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Melioidosis: An emerging yet neglected bacterial zoonosis

Abstract

Melioidosis (Whitmore's disease) is an emerging disease caused by the Gram-negative saprophyte bacterium *Burkholderia pseudomallei*. It is a common but sometimes neglected zoonotic disease with a wide range of hosts, including humans. It has emerged as the leading cause of morbidity and mortality in tropical countries, such as Thailand, northern Australia, etc., and is continually emerging on a wider geographical scale. Recent epidemiological studies have suggested that most parts of Africa and the Middle East countries are environmentally suitable for *B. Pseudomallei*. Bacteria can easily travel from Asia to the Americas via Africa, as shown by phylogenetic analyzes of sporadic cases recently reported in America. Although melioidosis is included in the category 2 bioterrorism agents, there is ignorance in general people and even among clinicians regarding the infection. The disease requires long-term treatment regimens with no assurance of bacterial clearance. Several vaccine candidates are being tested, but none have reached clinical trials in humans. Diagnostic tests are still in the development stage and have compromised specificity and sensitivity in endemic areas. Understanding the adaptations of this organism to environmental factors and basic awareness is of the utmost importance today. Therefore, this review aims to provide an overview of melioidosis, including risk factors, epidemiology, clinical presentation, diagnosis, and preventive measures, as well as recommendations to increase awareness of the disease as a major public health problem.

Keywords: *Burkholderia pseudomallei,* emerging disease, epidemiology, melioidosis, tropical nations, zoonosis

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Introduction

Throughout the world, emerging and reemerging zoonotic diseases represent a considerable public health burden and challenge. These groups of diseases include newly identified, otherwise undefined, and ancient diseases with new characteristics.[1] More than 30 new human diseases have been identified in the last three decades, 60% of them being zoonotic in nature and more than 75% originating from wildlife.[2] Due to the rapid transmission of infectious agents across borders, they pose challenges to effective prevention and control measures around the world.[3–6] One of the emerging zoonotic diseases is melioidosis, also called Whitmore disease. It was Captain Alfred Whitmore and Krishna swami who isolated this bacterium from morphine addicts at the Rangoon General Hospital in Burma in 1911–1912.[7,8] In the following years, a series of other cases with similar clinical presentations were described in Rangoon. Shortly after this, cases of melioidosis were reported in Malaya in animals at the Institute of Medical Research (IMR) in Kuala Lumpur.[7,9,10] In 2016, melioidosis was classified as a sapro zoonosis, a disease of animals and humans caused by an environmental organism[8] The bacillus isolated from clinical samples was comparable to the bacteria responsible for glanders (*Burkholderia mallei*) but was motile and the victims did not have close contact with horses. Subsequently, this newly emerging bacterium was identified as *Burkholderia pseudomallei*,[11] and Stanton and Fletcher[12] coined the name of the disease as melioidosis.

Melioidosis is reported to be an endemic disease in Southeast Asian countries such as Thailand, Vietnam, Cambodia, Malaysia, Singapore, and northern Australia.[8] However, recent data suggests that it is emerging on a wider geographical scale than previously predicted by epidemiologists. It still remains a topic of discussion whether the occurrence of melioidosis has increased in recent years or whether it was simply an under diagnosed disease previously because of insufficient diagnostic facilities. But whatever the reason, the facts clearly indicate that melioidosis is emerging as a life-threatening zoonotic bacterial disease that can affect humans and several species of animals, including camels, swine, goats, and others.[4,13]

The cross-border movement of humans and animals increases the possibility of a disease spreading to new places. The clinical presentation of the disease also varies from region to region. *Burkholderia pseudomallei* is a natural saprophyte, found in muddy water and top soil; therefore, the rainy season favors the outbreak of the disease.[8] The most common affliction caused by bacteria is severe lung infection, along with a disseminated visceral abscess[3,8] *Burkholderia pseudomallei* alone is responsible for an estimated 165 thousand cases of human melioidosis worldwide, with 54% case fatality rate.[14,15] Mortality rates are higher in people with underlying chronic diseases and in immunosuppressed individuals.[16] Patients may experience a variety of clinical symptoms ranging from mild to severe disease.[17] *Burkholderia pseudomallei* infects a wide range of animal host, including pigs, sheep, goats, horses, pet animals, etc. The clinical course of the disease also varies in animals depending on the affected organ or tissue, but is nonspecific.[4] Common signs are lethargy, depression, lack of appetite, and diarrhea.[18]

