Chapter 5
Melioidosis: The Great Mimicker

R Chandni

ABSTRACT
Melioidosis is an infectious disease of humans and animals, caused by Burkholderia pseudomallei, a Gram-negative soil bacterium. It is predominantly a disease of tropical climates with reports from various parts of India; lately, it has been listed as an important potential bioterrorism weapon. The bacteria causing melioidosis is found in contaminated water and soil and spreads to humans through inhalation or inoculation. Melioidosis is probably underreported in India. Early diagnosis and treatment is essential for better outcome. With its protean clinical manifestations ranging from asymptomatic infection to overwhelming sepsis, the diagnosis of melioidosis needs a high index of suspicion along with the isolation and identification of B. pseudomallei from clinical specimens. The diagnosis can be made easily, even in nonendemic areas, if duly considered by the clinicians and microbiologists.

INTRODUCTION
Melioidosis is a clinically diverse disease caused by the facultative intracellular Gram-negative bacterium, B. pseudomallei, an environmental saprophyte which is widely distributed in soil and fresh surface water in endemic regions. Melioidosis is a disease known as “the great mimicker” because of its similarity to other infections and the difficulty with its diagnosis.1

BACKGROUND AND HISTORY
Alfred Whitmore and CS Krishnaswami first described melioidosis as a “Glanders-like disease” among morphine addicts in Rangoon in 1911.2 Stanton and Fletcher in 19323 proposed the name “Melioidosis”, derived from the Greek melis meaning “a distemper of asses” and suffixes -oid (similar to) and -osis (a condition). Melioidosis is thus a condition similar to Glanders. This Gram-negative environmental bacterium has been previously known as Bacillus pseudomallei and since 1992 as Burkholderia pseudomallei.

EPIDEMIOLOGY
Melioidosis is an infectious disease endemic in southeast Asia, northern Australia, much of the Indian subcontinent, southern China, Hong Kong, and Taiwan (Figure 1).4 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.

The highest risk for melioidosis exists for military personnel, adventure travelers, ecotourists and construction workers whose contact with contaminated soil or water may expose them to the bacteria. B. pseudomallei has been isolated from ill troops of all nationalities who served in areas with endemic disease, with a latency of as long as 62 years and hence it is called the “Vietnamese time bomb”.5

Melioidosis is prevalent in many parts of India, but is underdiagnosed and under-reported.6 This was reported in a 9-year-old boy in 19957 from Vellore. Case series of melioidosis has been reported from Vellore8 and from coastal regions of Kerala and Karnataka. There are also other reports from India.9

B. pseudomallei are oxidase-positive, motile Gram-negative bacillus, showing bipolar staining. Currie Bj et al.10 have documented the incubation period for melioidosis from defined inoculating events to be 1–21 (mean 9) days. While most cases are considered to be from percutaneous inoculation,17 inhalation is also a well-recognized mode of infection. Melioidosis is highly seasonal, with 75–85% of cases occur during the rainy season and are often more severely ill after heavy monsoonal rainfall.18 It is a category B bioterrorism agent.

CLINICAL MANIFESTATIONS
Melioidosis can be categorized as an acute or localized infection, acute pulmonary infection, acute bloodstream infection or disseminated infection. Subclinical infections are also possible. Melioidosis may present as localized infection (such as cutaneous), pneumonia, meningoencephalitis, visceral abscesses (liver, spleen, kidneys, prostate), septic arthritis (Figure 2), osteomyelitis, fever of unknown origin (FUO) or chronic suppurative infection. The latter may mimic tuberculosis, with fever, weight loss, productive cough and upper lobe infiltrate, with or without cavitation. Melioidosis may also present as suppurative parotitis (in children). 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. Overall, about half of the patients are bacteremic and up to a quarter can present with septic shock. Without appropriate treatment, case-fatality ratio may reach 90% within 48 hours of developing symptoms. Although healthy people may get melioidosis,19 the major risk factors are diabetes, excessive alcohol use, liver disease, chronic renal disease, chronic lung disease, urolithiasis, thalassemia, cancer or another immunosuppressing condition not related to human immunodeficiency virus (HIV) and occupational exposure. The use of steroids increases the risk of melioidosis and it includes steroid-containing herbal remedies (yua chud) in Thailand.20 Morbidity and mortality of melioidosis are also higher in people with major risk factors.
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DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Melioidosis must be considered as a diagnostic possibility in patients presenting with fever, weight loss, cough, lymphadenopathy, hepatosplenomegaly, abscesses, anemia or sepsis. Among infections causing FUO, it must be thought of after excluding tuberculosis and other common infections presenting as abscesses.

