Melioidosis: A Neglected Infection in Bangladesh

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Abstract:
Bangladesh is an example of a highly populous, agricultural country where melioidosis may be a significantly under-diagnosed cause of infection and death. A recent regression model predicted 16,931 cases annually in Bangladesh with a mortality rate of 56%. However, we only manage to confirm (culture) around 80 cases in last 60 years. A lack of awareness among microbiologists and clinicians and a lack of diagnostic microbiology infrastructure are factors that are likely to lead to the underreporting of melioidosis. Melioidosis transmits through inoculation, inhalation and ingestion. Diabetes mellitus is the most common risk factor (12 times higher chance of getting the infection) predisposing individuals to melioidosis and is present in >50% of all patients. The clinical presentation is widely varied and can be mistaken for other diseases such as tuberculosis or more common forms of pneumonia giving rise to its nickname as the “great mimicker”. Disease manifestations vary from pneumonia or localized abscess to acute septicemia, or may present as a chronic infection. Culture is considered the current gold-standard for diagnosis and culture-confirmation should always be sought in patients where disease is suspected. It is strongly recommended that any non–Pseudomonas aeruginosa, oxidase-positive, Gram-negative bacillus isolated from any clinical specimen from a patient in an endemic area should be suspected to be Burkholderia pseudomallei (BP). In addition, based on antibiogram, any Gram-negative bacilli that are oxidase-positive, typically resistant to aminoglycosides (e.g., gentamicin), colistin, and polymyxin but sensitive to amoxicillin/clavulanic acid should be considered as BP. This bacteria is inherently resistant to penicillin, ampicillin, first generation and second-generation cephalosporins, gentamicin, tobramycin, streptomycin, and polymyxin. For intensive phase (10 to 14 days), ceftazidime or carbapenem is the drug of choice. For eradication phase (3 to 6 months), oral trimethoprim/sulfamethoxazole is the drug of choice. Surgery (drainage of abscess) has an important role in the management of melioidosis. Preventive measures through protective gears could be useful particularly for the risk groups.

Introduction
Burkholderia pseudomallei (BP), the causative agent of melioidosis has been described almost a century ago¹ and considerable progress in terms of diagnosis and treatment was achieved, BP is still “the unbeatable foe”, for several reasons like under-recognition, high case-fatality rate, unacceptable relapse rate and a “time-bomb” effect for sero-positive individuals. There is a growing body of evidence that, once considered an obscurity, melioidosis is now recognized as an emerging disease of global significance. It represents an excellent example of an emerging disease in two respects: it is being reported increasingly in many countries; and it is being recognized for the first time in countries where it has not previously been described.

It is classically characterized by pneumonia and multiple abscesses, which are associated with high case-fatality rates in animals and humans. It is an important cause of community-acquired sepsis in Southeast Asia and northern Australia. Its known global distribution is expanding, a reflection of improvements in diagnosticmicrobiology²⁻³. A recent
A regression model estimated around 1,65,000 human Melioidosis cases in 2015 worldwide (incidence rate of 5/100,000 people at risk per year) from which 89,000 people died. The model predicted 16,931 cases annually in Bangladesh with a mortality rate of 56% (9500 deaths). Bangladesh is an example of a highly populous, agricultural country where melioidosis may be a significantly under-diagnosed cause of infection and death. A lack of awareness among microbiologists and clinicians and a lack of diagnostic microbiology infrastructure are factors that are likely to lead to the underreporting of melioidosis. This review will highlight the status of this infection in Bangladesh covering the epidemiology to treatment and prevention.

**History and epidemiology of Melioidosis in Bangladesh**

The pioneering work of Indian bacteriologist C. S. Krishnaswami and British pathologist Alfred Whitmore first identified the organism BP, among Burmese morphine addicts in 1911. Since then, it took a century to determine its source in the environment of Indian sub-continent. The organism was recovered for the first time in 2011 from soil of Gazipur district of Bangladesh. However, the first reported, confirmed case of melioidosis that was acquired from Bangladesh (at that time known as East Pakistan) was a British sailor, who was travelling east of Suez. In October 1960, his ship was carried half a mile inland near Chittagong by a cyclone, and was deposited in a paddy field. The crews stayed there for three months and were repatriated in January 1961. The patient developed symptoms in May in the United Kingdom (UK) of that year and eventually received a diagnosis of melioidosis based on pus cultures in Liverpool.

