NCDC Delhi.

ACKNOWLEDGEMENT

We would like to express our sincere gratitude to Dr. Chiranjay Mukhopadhyay, Professor & Associate Dean, Department of Microbiology, Dr. Vandana KE, Professor, Department of Microbiology, KMC Manipal, Dr Kavitha Saravu, Professor of Medicine & Unit Chief, Kasturba Medical College, Manipal, Mr. Tushar Shaw, Dr. Chaitanya TAK (IMRF, MAHE, Manipal) and Dr Rama Chaudhry, Prof, Dept of Microbiology, AIIMS, New Delhi for their scientific contribution in preparation of this document. Further our gratitude is extended to expert from WHO-SEARO Dr Gyanendra Gongal, State Surveillance Units of Karnataka, EIS Officers, NCDC, Delhi and Officers from Zoonosis Division, NCDC, Delhi.

....about CD Alert

CD Alert is a technical bulletin of the National Centre for Disease Control, Directorate General of Health Services, Govt of India, to disseminate information on various aspects of communicable diseases to medical fraternity and health administrators. The bulletin may be reproduced, in part or whole, for educational purposes.

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