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Review Article

Burkholderia pseudomallei Infection- A Review

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***ABSTRACT*:**
Clinical patterns of infection caused by Burkholderia pseudomallei are generally consistent with those from South and Southeast Asia interms of common primary presentations with diabetes as a major risk factor. Early diagnosis and appropriate management is a key limiting factor, which needs to be addressed to reduce serious complications and high mortality and recurrence rates. Promoting awareness among the local healthcare personnel is crucial to improving diagnostics and early treatment, as well as educating the public on disease symptoms and risk factors. This review provides a non exhaustive overview of epidemiological data, clinical studies, risk factors, and mortality rates from available literature and case reports.
Key words- Burkholderia pseudomallei, Management, Risk factors

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Introduction

The genus Burkholderia is currently composed of many species, but only three are notable pathogens for humans or animals: the former cepacia complex pseudomallei (the agent of melioidosis), and mallei (the agent of equine glanders). All three anaerobic, non sporulating, straight or slightly curved gram-negative bacilli that were formerly placed in the genus Pseudomonas.[1]

History

In 1912, Whitmore and Krishnaswami[2] described cases of a newly recognized septicemic disease in morphine addicts in Rangoon, Burma. Fatal cases were characterized by widespread caseous consolidation of the lung and abscesses in liver, spleen, kidney, and subcutaneous tissues. The bacillus isolated from tissues was similar to that causing glanders (Burkholderia mallei) but was motile. Various names were used for the causative bacterium, including Bacillus whitmori and, for many years, Pseudomonas pseudomallei. In 1992, seven Pseudomonas species were moved to a new genus, Burkholderia. B. cepacia is the type species in the genus, which includes the organisms causing melioidosis (B. pseudomallei) and glanders (B. mallei).

Structure

B. pseudomallei is a small, gram-negative, oxidase-positive, motile, aerobic bacillus with occasional polar flagella. On staining, a bipolar"safety pin" pattern is seen. The organism is easily recovered on standard culture medium but may be misidentified as B. cepacia, P. stutzeri, or other Pseudomonas species.[3]

Modes of Transmission

The B. pseudomallei natural environmental habitat in endemic areas is soil and water. Most cases of melioidosis occur in persons with regular contact with contaminated soil or water, via penetrating wounds or pre-existing skin abrasions. Inhalation via contaminated dust or water as in

severe wetweather conditions is the next most common route of entry and is characterized by pneumonia andmore severe infection. Heavy rains precipitate flooding, which facilitates churning of B. pseudomallei to the surface soil, aerosolizing the bacteria and increasing exposure potential. Zueter et al[4]. in their case series from Kelantan observed that the highest frequency of admissions occurred during the rainy season from November to February. Hassan et al[5]. found that cases and deaths from melioidosisin the Alor Setar region of Kedah increased linearly with mean monthly rainfall. Occasional laboratory-acquired infections are described, but person-to-person spread and zoonotic infection are very uncommon.

Demography and Risk Factors

Melioidosis may occur at any age, including newborns. The peak incidence in the Malaysian case series is between 40 and 60 years of age, the age range during which most co-morbid conditions develop. A preponderance of the disease among males was noted; the gender difference may be due to a higher potential for males to be involved in soil-related occupations and activities facilitating exposure.[6]

Most cases (58–85%) had at least one risk factor reiterating B. pseudomallei's classification as an opportunistic pathogen and that susceptibility of the host is a vital factor in the acquisition of infection. More than one risk factor was reported in 8.1–36% of cases. No risk factor was reported in 15–42%of cases, possibly reflecting under-reporting, unknown residual factors, and high bacterial load or inhalation route in some cases.