Since then, melioidosis has been sporadically detected in Bangladesh over last several decades. But the first melioidosis case in a native Bangladeshi child was diagnosed in 1988. Subsequently, five more cases were detected in UK among Bangladeshi immigrants from Sylhet region from 1991 to 1999. Analysis of the reported cases strongly indicate that the disease is potentially endemic in at least ten districts of Bangladesh particularly in north eastern regions (Gazipur, Tangail, Mymensingh, Sylhet) of the country (Figure 1). So far, 78 culture positive melioidosis cases have been diagnosed in Bangladesh.

Melioidosis endemic countries of the world have been categorized into ‘definite’ ‘probable’ and ‘possible’ country based on the presence BP in human and in environment in the respective countries. There was ‘definite’ evidence for the presence of environmental BP in 18 countries. Initially Bangladesh was considered as ‘probable’ country. However, the organism was recovered in 2011 from soil of Gazipur district of Bangladesh for the first time in Indian sub-continent and since then Bangladesh was considered as ‘definite’ country for melioidosis.

![Fig.-1: Chloropleth map illustrates the frequency by district of culture-confirmed cases of melioidosis in Bangladesh.](image)

**Routes of transmission**

Melioidosis primarily affects persons who are in regular contact with soil and water. Infection results from percutaneous inoculation (e.g., by means of a penetrating injury or open wound), inhalation (e.g., during severe weather or as a result of deliberate release), or ingestion (e.g., through contaminated food or water). In most regions, the disease is highly seasonal, with rainy season peaks corresponding with higher infection rates. Vertical and sexual transmission, zoonotic transmission from animals with melioidosis and transmission to laboratory staffs are very uncommon but have been documented. Although incidence peaks between 40 and 60 years of age, but melioidosis is well recognized in children. Though human-to-human transmission is rare, a reported case of transmission to an infant from a mother with melioidosis mastitis via ingestion of breast milk has been described.

**Risk factors**

Since up to 80% of patients with melioidosis have one or more risk factors for the disease, it has been suggested that melioidosis should be considered an opportunistic infection that is unlikely to have a fatal outcome in a previously healthy person. Diabetes mellitus (DM) is the most common risk factor predisposing individuals to melioidosis and is present in >50% of all patients. Those with diabetes mellitus are thought to have a 12-fold higher risk of melioidosis (after adjusting for age, sex and other disease-specific risk
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factors. Heavy alcohol use (in 12 to 39%), chronic pulmonary disease (in 12 to 27%), chronic renal disease (CKD in 10 to 27%), thalassemia (in 7%), glucocorticoid therapy (in <5%), chronic liver disease (CLD) and cancer (in <5%) are the other commonly encountered risk factors reported. Individuals with regular exposure to mud and surface water, such as rice farmers, are particularly susceptible, especially during the rainy season. Amongst the Bangladeshi culture confirmed patients, the commonly noticed risk factors are DM (83%), CKD (4%), hypertension (4%), smoking (6%) and others (alcoholism, ischemic heart disease, thalassemia). The background mechanisms for most of the risk factors for melioidosis are likely to be due to multi-level defects in innate, humoral and adaptive cellular immunity. Healthy individuals can get melioidosis if a large bio-burden of infection is received, for example in adventure race athletes in endemic regions or in tsunami survivors. However, a healthy individual who has intact immune status is unlikely to die from melioidosis.