Burkholderia pseudomallei and B. mallei are considered tier I agents by CDC due to their potential for misuse as biological weapons.[19] Furthermore, it mimics other severe infections with the display of nonspecific clinical manifestations[8,9,12] which further results in delayed diagnosis and poses risks for the dissemination of the agent in nonendemic areas. The incubation period also ranges from days to months or years. According to the CDC,[20] *B. pseudomallei* can be difficult to diagnose because it is often mistaken for tuberculosis. Therefore, the objectives were to review the importance of public health and geographical distribution of melioidosis; understand the epidemiology and pathogenesis of disease; and assess the status of disease diagnosis, prevention, and control measures.

Etiology and Morphology

Melioidosis, or Whitmore disease, is caused by *Burkholderia pseudomallei,* a Gram negative bacillus with a characteristic "safety pin" appearance (bipolar staining) on Gram Staining. The causative agent is an aerobic, non spore-forming, oxidase positive rod-shaped saprophytic bacterium.[8] Previously, the bacterium was known as *Pseudomonas pseudomallei,* but seven *Pseudomonas* species were switched to a new genus, *Burkholderia,* in 1992, and thus the new name was derived. The term "melioidosis" originated in Greek literature where "melis" means "distemper," "oid" means "resemblance," and "osis" means "condition".[12] Although the bacterium is a close relative to *glanders bacillus* (*B. mallei*), there are several notable differences, such as it is a motile organism, can grow rapidly on agar and is unable to induce the typical Strauss reaction.[21] *Burkholderia pseudomallei* is a resilient environmental bacterium that can tolerate extreme temperatures, acidic and alkaline settings, disinfectants, and antiseptic solutions.[8] Being a facultative intracellular pathogen, *Burkholderia pseudomallei* employs numerous mechanisms to facilitate its survival in the host environment.

Epidemiology

Geographical distribution

Being a saprophyte, *B. pseudomallei* naturally resides in soil, muddy water, and the rhizosphere in parts of Asia and Australia.[11,22] However, case reports of melioidosis and predictive modeling studies suggest that it is probably widely present in many countries across the tropical border. Melioidosis is endemic in parts of the Indian subcontinent,[23,24] southern China,[25] Hong Kong,[26] Taiwan[27] and northern Australia.[28] Melioidosis is classified as one of the top three infectious diseases in Thailand with a high rate of case fatality due to the prevalence of its septicemic form.[22,29] Ecological reports have shown that *B. pseudomallei* can survive as a free-living organism in environmental niches, such as top soil and water, or as a parasite living in host organisms, such as ameba, plants, spores of mycorrhizal fungi, and animals.[30,31] Therefore, the real extent of the geographical distribution of the bacteria remains unspecified, and it has been estimated that it has never been reported in the 45 countries in which it is probably endemic.[24,29,32]

Host range

In addition to humans, *B. pseudomallei* can infect a wide range of animals. It is typically reported in sheep, cattle, goats, and swine.[18] However, sporadic cases or small outbreaks are reported in monkeys, gibbons, orangutans, kangaroos, wallabies, deer, buffaloes, camels, llamas, zebras, koalas, dogs, cats, horses, mules, parrots, rats, hamsters, rabbits, guinea pigs, ground squirrels, seals, dolphins, crocodiles, etc.[4,33] Hinjoyet al.[27] reviewed several reports from Thailand illustrating culture-confirmed melioidosis cases in captive zoo animals and domestic animals. In an interesting case study, *B. pseudomallei* infections were reported in two pet iguanas (*Iguana iguana*) in California, USA, and it was found that the pets were traded from Central America and had prolonged incubation periods of > 1.5 years.[34] Damrongsukij and co investigators[35] reported a 57.1% seroprevalence of melioidosis from macaque fecal samples. However, melioidosis is rare in wild birds, but the disease can occur in captive or exotic birds transported to regions.[36]

