Melioidosis is the etiological designation of a spectrum of clinical manifestations caused by the Gram-negative bacillus *Burkholderia pseudomallei*. Until recently, this organism was classified under *Pseudomonas* due to similarities in culture and morphological characteristics and biochemical properties with species of *Pseudomonas*. It is now assigned to a new genus, *Burkholderia*, along with other members of ribosomal RNA (RNA) homology group II.1

The bacterium *B. pseudomallei* was first isolated in 1911 by Captain A Whitmore, a British pathologist at Rangoon General Hospital, Burma, treating a young boy dying with pneumonia.2 In 1921, Stanton and Fletcher coined the term melioidosis.3

**EPIDEMIOLOGY**

**Geographic Distribution**

Melioidosis is no longer perceived as an esoteric tropical infection, but is recognised as an important public health problem in some parts of the world. It is endemic in Southeast Asia and tropical Australia, and has been reported sporadically elsewhere. Among individual countries, Thailand has by far the greatest number of recorded cases.4

**The Indian Subcontinent**

Until 1990, only two or perhaps three foreigners who developed melioidosis subsequent to travel to India had been reported in the medical literature, indicating the presence of the causative organism on the Indian soil.5,6 In 1991, a case of melioidosis was reported in a child in Maharashtra7 and then in 1993 a confirmed case of melioidosis was reported from Kerala.8 However, only after the recent plague scare have we become aware of the possibility.7-11 Melioidosis is suspected to be widespread in India. Cases of human melioidosis have been reported from several Indian states in recent years, including Maharashtra, Kerala, Orissa, Tripura, Tamilnadu, West Bengal and Assam.

**ECOLOGY**

*B. pseudomallei* is a widely distributed environmental saprophyte. It is now believed that the organism may exist in a viable, non-cultivable state in the environment, that it probably forms biofilms, and that interactions with other organisms particularly protozoa, might explain the adaptation of *B. pseudomallei* to an intracellular niche.12

**Acquisition**

There are several modes of acquisition of melioidosis for which there is strong evidence. These include the inoculation of environmental organisms through penetrating wounds or into existing skin lesions, the aspiration of contaminated water during near-drowning episodes,13,14 iatrogenic inoculation and laboratory-acquired infection15 resulting in the classification of *B. pseudomallei* as a containment level-3 pathogen. The evidence for other modes of infection, such as person-to-person, animal-to-person and inhalation of environmental organisms, is relatively weak.

**Descriptive Epidemiology**

Melioidosis predominantly affects people in regular contact with soil and water (e.g. rice farmers in South East Asia).16,17 The disease is particularly common in rice areas.18,19 It has been identified in patients who have been in contact with soil, dust, or contaminated water and who had skin lesions, respiratory tract infections, and/or had been burned or injured by water or soil.18,20
Asia and aboriginal in Australia). Males usually outnumber females, by 4:1 in Australia but by only 3:2 in Thailand. This is probably because in differences in the involvement of women in farming.

An important risk factor for the development of melioidosis is the presence of underlying disease, which is found in up to 76% of cases. The association with diabetes mellitus is particularly strong, and may increase the relative risk of infection by up to 100-fold. Chronic renal disease, alcoholism, malignancy, connective tissue diseases, chronic lung disease and therapy are other underlying diseases which are risk factors for the development of melioidosis.

**THE DISEASE**

The clinical spectrum of melioidosis is extremely broad, and melioidosis has been referred to as “the remarkable imitator”. Melioidosis may be recognized as inapparent infection, acute localized suppurative infection, acute pulmonary infection, acute septicemia infection or chronic suppurative infection. The incubation period has not been defined; however, based on development of infection after injury it may be as short as two days. Clinically inapparent infection may remain latent for a number of years after a person leaves an endemic area and before apparent disease ensures.

**Mild and Subclinical Infections**

Infection with *B. pseudomallei* may produce minimal or no symptoms resulting in a chronic carrier state. In these cases, the immune system is probably suppressing the infection, and no clinical disease develops.

