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Melioidosis: a neglected tropical disease

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Introduction

Melioidosis, a bacterial infection caused by *Burkholderia pseudomallei*, is endemic in the tropics between 20° S and 20° N of the equator [1]. Sri Lanka, positioned between 5-10° N, is situated in the endemic belt. *B. pseudomallei* is a soil saprophyte and infection is probably acquired from contaminated soil and water. Risk factors include occupational exposure to surface water and mud, particularly during rice cultivation [2]. Sri Lanka provides the ideal environmental conditions for this pathogen.

Geographical distribution

B. pseudomallei was first described by Whitmore and Krishnaswami in 1912, as the cause of an unknown infective disease occurring in Rangoon, Burma [3]. Stanton and Fletcher described a wide variety of manifestations of the disease in Kuala Lumpur. They proposed the name “melioidosis” because many of the manifestations resembled glanders, which was called ‘melis’ in Greek [4]. Further cases were reported from Singapore (1920) and Vietnam (1925-30) [5]. Sri Lanka, then Ceylon, described its first patient in 1927 [6]. Melioidosis, next emerged as a problem of military medicine. Melioidosis was seen in soldiers during World War II and in French and US troops returning from the Vietnam War [7].

Since then, the number of countries reporting melioidosis has expanded to encompass most of the tropical belt. Northeastern Thailand, the ‘Top End’ of Australia, Malaysia and Singapore have emerged as ‘hyperendemic’ areas for melioidosis, with a high incidence of community acquired infection [1]. This is probably due to the combination of high rates of transmission and good laboratory diagnostic facilities. It is instructive to note that melioidosis was once considered a ‘rare’ infection in these countries until the true burden of disease was ascertained, giving rise to the ‘tip of the iceberg’ sobriquet [8]. It is likely that melioidosis remains under-diagnosed in other endemic countries due to lack of awareness among clinicians and inadequate laboratory services.

A recent study estimated that 3 billion people live in areas at risk of melioidosis and that the incidence rate in such areas is around 5 per 100,000. Using mathematical modelling, the authors calculated that 165,000 (68,000-412,000) melioidosis cases and 89,000 (36,000-227,000) deaths occurred in



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2015, globally. The highest burden (44% of cases) was projected to be in South Asia with 73,000 (31,000-171,000) cases and 42,000 (18,000 - 101,000) deaths. The case load for Sri Lanka was predicted as 1881 (705-4488) cases with 619 (230-1501) deaths. The authors emphasised that melioidosis is probably grossly underreported in the 45 known endemic countries and in a further 34 countries that have still to report a single case [9].

Epidemiology

Melioidosis is an infection of rural, agricultural communities, as one may expect of an infection associated with occupational exposure to soil and water. Perhaps for the same reason, it affects males disproportionately. Infection has been reported in all ages, including neonates and the elderly. Risk factors include farming, especially rice farming, cultivation, military, construction and use of untreated water sources [10].

Infection is usually sporadic but increases in the wet season [11]. Case clusters have been seen after stormy weather [12] and after natural disasters, such as the tsunami of 2004. Outbreaks are rare and attributable to a single environmental source [13].

Transmission and infection

B. pseudomallei is acquired directly from soil and water [7]. Infection is accidental, occurring during occupational, recreational or cultural exposure to soil and water. People resident in endemic areas are at risk, especially in rural settings where most of the population would be involved in some form of cultivation. Most infection probably occurs via direct inoculation from soil and water into unapparent minor wounds on the feet. Inhalation is also a likely route of acquisition which would explain the increased incidence seen during the rainy season or in stormy weather [12]. Ingestion may account for outbreaks of melioidosis due to contaminated water supplies [13].

It is likely that exposure is very common in endemic countries but is rarely followed by clinical disease which usually requires the person to have some co-morbidity [7]. *B. pseudomallei* may be considered a free-living inhabitant of soil and water and an accidental, opportunistic pathogen that only infects the human host when there is lowered resistance in the host or when there are favourable transmission dynamics eg large dose, traumatic inoculation, aerosolisation, aspiration etc [10].

Risk factors

The vast majority of people who develop clinical melioidosis have some form of immune compromise [7]. Diabetes is the most significant predisposing factor for melioidosis, found in up to 74.7% of patients [14]. Melioidosis is also more common in people with renal or liver disease and chronic lung disease. Alcoholism and

thalassaemia are other common predisposing conditions. However, melioidosis can affect healthy individuals of any age [7].