Mode of transmission

The most common routes to contract *B. pseudomallei* infection in humans and animals are thought to be percutaneous inoculation, inhalation, and ingestion.[31] Inhalation and ingestion of contagious dust and water droplets, percutaneous exposure of skin wounds or abrasions with contaminated soil or water, for example, during rice farming, heavy rain or monsoon season, etc., are extensively reported modes of transmission in endemic areas.[29,37] Infected animals can shed the organism in various secretions, such as exudates, abscesses, milk, nasal secretions, feces, urine, etc.[18,33]

Although the bacterium has its own conventional route of transmission, it may occasionally be acquired via several alternative routes. Some cases of zoonotic transmission from direct or indirect contact of the skin lesion with infected livestock or infected tissues or animal products (e.g. milk, meat) have been reported.[8,28] The transmission of melioidosis from mother to baby through breast milk[38] and vertical transmission in childbirth[39] were also documented. Though, less likely still there are few chances of human-to-human or sexual transmission. In extreme cases, infection can be transmitted from patients to health care workers or family members in close contact during nursing.[40] There is also the possibility of animal-to-animal transmission.[41] Tran placental transmission has been documented in several species (goats, pigs, and spider monkeys). Less frequently, but nosocomial transmission can also occur in animals in veterinary hospital settings.[40]

Risk factors

There are two types of risk factors associated with disease outbreaks: environmental and human-related factors. Environmental predisposing factors are responsible for the endemicity of an infection, including its latitude, soil composition, and climate of a region. Because the bacterium thrives in warm, wet environments, it is mainly considered a tropical disease. There has been a sudden peak in the incidence rate of melioidosis after heavy rains and winds.[37] Some groups of people are at high risk, such as agricultural workers (that is, rubber plantation and field work, etc.), who fail to wear protective clothing and suffer repeated minor injuries.[42] *Burkholderia pseudomallei* can survive for months or years in contaminated soil and water.[40]

Under human-related factors, it has been reported that up to 80% of patients who contract melioidosis infection have underlying co morbidities, including diabetes, excessive alcohol use, chronic lung disease, chronic nephrosis, thalassemia, cancer or other immune-suppressive conditions.[23,35,43] According to Currie,[16,44] more than 50% of all melioidosis patients show diabetes, usually type 2, as a preexisting risk factor in their clinical case history. Individuals with diabetes have a 12-fold higher risk of melioidosis after adjustment for age, sex, and other risk factors.[16,44] People working in other occupational settings, such as laboratories and primary care units are particularly susceptible to occupational exposure.[29,44] Human melioidosis can affect all age groups, but the active age group (40–60 years) is more susceptible.[42]

Pathogenesis

Burkholderia pseudomallei are an opportunistic intracellular facultative pathogen. It has a huge genome, which encodes a variety of virulence elements that promote survival in animal models and in harsh environmental conditions.[10,45] In the environment, bacteria employ several mechanisms to defend against salt stress, oxidative stress, high iron concentration, niche competition, etc.,[31] which give rise to more resistant strains. After entering a living tissue or cell, it is subjected to a variety of adverse conditions, including the host's immune system, oxygen deficiency, and nutrient limitation. Therefore, by manipulating and controlling the machinery of the