**Incubation period**

The time between an exposure to the bacteria that causes the disease and the emergence of symptoms is not clearly defined but may range from one day to many years. The average incubation period of acute infections is 9 days, ranging from 1–21 days, although a more severe form of the disease with shorter incubation can occur after inhalation or aspiration of contaminated fresh water. The incubating dose, strain virulence, mode of infection, and risk factors in the host are all likely contributors to the incubation period, clinical presentation, and outcome. An incubation period of a day or less was documented after aspiration of BP in a near-drowning event, whereas the longest recorded apparent incubation period was 62 years.

**Molecular characterization of BP isolated in Bangladesh**

Prof. MSA Jilani (the senior author of this review) and his team first explored the molecular characterization of this bacterium in Bangladesh. Gene cluster analysis targeting Yersinia-like.

Fimbrial (YLF) and *B. thailandensis*-like flagellum and chemotaxis (BTFC) gene demonstrated that all the isolates from Bangladesh contained YLF gene cluster. None of the isolates was positive for BTFC gene cluster. YLF gene cluster is predominantly found among *BP* derived from Southeast Asia. Phylogenetic analysis of 24 BP isolates by MLST revealed thirteen different sequence types (STs) of which four STs (ST-1352, 1124, 761 and 756) were of novel types and identified for the first time. All these isolates were from Bangladeshi patients. Presence of same ST from the soil and clinical isolates indicates soil as the source and reservoir of this organism in Bangladesh. These STs were also found in our neighboring countries including Thailand, Cambodia, China and others. YLF strains are more virulent than BTFC strains, which signify potentially higher risk of developing severe infection amongst Bangladeshi population.

**Clinical presentation of Melioidosis**

The clinical presentation of melioidosis can be widely varied (Table-1). It has a wide range of signs and symptoms that can be mistaken for other diseases such as tuberculosis or more common forms of pneumonia giving rise to its nickname as the "great mimicker". Disease manifestations vary from pneumonia to localized abscess or acute septicemias, or may present as a chronic infection. Clinical presentations and severity may differ depending on the route of exposure, host immune system, as well as bacterial strain-specific virulence factors and inoculating dose (Initial bacterial multiplication at the site of entry may lead to a local lesion such as skin sore, abscess formation, or to pneumonia following inhalation). Most cases (85%) of melioidosis result in an acute infection. Apart from those with cutaneous-only melioidosis, most of these patients (regardless of the route of infection) present with bacteremia with or without pneumonia, and/or localized abscesses. Of these, approximately 20% develop septic shock (mortality up to 90%).

In a descriptive study involving 51 culture positive patients in Bangladesh done by Chowdhury et al, 2018, the primary presenting feature was skin and soft tissue infection (27%), followed by septic arthritis (20%), pneumonia (14%), deep seated abscess (14%), urinary tract infection (10%), bacteremia without evident focus (8%), and neurologic involvement (6%). The same study revealed 27% mortality in Bangladesh. Out of that pneumonia, sepsis and neurological involvement was

**Table-1: Symptoms of different types of melioidosis**

<table>
<thead>
<tr>
<th>Localized Infection</th>
<th>Pulmonary Infection</th>
<th>Bloodstream Infection</th>
<th>Disseminated Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized pain or swelling</td>
<td>Cough</td>
<td>Fever</td>
<td>Fever</td>
</tr>
<tr>
<td>Fever</td>
<td>Chest pain</td>
<td>Headache</td>
<td>Weight loss</td>
</tr>
<tr>
<td>Ulceration</td>
<td>High fever</td>
<td>Respiratory distress</td>
<td>Stomach or chest pain</td>
</tr>
<tr>
<td>Abscess</td>
<td>Headache</td>
<td>Abdominal discomfort</td>
<td>Muscle or joint pain</td>
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<td></td>
<td>Anorexia</td>
<td>Joint pain</td>
<td>Headache</td>
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<td></td>
<td></td>
<td>Disorientation</td>
<td>Central nervous system/ brain infection</td>
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<td></td>
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<td></td>
<td>Seizures</td>
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the leading cause. Current worldwide mortality rates for melioidosis are approximately 40% in northeast Thailand (35% in children)\textsuperscript{12} and less than 14% in Australia\textsuperscript{18}. This difference is likely due to a combination of access to diagnostic facilities and melioidosis-specific antibiotics, as well as state-of-the-art intensive care support.