Several underlying medical conditions or drug therapy that may impair host defense predispose individuals to melioidosis. As reported in other endemic areas of the world, type 2diabetes mellitus is the most common co-morbid condition associated with melioidosis in Malaysia;38–75% of melioidosis patients were either newly diagnosed or had pre-existing type 2 diabetes mellitus. Other co-morbid conditions associated with melioidosis include chronic renal disease (6–19%), tuberculosis (9–16%), immune disorders/steroid therapy (2.9–9.5%), solid tumors(0.7–10%), haematological malignancies (0.7–8%), chronic lung disease (2.8–3.0%), chronic heart disease (7.0%), smoking (10%), chronic alcoholism (0.7–2.0%), hemolytic anaemia (0.7–2.0%),and malnutrition/anaemia (8%).[7]

Pathogenesis

Serology studies have shown that most infection with B. pseudomallei is asymptomatic. In north-east Thailand, most of the rural populationis seropositive by indirect hemagglutination (IHA), with most seroconversion occurring between 6 months and 4 years of age. Although melioidosis occurs in all age groups, severe clinical disease such as septicemic pneumonia is seen mostly in those with risk factors such as diabetes, renal disease, and alcoholism. B. pseudomalleiare also likely to influence the severity of disease.[8] However, it has been noted that despite the large bacterial load in severely ill patients with septicemic pulmonary melioidosis, person-to-person transmission is extremely unusual. This, together with the rarity of fulminant melioidosis in healthy people, supports the primary importance of host risk factors for development of melioidosis.

Isolates of B. pseudomallei from animals, humans, and the environment that virulence differs among B. pseudomallei isolates, the importance of this variation in virulence in determining clinical aspects of melioidosis remains uncertain. Molecular typing that shows clonality of isolates in animal and human clusters has revealed that the same outbreak strain can cause different clinical presentations, with host factors being most important in determining the severity of disease. Whole-genome sequencing and subsequent molecular studies have shown that B. pseudomallei has two chromosomes, multiple genomic islands that are variably present in different strains and have a great propensity for horizontal gene transfer.[9]

B. pseudomallei is a facultative intracellular pathogen that can invade and replicate inside various cells, including polymorphonuclear leukocytes and macrophages and some epithelial cell lines. Animal models have been unable to confirm a clinically relevant exotoxin for B. pseudomallei. However, resistance to human serum (conferred by lipopolysaccharide [LPS]) and the ability of B. pseudomallei to survive intracellularly (conferred in part by capsular polysaccharide) appear to be critical in the pathogenesis of melioidosis. Type III secretion systems in B. pseudomallei have also been found to be important in cell invasion and intracellular survival. Quorum sensing may play an important role in many aspects of virulence of B. pseudomallei, including cell invasion, cytotoxicity and antimicrobial resistance.[10]

Evidence suggests that there may be a predisposition to melioidosis in those with diabetes, alcohol excess, or chronic renal disease, which may reflect impairment of their neutrophil and other phagocytic cell functions, such as mobilization, delivery, adherence, and ingestion. Melioidosis has also been described in chronic granulomatous disease.

Clinical Presentation

Melioidosis presents as a febrile illness with protean clinical manifestations, ranging from acute fulminant pneumonia and/or septicemia mimicking other community-acquired infections, to a chronic infection that may mimic tuberculosis or malignancy. The disease is characterized by abscess formation in multiple organs and is referred to as 'the great mimicker' because of its similarity to other infections that obscure its correct diagnosis.

The earliest descriptions of melioidosis documented the fulminant end of the clinical spectrum, with abscesses throughout both lungs and in many organs. At the other end of the spectrum are asymptomatic infections and localized

skin ulcers or abscesses without systemic illness. Howe and colleagues have classified melioidosis as acute, subacute, and chronic.[11]

Pneumonia is the commonest clinical presentation of patients with melioidosis in all studies, accounting for around half of cases. Secondary pneumonia after another primary presentation occurs in around 10% of cases. Acute melioidosis pneumonia has a spectrum from fulminant septic shock to mild undifferentiated pneumonia, which can be acute or subacute in nature, with little mortality. Septicemic patients present acutely unwell with high fevers and prostration and

often little initial cough or pleuritic pain. On chest radiographs, diffuse nodular infiltrates often develop throughout both lungs and they coalesce, cavitate, and progress rapidly, consistent with the caseous necrosis and multiple metastatic abscess formation seen at autopsy.[12]

Non septicemic patients with pneumonia and some with septicemic pneumonia have a more predominant cough, with productive sputum and dyspnea, and their chest radiographs show discrete but progressive consolidation in one or more lobes. More than 90% of cases were of acute onset, presenting as acute respiratory infection, acute bacteraemia, or soft tissue infection with fever almost always present.