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host cell and other elements of the immune system, *B. pseudomallei* adapts itself to survive, functionally modulates several genes and ultimately causes disease in the host.[15] Depending on the route of entry, *B. pseudomallei* first enters and replicates in epithelial cells of the mucosal surface or broken skin and then spreads to various cell types.[8] One of the most important features of *B. pseudomallei* is its ability to sequester itself within human macrophages and lympho reticular organs (lymph nodes, spleen, thymus, etc.) in a dormant state for several years.[7,8,10,31] Various virulence factors play a vital role in the infection of *B. pseudomallei,* including capsular polysaccharide, adhesins, specialized secretion systems (i.e., type 3 secretion system (T3SS, T5SS, T6SS), lipopolysaccharide (LPS) and flagella, and numerous bacterial products and enzymes[45,46] that allow survival within a host and contribute to the pathogenesis of melioidosis. In addition, it also produces a variety of small-molecule secondary metabolites that serve as siderophores, cytotoxins, and antibiotics.[47] For example, Bsa (*Burkholderia* secretion apparatus) T3SS-3 is well characterized and an important intrinsic virulence factor of *B. pseudomallei* for invasion, intracellular replication, and escape of autophagy.[15] Similarly, *B. pseudomallei* utilizes type VI secretion systems (T6SS) as contact-dependent inhibition or killing of gram-negative bacteria by puncturing and delivering toxic effector molecules into competitor bacteria.[47] In addition, *B. pseudomallei* modulates its surface molecules to escape from the host immune radar system by down-regulating genes involved in the synthesis of capsule, flagella, LPS and chemo taxis.[48]

Clinical signs and symptoms in humans

Melioidosis shows myriads of clinical features related to several diseases, leading to frequent misdiagnosis of the condition.[43,44] Patients may present with a variety of clinical symptoms ranging from mild to severe disease, including, but not limited to, fever, headaches, muscle pain, labored pneumonia, cough, and abscesses.[17] The clinical presentation may depend on the site of infection or inoculation. The incubation period, or the time of onset of clinical symptoms, is highly variable for melioidosis. It may range from a day to 21 days (average 9 days) and may extend for many years.[42]

The clinical presentation of melioidosis can be classified into a few forms such as subclinical, acute (fulminant febrile disease), chronic (debilitating or localized infection with abscess formation) and latent form (infection residing in dormant form).[32] In subclinical forms, there are apparently no symptoms and could be the result of asymptomatic seroconversion in a population residing in an endemic area. However, there is not enough evidence to support the emergence of clinical cases of seroconversion, and it is believed that all new cases are believed to have a recent infection history.[44] An acute form of the disease can lead to severe septicemia, shock, and even death. Typically, patients are exposed to bacteria via inhalation or aspiration routes and symptoms last for less than 2 months. The lungs could be the most commonly affected organ.[13] Chakravorty and Heath[42] have reviewed that more than 50% of patients show bacteremia after acute exposure, of which approximately 20% develop septic shock. More than 50% of adult infection cases and approximately 20% of pediatric cases have lung disease.[16] However, children are more frequently affected by skin infections (60%) than adults (13%). Bacteria can enter the circulatory system and colonize other organs, such as the spleen, liver, brain, kidney, and genitalia, and cause inflammation and visceral abscess formation. Almost every organ can be involved in the disease, but the central nervous system is the least affected.[44]

If symptoms last for more than 2 months, the melioidosis infection is considered chronic. Acute melioidosis is more common than the chronic form of the disease. Chronically infected patients account for approximately 11% of all cases and may mimic clinical signs of cancer, tuberculosis, or fungal infections, e.g., febrile illness, weight loss, and cough with or without blood.[32] Sometimes, activation and/or relapse of dormant bacteria can occur after months or even years. In that scenario, it is considered to be in latent form.[13,49] Osteomyelitis and septic arthritis are also reported, either due to penetrating injuries or dissemination through blood dissemination.[42,50]