Laboratory Diagnosis of Melioidosis

An early diagnosis is important, particularly in resource poor settings where cases of suspected bacterial sepsis are likely to be treated with empiric antibiotic regimens that do not provide adequate cover for melioidosis. Melioidosis should be considered as a potential diagnosis for any patient who comes from or has traveled to endemic areas and laboratories should be aware of the differential features of the disease and the causative organism.

The culture of *B. pseudomallei* from any specimen in a patient with appropriate clinical features remains the diagnostic gold standard. Samples of blood, urine and respiratory secretions should be obtained for culture from all patients, together with synovial, peritoneal and pericardial fluid, sputum, pus and wound swabs when relevant. The laboratory should be notified when melioidosis is suspected, since selective techniques may increase the isolation rate and the organism may be overlooked or discarded as a contaminant by the unwary (Figure 3). Furthermore, it is classified as a “category 3” pathogen because of the risk of infection to the laboratory staff. Colonial morphology and simple biochemical tests would suggest the identity of the organism, which can then be confirmed by additional tests (Figures 4 to 6).

The most widely used serologic test for melioidosis is the indirect hemagglutination assay, but its utility is limited. False-negative serology has been reported in acute sepsis, and significant background rates of positive antibody to *B. pseudomallei* occur in healthy individuals in endemic areas. Sensitive polymerase chain reaction (PCR) amplification techniques for detecting the deoxyribonucleic acid (DNA) of *B. pseudomallei* in clinical specimens have been found useful for diagnosis.

Diagnosis can be made by microscopic demonstration of small bipolar Gram-negative rods with the characteristic “safety pin” appearance (Figures 7A and B) which is confirmed by culture of the bacteria with a fourfold or greater rise in the titer of serum antibody to the organism.

Chest radiography findings in acute pneumonia due to melioidosis may include small infiltrates, discrete, diffuse or patchy lobar or multifllobar consolidation, necrotizing lesions, cavitation...
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Figure 3: Blood culture—brain heart infusion both showing pellicle formation on surface (likely to be mistaken for contaminants)

Figure 4: Blood culture of *B. pseudomallei*. Blood agar—hemolytic colony

Figure 5: Blood culture of *B. pseudomallei*. MacConkey’s agar—non-lactose fermenting colonies converted to lactose fermenting dry colonies (48 hours after incubation)

Figure 6: *B. pseudomallei* colony morphology as demonstrated on Ashdown’s selective medium (violet colored rugose colonies)

Figure 7A and B: Gram’s stain—bipolar staining with safety pin appearance

and abscesses with fluid levels and pleural effusions (Figures 8 and 9). To evaluate for asymptomatic abscesses in the prostate, spleen (frequently multifocal), liver (Figures 10A and B) and kidneys, a computed tomography (CT) scan of the abdomen and pelvis should be performed.

TREATMENT

Treatment of melioidosis is a challenge even where there are adequate resources to support patients with multiple organ failure and extensive clinical experience. There is an emerging consensus on the initial (Phase 1) treatment, subsequent eradication (Phase 2) therapy and most recently postexposure (Phase 0) prophylaxis (Table 1). The combination of agents used, duration of therapy and need for adjunct modalities depends on the type, severity and antimicrobial susceptibility of infection.22,23

The response to therapy is often poor, with a mean duration of fever of 9 days. Treatment failure has been defined in studies as fever for longer than 14 days or bacteremia for longer than 7 days.