Soft tissue infections include infections of non skeletal tissue surrounding or supporting organs and other structures including subcutaneous tissue, muscle, lymph nodes, blood vessels, and soft tissue organs. Less than 10% of cases were chronic in onset, presenting as chronic pneumonia, chronic skin ulcers/abscesses, and disseminated infection progressing to sepsis, while subclinical infections have also been documented. The major reasons for emergency hospital admissions were acute pulmonary infection progressing to acute respiratory failure, acute bacteraemia progressing to septic shock, severe soft tissue infection, or pyrexia of unknown origin.[13]

Patients may present with a history of fever, respiratory distress, abdominal discomfort, muscle tenderness, and disorientation. The clinical picture may vary from a simple bacteraemia with no evident focus of infection, to fulminant septic shock and multiorgan abscesses with 16–34% of cases presenting with septic shock. Disseminated infection, occurring in 16–37% of cases, presents with symptoms of fever, weight loss, abdominal pain, muscle and joint pain, headache, and seizures, and with clinical signs of abscess formation in multiple organs with or without bacteraemia. Acute localized infection, occurring in about 10% of cases, may present as skin ulcers, subcutaneous tissue abscesses, parotid abscess, or ocular infection. The infection may remain localized or may rapidly progress through the blood stream to more widespread infection.[14]

Laboratory diagnosis

Definitive diagnosis of melioidosis requires a positive culture of B.pseudomallei. Melioidosis must be considered in febrile patients in or returning from endemic regions to enable appropriate samples to be tested. B. pseudomallei readily grows in commercially available blood culture media, but it is not unusual for laboratories in non endemic locations to misidentify the bacteria as a Pseudomonas species, especially because some commercial identification systems are poor at identifying B. pseudomallei.[15] Culture from non sterile sites increases the likelihood of diagnosis but can be problematic. The rate of successful culture is increased if sputum, throat swabs, ulcer or skin lesion swabs, and rectal swabs are placed into Ashdown's medium, agentamicin-containing liquid transport broth that results in the selective growth of B. pseudomallei. B. pseudomallei can be identified by combining the commercial API 20NE or 20E biochemical kit with a simple screening system involving the Gram stain, oxidase reaction, typical growth characteristics, and resistance to certainantibiotics.[16]

There are a variety of locally developed antigen and DNA detection techniques used in endemic regions for early identification of B. pseudomallei in culture media and patient blood or urine, but these are notyet widely available. An indirect hemagglutination test (IHA), various enzyme-linked immunosorbent assays (ELISAs), and other serologic assays are available. In endemic areas, their usefulness is limited by high rates of background antibody positivity. In acute septicemic melioidosis, IHA and ELISA are often initially negative, but repeat testing may show seroconversion. A positive IHA or ELISA ina tourist returning from a melioidosis-endemic region is useful in supporting the possibility of melioidosis, but definitive diagnosis still requires a positive culture.[17]

Treatment

B. pseudomallei is characteristically resistant to penicillin, ampicillin, first- and second-generation cephalosporins, gentamicin, tobramycin,and streptomycin. Before 1989, "conventional therapy" for melioidosis consisted of a combination of chloramphenicol, sulfamethoxazole trimethoprim, doxycycline, and sometimes kanamycin, given for 6 weeks to 6 months. However, there were also reports of the successful use of sulfamethoxazole-trimethoprim alone and tetracycline or doxycycline alone.[18]

CONCLUSION

The B. pseudomallei natural environmental habitat in endemic areas is soil and water. Most cases of melioidosis occur in persons with regular contact with contaminated soil or water, via penetrating wounds or pre-existing skin abrasions. Careful analysis of case with proper laboratory diagnosis and prompt treatment may control the disease caused by it.

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