**Latent Infections**

Melioidosis is unusual for a bacterial infection in that long periods of latency (up to 29 years) have been observed before the disease becomes clinically apparent. recrudescent infections in veterans of the Vietnam war have given rise to the nick name “Vietnamese time bomb”. Relapses usually occur at times of intercurrent stress (e.g. other acute infection, burns or trauma, malignancies) when cellular immunity is likely to be suppressed.

**Acute Septicemia Infections**

Most of these present clinically community-acquired sepsis syndrome, with a short history (median, 6 days, range, 1 day to 2 months) of high fever and rigors, although some have a less acute, typhoidal illness with a swinging fever, often associated with profound weight loss. only half have evidence of a primary focus of infection, usually in the lung or skin and subcutaneous tissues. In-patients with bacteremia complicating pneumonitis symptoms may include disorientation, extreme dyspnea, and severe cutaneous pustular lesions on the head, trunk or extremities. Confusion and stupor, jaundice and diarrhea may also be prominent features. Muscle tenderness may be striking. On examination of the chest, signs may be absent, or rales and rhonchi or pleural rubs may be heard. The liver and spleen may be palpable, signs of arthritis or meningitis may ensue. Once septic shock has supervened the mortality approaches 95%.

**Acute Pulmonary Infection**

The most common form of disease is pulmonary infection, which may represent a primary pneumonitis or hematogenous pneumonitis as a manifestation of septicemic form. The onset may be abrupt without prodromal symptoms or more gradual with headache, anorexia, and generalized myalgia. Fever occurs in almost all patients A nonproductive cough or productive cough with non-specific sputum, or haemoptysis characterizes the illness. Laboratory findings include total leukocyte counts ranging from normal to 20,000/mm³. Mild normochromic, normocytic anaemia may appear during the illness. C-reactive protein concentrations are increased (> 5 mg/dl). The pneumonia is usually a subacute cavitating pneumonia accompanied by profound weight loss, which is often confused with tuberculosis. There is a predilection for the upper lobes, although any lung zone may be affected. Relative sparing of the apices and the infrequency of hilar adenopathy may help to distinguish the two. Complications include pneumothorax, empyema and purulent pericarditis, and ultimately progression to septicemia.

**Acute Localized Suppurative Infection**

Infection by inoculation of a break in the skin usually results in a nodule with an area of acute lymphangitis and regional lymphadenitis. This form of infection may rapidly progress to the acute septicemic form.

**Chronic Suppurative Infection**

In some patients secondary abscesses develop that dominate the clinical picture. Organs involved include skin, brain, lung, myocardium, liver, spleen, bones, joints, lymph nodes and even the eye the presence of an abscess especially if associated with a splenic abscess is indicative of immediate treatment.

**Pathogenesis**

The pathogenesis of melioidosis is not completely understood. The outcome of infection with *B. pseudomallei* depends on the balance between the host’s immune system, the virulence of the infecting strain and the size and route of the initial inoculum.

The behaviour of *B. pseudomallei* as an opportunistic pathogen implies that host response is critical in determining the outcome of infection. Little is known about the specific immunologic mechanisms responsible for protection. Cell-mediated immunity is probably of particular importance, although surprisingly, human immunodeficiency virus (HIV) infection has rarely been associated with melioidosis. In inbred mouse animal model, it has been seen that interferon-γ plays a key role in controlling melioidosis. More recent in-vitro studies have suggested that not only natural-killer cells, but also CD8+T cells, activated by a cytokine-dependent bystander mechanism are the most important sources of the rapid production of IFN-γ that occurs in the innate response to *B. pseudomallei* and probably other intracellular pathogens.
Diagnosis

Melioidosis should be considered in the differential diagnosis of any febrile illness in a person who has been in an endemic area, especially if the presenting features are those of fulminant respiratory failure, if multiple abscesses develop, or if there is a radiological pattern of tuberculosis from which tubercle bacilli cannot be demonstrated.