There are a few important differences in clinical presentation noted between patients in Australia and Southeast Asia including Bangladesh. Neurologic melioidosis (in the form of brainstem encephalitis, motor weakness and cranial nerve palsies) is reported in 4\% cases in Australia, whereas it is rare in Northeast Thailand, India and Bangladesh\textsuperscript{14,21}. On the other hand, suppurative parotitis is a common manifestation (up to 40\%) in children of Thailand, although it is extremely rare in Australia\textsuperscript{14}. These differences could possibly be explained by genetic variation of the strains (e.g., the presence of the \textit{bimABm} gene that encodes neurological manifestations in strains restricted to Australia\textsuperscript{21,25}, genetic variation of the human host, and differences in diagnosis rates.

**Diagnosis of Melioidosis**

Microbiological culture is the gold standard for the diagnosis of melioidosis. \textit{BP} is not part of the normal colonizing microbiota in humans and its isolation from any site is considered diagnostic. Culture is considered the current gold-standard for diagnosis and culture-confirmation should always be sought in patients where disease is suspected\textsuperscript{9}. The likelihood of diagnosing melioidosis is maximized when appropriate clinical samples from a variety of sites and specimen types are sent to the microbiology laboratory for microscopy and culture\textsuperscript{3,26}.

Blood culture should be performed for all patients with suspected melioidosis where possible\textsuperscript{14}. The \textit{BP} bacterial count in venous blood can reach high levels in septic patients, making conventional blood culture an effective means of establishing a bacteriological diagnosis. Samples from non-sterile sites are less helpful since \textit{BP} is often outcompeted by commensal species and the bacterial count may be much lower. However, this problem can often be overcome through the use of selective culture media such as Ashdown’s media\textsuperscript{27}.

Urine and throat swab specimens should be cultured using selective media, even in those patients where pharyngitis or urinary symptoms are not present. The sensitivity of urine culture may be improved by centrifuging the specimen and culturing the resulting pellet. In patients with localized lesions, abscesses or pneumonia, sputum specimens, surface lesions swabs, and sterile aspirates (pus, pleural fluid, peritoneal fluid, CSF) should be collected when available and cultured using selective media. Rectal swabs should...
also be cultured using selective media. It is recommended that cultures are repeated for any culture-negative patient whose symptoms are strongly suggestive of melioidosis. It is strongly recommended that any non—\textit{Pseudomonas aeruginosa}, oxidase-positive, Gram-negative bacillus isolated from any clinical specimen from a patient in an endemic area should be suspected to be \textit{BP}. In addition, based on antigenogram, any Gram-negative bacilli that are oxidase-positive, typically resistant to aminoglycosides (e.g., gentamicin), colistin, and polymyxin but sensitive to amoxicillin/clavulanic acid should be considered as \textit{BP}.

A monoclonal antibody-based latex agglutination test is now in use in Thailand and some other countries with the sensitivity varies between 69.5% to 95.1% and specificity between 56.9% to 99.7%. The latex test could be a useful test worldwide, particularly in resource-poor settings to improve the rate of diagnosis. Melioidosis diagnostic experts are encouraging the availability and use of this tool to screen all suspected cases.

A rapid diagnostic test and suitable alternatives to culture are currently research tools only. Several antigen detection assays such as immunofluorescence assay (IFA), polymerase chain reaction (PCR), and lateral flow immunoassay (LFI) are being evaluated for rapid detection of \textit{BP} with low sensitivity. Serological diagnosis is difficult and challenging because of the background high seropositivity of healthy endemic populations, and poorly characterized antigen. A promising tool to improve serodiagnosis could be protein microarray.