Diagnosis

Diagnosis of melioidosis on clinical grounds alone is very difficult due to overlapped clinical symptoms. A history of traveling to an endemic area, preexisting diseases like diabetes, and exposure to occupational or agricultural risk factors can be presumptive of melioidosis in nonendemic areas. In the case of suspected infection, overall screening of all available samples (blood, urine, throat swab, respiratory secretions, pus and swabs of surface wounds) from the patient is typically recommended.[51] The most conventional method still consists of Gram staining (gram negative bipolar coccobacilli), cultural and biochemical tests. Ashdown selective agar (ASA)[30] is the most commonly used selective medium in endemic areas and shows large circular purplish wrinkled colonies, but recently it has been reported to inhibit the growth of some strains of bacteria. Therefore, a new media known as *Burkholderia pseudomallei* selective agar (BPSA) was produced to improve the isolation procedure[52] ASA selectively enriches on the basis of resistance to gentamicin, a characteristic of most *B. pseudomallei*, while BPSA can also enrich gentamicin susceptible strains too. Smooth colonies are produced on isolation agar such as horse blood agar, (HBA), chocolate agar or MacConkey agar.[8] Being a slow-growing organism, it is recommended to culture the microorganism at least for 4 days with daily inspection. Bio typing can be done using several commercial kits such as 1156576 and 1156577 (provided by API 20NE), Vitek 2, and Walk Away 9, but the sensitivity and specificity of the test are still questionable.[30] It is easily misunderstood as *Pseudomonas* or a contaminant during the routine cultural identification process. However, the isolation and identification of *B. pseudomallei* from clinical samples is absolute evidence of the disease because it is not present in natural flora.[10] An antibiotic disc diffusion test can be used as a presumptive test. It is based on the fact that most isolates are generally resistant to colistin and gentamicin but sensitive to amoxicillin/clavulanate (also known as co-amoxiclav).[8] Although it is not a conclusive test, as gentamicin-susceptible isolates of *B. pseudomallei* are also prevalent in some regions of the world.[52]

Sero diagnostic tools, such as indirect hem agglutination, immunofluorescence, and complement fixation tests, have been found to have low sensitivity and specificity.[53] Antibody-based assays are susceptible to produce false positive data because of high background antibody positivity (up to 50% of cases) in endemic regions and there may be cross-reactions with closely related species such as *B. mallei* or *B. cepacia*.[54] Therefore, confirmatory tests must only be performed using the bacterial culture method.

The handling of *B. pseudomallei* must be in a bio safety level 3 laboratory.[55] Therefore, commercial availability of detection kits is of the highest priority, and yet commercial kits are not available. Nowadays, recombinant antigens are being investigated for the sero diagnosis of melioidosis. Druar and co investigators[56] demonstrated the specificity of BipD (dumbbell-shaped protein) for *B. pseudomallei* strains, which can be used to differentiate melioidosis from *Mycobacterium tuberculosis* and other diseases mimicked by *B. pseudomallei*. Recombinant BipD (rBipD) could be a potential target

in diagnostic tests for melioidosis[15] A lateral flow immunoassay (LFI) developed by InBiOS (Active Melioidosis Detect/AMD) is another diagnostic tool using monoclonal antibodies (mAb 3C5) for the detection of capsular polysaccharide of *B. pseudomallei* in clinical specimens.[57] AMD LFI could be a promising tool for the detection of *B. pseudomallei*. It is a user-friendly, affordable, rapid and robust, equipment-free diagnostic test, but it has poor sensitivity for non blood samples.

Numerous molecular techniques for species identification have been established, including 16S rDNA sequencing, specific PCRs, and rtPCR, along with some pros and cons[40] Matrix-assisted laser desorption/ionization of time-of-flight mass spectrometry (MALDI-TOF MS) has also shown potential for quick detection of *B. pseudomallei* at a low cost.[55] Additionally, imaging, such as chest radiography, ultrasound or CT, is often very useful for determining the severity of the disease and to check for subclinical abscesses.[50,58]

Treatment

Burkholderia pseudomalleus is naturally resistant to many drugs, including common antibiotics used to treat bacterial infections.[8] It is resistant to gentamycin, penicillin, ampicillin, first and second-generation cephalosporin, but susceptible to tetracycline.[50] The treatment strategy is divided into two steps: the first is to treat acute conditions with intensive therapy and the second is to prevent infection relapse later in life with eradication therapy.[55] The first step is achieved by giving an intravenous injection of antibiotics, also called the intravenous phase. Initial intensive therapy should last at least 10-14 days, but can be extended (4-8 weeks) in critical cases, such as severe pneumonia, distantly disseminated infections such as visceral organ abscesses, osteomyelitis, or neurological melioidosis[39] Ceftazidime or a carbapenem antibiotic is the treatment of choice. Most isolates are susceptible to beta-lactam group antibiotics, e.g. ceftazidime, imipenem, meropenem, and co-amoxiclav, but the sensitivity can vary.[59] The second step, or eradication therapy, or oral phase, is followed just after the initial intravenous phase/therapy. Here, oral antibiotics are recommended to prevent reactivation of the infection or relapse of the patient, who may develop immunosuppression in a later stage of life. Trimethoprim-sulfamethoxazole is the preferred agent for eradication therapy, and co-amoxiclav or doxycycline is the second choice.[8]