PROGNOSTIC FACTORS AND OUTCOME

Mortality in melioidosis is high (19–35%). Markers of organ dysfunction, including leukopenia (particularly lymphopenia), hepatic dysfunction, renal dysfunction, respiratory failure, metabolic derangements (hypoglycemia and acidosis) and bacteremia predict mortality.24
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Figure 8: Chest X-ray posteroanterior (PA) view. Nonhomogeneous opacities in both lung fields

Figure 9: Chest X-ray posteroanterior (PA) view. Right upper lobe cavity with air fluid level with no evidence of fibrosis

TABLE 1  Treatment of melioidosis: postexposure (Phase 0), initial (Phase 1) and subsequent eradication (Phase 2) therapy

<table>
<thead>
<tr>
<th>Application</th>
<th>Agent</th>
<th>Amount*</th>
<th>Route</th>
<th>Frequency</th>
<th>Duration</th>
<th>Variations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 0: Postexposure prophylaxis</td>
<td>Within 24 hours of high probability exposure†</td>
<td>TMP-SMX</td>
<td>320:1600 mg</td>
<td>PO</td>
<td>12 hourly</td>
<td>3 weeks†</td>
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<table>
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<tr>
<th>Phase 1: Acute and severe infection, induction stage</th>
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<tbody>
<tr>
<td>Alternative agents for primary therapy</td>
</tr>
<tr>
<td>Ceftazidime</td>
</tr>
<tr>
<td>or Meropenem</td>
</tr>
<tr>
<td>or Imipenem</td>
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<tr>
<th>Adjunct therapy for deep-seated focal infection</th>
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<tbody>
<tr>
<td>and TMP-SMX</td>
</tr>
<tr>
<td>and folic acid</td>
</tr>
<tr>
<td>and consider G-CSF</td>
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<table>
<thead>
<tr>
<th>Phase 2: Eradication stage (after Phase 1 or for primary use in superficial infections)</th>
</tr>
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<tbody>
<tr>
<td>2 of, in order of preference</td>
</tr>
<tr>
<td>TMP-SMX</td>
</tr>
<tr>
<td>Doxycycline</td>
</tr>
<tr>
<td>AMOX/CLAV</td>
</tr>
<tr>
<td>Folic acid</td>
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Abbreviations: TMP-SMX, Trimethoprim-sulfamethoxazole; PO, Oral; AMOX/CLAV, Amoxicillin/clavulanic acid; IV, Intravenous; CNS, Central nervous system; G-CSF, Granulocyte-colony stimulating factor; SC, Subcutaneous

† Doses may require adjustment in renal failure
‡ Suggested by expert consensus, but lacks trial-based clinical evidence
§ Doses provided as guide only based on 70 kg male
Some recommend 6 months eradication therapy

After apparently successful treatment, relapse is well described and associated with mortality similar to that for the initial episode. It occurs in 13–23% of cases and a median of 6–8 months (but up to many years) later.25

PREVENTION

Currently, no vaccines are available for human use to protect against melioidosis. The efficacy of postexposure prophylaxis in preventing human disease after exposure is unknown. In areas of endemic disease, skin lacerations, abrasions or burns that have been contaminated with soil or surface water should be immediately and thoroughly cleaned.

CONCLUSION

Melioidosis is an infection caused by B. pseudomallei, a widely distributed environmental saprophyte in soil and fresh surface water in endemic regions. The predominant modes of transmission are percutaneous inoculation and inhalation. The most important risk factors for melioidosis are diabetes, hazardous alcohol use and chronic renal disease. The common clinical manifestations are...
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Pneumonia and localized skin infection. Culture is the mainstay of diagnosis and serologic testing alone is not reliable for diagnosis. All cases of melioidosis, even mild disease, should be treated with initial intensive therapy of 2 weeks followed by eradication therapy of 3 months. An increased awareness, high index of suspicion, early diagnosis and initiation of appropriate therapy is necessary for a favorable outcome.

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REFERENCES

Figures 10A and B: Computed tomography (CT) abdomen. Multiple well-defined hypodense areas of varying sizes in liver and spleen are suggestive of multiple abscesses.