**Management of Melioidosis**

Melioidosis has a notoriously protracted course; cure is difficult without a prolonged course of appropriate antibiotics. \textit{BP} is inherently resistant to penicillin, ampicillin, first generation and second-generation cephalosporins, gentamicin, tobramycin, streptomycin, and polymyxin. Of the newer antibiotics, ertapenem, tigecycline, and moxifloxacin have limited in vitro activity against clinical isolates of \textit{BP}, and the minimum inhibitory concentration for doripenem is similar to that for meropenem. Various mechanisms of acquired antibiotic resistance have been identified, including efflux pumps, enzymatic inactivation, bacterial-cell-membrane impermeability, alterations in the antibiotic target site, and amino acid changes in \textit{Pena}, the gene encoding the highly conserved class \textit{A à-lactamase}.

Treatment for Melioidosis has been mainly divided into two phases-

1. Initial intravenous phase which lasts approximately for 14 days (can be prolonged if there is severe infection)
2. Followed by an oral eradication phase. The duration of eradication therapy is approximately 8-12 weeks (can be extended to 6 months in some special situation)

**Intensive-Phase Antibiotic Treatment**

The drug of choice for this stage is intravenous ceftazidime or meropenem for a minimum period of 10 to 14 days depending on the nature and severity of clinical presentations. This should be increased for severely ill patients, including those with extensive pulmonary disease, deep-seated collections or organ abscesses, osteomyelitis, septic arthritis, or neurological Melioidosis. In resource-poor settings it may not be affordable to extend intensive-phase treatment duration, but a minimum of 10 to 14 days is recommended. In this situation, completing a full course of oral eradication therapy is essential. In patients with a collection (including skin ulcers/abscesses and abscesses in internal organs), and in bone/joint, genitourinary, or in CNS infections (but not for pneumonia), intravenous or oral trimethoprim/sulfamethoxazole may be added. If trimethoprim/sulfamethoxazole is included, it should be continued for the entire duration of the intensive-phase treatment.

**Oral Eradication-Phase Antibiotic Treatment**

The drug of choice for this stage is oral trimethoprim/sulfamethoxazole for a minimum of 3 months post cessation of IV therapy. It can be extended to 6 months if neurological melioidosis, osteomyelitis or vascular mycotic aneurysms are present. The alternative drug of choice is amoxicillin/ clavulanic acid. It dramatically reduces the relapse of melioidosis, which is very common. Even after full course of eradication therapy 10%. Relapse can reach up 30% if the duration of oral eradication therapy lasts for less than 8 weeks. Relapse can be manifested as acute severe illness and could be fatal.

**Surgical Management**

Surgery has an important role in the management of melioidosis. Drainage is required for the localized pus such as big abscesses in internal organs (liver, prostate etc. and muscles. Repeated joint aspiration and washout may be required in septic arthritis if the collection is massive. Other internal abscesses rarely need to be drained as they frequently resolve with medical therapy. Repeated surgical debridement of the necrotic bones is an essential part of managing osteomyelitis. Urgent surgical intervention is warranted if Mycotic aneurysm is suspected.

**Control and Prevention**

As of today, there is no available vaccine to prevent melioidosis. Some preventive measures such as avoid contact with soil and standing water, wearing appropriate clothing and footwear, wash or shower after exposure to contaminated water or soil, cleaning of wounds, maintain regular hand hygiene and others have shown effective to preventing melioidosis.
Conclusion
Melioidosis may be a significant undiagnosed cause of infection and death in Bangladesh based on anecdotes and case reports. However, the internal medicine consultants in Bangladesh believe that melioidosis is not a considerable problem. Although mathematical model predicted around 16931 cases annually, we only managed to confirm less than 100 cases so far in Bangladesh. The probable reason behind the mismatch of case numbers between the Limmmathurosakul prediction model and the published literature is the lack of awareness among clinicians and microbiologists, and lack of diagnostic facilities. This is high time to work on these gaps so that many lives could be saving from this deadly bug. Director, center for disease control (CDC) and non-communicable disease control (NCDC) should launch special program to enhance its detection, management and prevention through their operational plan.

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