Prevention and control

Although *B. pseudomallei* is classified as a potential bio threat and imposes a high burden on disability adjusted life years (DALY) in endemic areas,[10] no successful vaccine candidate registered or even not been reached in human clinical trials,[29,55] Wang and co-workers[54] critically discussed the various types of vaccines against *B. mallei* and *B. pseudomallei,* such as killed, attenuated, viral vector-based, glycol conjugate, subunit, and DNA vaccines and current advances in vaccine development. However, subunit or epitope-based vaccines show attractive potential because of their increased safety and capability for large-scale production.[19] For effective control measurements, veterinarians or concerned healthcare workers who suspect even a single case of melioidosis should follow their national and/or local guidelines to report the disease to higher authorities as soon as possible.[22,27]

Identifying environmental factors to determine the endemicity of *B. pseudomallei* is the first and foremost step of any prevention and preparedness strategies. An awareness campaign should be organized on risk factors, disease prevalence and true mortality rate, preventive measures, and reporting protocol, especially in endemic areas. The use of protective gear (up to knee boots, gloves and masks) should be promoted to avoid direct contact with soil or water, only drink treated water or perfectly boiled water, and avoid outdoor exposure to heavy rain or dust winds. There must be provisions for providing safe drinking water (e.g., by filtration and chlorination) to the whole community. Individuals at high risk, for example people with diabetes, renal failure, cystic fibrosis, and immunosuppressive conditions, should be advised to suspend travel during hyper endemic periods, such as during the monsoon season.[22] Laboratory staff working with *B. pseudomallei* should undergo training regarding the handling of this organism in facilities of bio safety level 3 (BSL3) within a bio safety cabinet.[10,55]

In cases of animal outbreaks, it is often recommended to euthanize infected animals, even in endemic areas, and thoroughly disinfect the premises. It is imperative as the disease has zoonotic potential with a difficult line of treatment. Adoption of the One-Health Approach involves interdisciplinary collaborations of health professionals at the local, national, and universal levels with the goal of achieving optimal health for humans, animals, and their shared environment[8] to promote cooperation and strategic planning between physicians, ecologists, environmental scientists, and veterinarians.

Conclusions and recommendations

Melioidosis caused by *B. pseudomallei* is an understudied, neglected tropical disease that continues to be endemic in many developing countries around the world. However, it is not included in most lists of neglected tropical diseases, including the list provided by the World Health Organization. Thus, sustained education and awareness are required on the part of clinicians and general people. Training, improved diagnostic laboratories, and extension education facilities are urgently needed at the ground level. Implementing interdisciplinary initiatives combined with field efforts is the need of the hour to address both endemic and emerging melioidosis.

The following recommendations are forwarded

- Prevention and control of the mortality rate of diseased people should be the two prime priorities for melioidosis research.

- Development of a vaccine could be a cost-effective intervention in tropical developing countries, particularly if used in high-risk populations.

- Establishing basic clinical microbiology laboratories and education of both clinicians and laboratory technicians.

- Research should be oriented to getting new insights into the phylogeny and virulence characteristics of this bacterium.

- An efficient disease and surveillance reporting system along with an accurate geographical risk map is needed.

-Adopting of One Health Initiative: There should be cooperation and strategic planning between physicians, ecologists, environmental scientists, and veterinarians in the prevention and control of the disease.

It should be on the radar of policymakers, either at a state or a national level.

The author's contribution

All authors contributed equally. They read the final version and approved it for publication.

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Conflict of interest

The author declares no conflicts of interest.

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