Microscopic examination of exudate will reveal bipolar or unevenly staining Gram-negative rods, but this has a low specificity and sensitivity. Direct immunofluorescent microscopy may be helpful in endemic areas, but is not widely available.24

Bacterial identification by culture is the only accepted ‘gold standard’. Preliminary clues to spot B. pseudomallei in a specimen culture include the following: a sweet smell of putrefaction in fresh culture; wrinkled appearance of older colonies; an oxidase-positive, Gram-negative bacillus with bipolar or irregular staining; and resistance to aminoglycosides and older-generation penicillins and cephalosporins.

Serology

Detection of Antibodies

A number of serological tests for the detection of specific B. pseudomallei antibodies have been developed. One of the main drawbacks of antibody assays that limits their value in clinical situations in the presence of background antibody in some healthy individuals in the endemic area. Enzyme linked immunosorbent assay (ELISAs) which detect IgG exhibit a sensitivity of 96% and a specificity of 97%, whereas the immunoglobulin M ELISA has a sensitivity of 74% and a specificity of 99%.25 However, an internationally standardized serodiagnostic test for melioidosis is much needed.

Detection of antigens

This approach is more logical and is superior to antibody detection because it indicates active disease. Many immunological methods have been developed for the detection of B. pseudomallei antigen, including the detection of soluble secreted product in blood and urine, and the detection of whole organism in for example, pus, wound, sputum and throat swabs. Other assay systems that have been developed and evaluated include immunofluorescence24 and latex agglutination.26

Molecular approach

The hybridization techniques using specific DNA probes did not have sufficient sensitivity for B. pseudomallei infection.27 Therefore, in more recent years, the PCR approach has been more commonly performed with satisfactory results with a sensitivity of 952% and specificity of 91.7%.28

Treatment

Ceftazidime is currently the treatment of choice and should be given in full doses (120 mg/kg/day or a dose appropriately adjusted for renal function) for 2 to 4 weeks according to the clinical response. The carbapenem antibiotics have some potential advantages over ceftazidime, but await further clinical evaluation before they can be recommended as first choice treatment.29 Following parenteral treatment, prolonged oral antibiotics are needed to prevent relapse, which occurs in up to 23% of patients and is commoner in patients with more severe disease.

Prognosis

Even with optimal treatment, the mortality from acute severe melioidosis is high (30% to 47%). In-patients who survive, there is often chronic morbidity resulting both from the disease itself and the underlying conditions.

Prevention and Control

B. pseudomallei is ubiquitous in the environment in endemic areas, so it is difficult for those occupations that involve soil and water contact. To avoid exposure it is recommended people wear gloves and rubber boots while working in rice fields and that thorough cleansing of skin abrasions is done in endemic areas.

Vaccine

There is no B. pseudomallei vaccine licensed for human use, although experimental vaccines are under development. One of the promising candidate vaccine construct is the flagellin-PS (the C-polysaccharide) conjugate which possesses a number desirable attributes.30 Firstly, the incorporation of two protective antigens from the same organism enhances the immunological repertoire of the vaccine recipient, while concomitantly affording protection against strains that may become antigenically varied with respect to one of the two components via spontaneous mutations or gene recombination events. The conjugation of the PS to the flagellin carrier has also enabled to augment immune responses against the T-cell-independent type-2 PS component while simultaneously evoking desirable immunoglobulin-class-switching events. Most importantly, the use of an active vaccine containing only the PS portion of LPS, but not the toxic lipid A components, conjugated to the flagellin carrier has obviated the potential for toxic side effects associated with intact LPS. This molecule does, however, take advantage of the protective capacities inherent to the PS moiety.

Conclusion

There has never been more interest in melioidosis than there is at present. The genome of B. pseudomallei has almost been unravelled, and molecular and immunological techniques are helping to piece together the pathogenesis jigsaw. This contrasts with huge gaps in our knowledge about the distribution and incidence of the disease, the lack of really good rapid diagnostic techniques and the absence of effective treatments that are affordable in the countries where the disease is endemic. We must hope that the growing international research effort helps answer some of these questions before it is too long.

References

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**Announcement**

**ESICON 2004**

34th National Conference of Endocrine Society of India to be held from 26th – 28th November 2004 at Guwahati.

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