Incubation period

The incubation period of melioidosis is highly variable. While most cases are acute and occur 2-21 days (mean 9 days) after exposure the bacterium can remain latent in the body and manifest months, years or decades later. Long incubation periods, ranging from months to many decades, were reported in French and American soldiers returning from Vietnam and gave the disease the epithet "Vietnamese time-bomb disease". *B. pseudomallei* is a facultative intracellular pathogen that is capable of infecting, surviving and replicating inside phagocytes, which may account for its tendency to remain latent for long periods.

Pathology and clinical presentation

The underlying pathology is variable, ranging from acute pyogenic suppuration to chronic granulomatous inflammation. This, in turn, gives rise to protean clinical presentations ranging from fulminating septicaemia with rapid mortality to a more chronic state with the formation of abscesses in different organs. Melioidosis presenting as acute sepsis with a rapid course and high mortality may be mistaken for cholera, malaria or typhus. Subacute febrile illness may be misdiagnosed as enteric fever, leptospirosis, miliary tuberculosis or plague [5]. Suppuration is a characteristic feature and lung, splenic, liver, brain, kidney, prostate and parotid abscesses may be seen. The lung is the most common organ involved and infection may manifest as acute lobar or bronchopneumonia, empyema, lung abscess or even mimic caseating tuberculosis [7]. The spleen is often affected and this may give a clue that this is melioidosis. Liver abscess may be misdiagnosed as amoebic abscess. Cystitis and pyelonephritis are infrequent but secondary abscesses in the kidney are common. Skin involvement varies from an acute pustular rash to multiple subcutaneous abscesses and bullae to chronic leprosy-like lesions. Wound infection is common, including that following trauma, such as during the Indian Ocean tsunami. Lymph node and intramuscular abscesses are reported. Septic arthritis is a common secondary complication. Chronic osteomyelitis with sinus formation has been described. The clinical spectrum varies geographically, with parotid abscess being more common in Thailand and prostatic abscess and encephalomyelitis more common in Australia.

It is preferable to consider melioidosis (like tuberculosis) as a collection of clinical syndromes with a common bacterial aetiology than as a disease with a well characterized clinical presentation and pathology. The most striking clinical feature of melioidosis is the involvement of more than one tissue or organ system.

Outcome

Melioidosis is typically progressive with a very high mortality. Melioidosis was almost uniformly fatal in the pre-antibiotic era. More recently, overall mortality in endemic areas has come down to 9% in Australia [15] and 40.5% in Thailand [16]. Even after successful treatment of acute infection the bacterium tends to persist and relapse of infection is well described. In one study over 20 years, relapse was seen in 6% [15]. A prolonged course of oral antibiotics (eradication therapy) is required to reduce the rate of relapse.

Laboratory diagnosis

The protean clinical manifestations mean that it is very difficult to make a clinical diagnosis. Therefore, confirmation is dependent on isolation of the pathogen from patient samples including blood, pus, sputum or urine. The indirect haemagglutination assay (IHA) is the most widely used serological method. However, false positives may occur due to prior exposure to the organism in indigenous populations and false negatives may occur early in infection.

Treatment guidelines

Standard treatment guidelines use ceftazidime, imipenem or meropenem for a minimum of 10-14 days for the acute parenteral phase and cotrimoxazole, doxycycline or co-amoxiclav for 3-6 months for the oral eradication phase [17]. The aim of the acute phase treatment is to minimize mortality from acute infection and the goal of the eradication phase is to prevent relapses. The response to treatment is slow and spread of infection and culture positivity may continue but does not warrant change of antibiotics. A careful search for abscesses (especially prostatic abscess) and other collections (eg. joint effusions) and drainage is recommended. Mild, localized cases (eg. lymphadenitis) have responded to drainage alone or drainage followed by oral therapy [10]. Therapy according to treatment guidelines has decreased mortality and reduced the relapse rate. However, the difference in case fatality rates between Thailand and Australia point to other factors such as the availability of state of the art intensive care facilities, better metabolic control and management of organ failure as being important for the more severe cases.

Melioidosis in Sri Lanka

Active surveillance has established that melioidosis is endemic in Sri Lanka, with a wide geographic and demographic distribution [18, 19]. Methodical case finding, education of laboratory staff and clinicians and laboratory capability-building with external reference centre support was able to reveal the widespread distribution of a previously undetected infection. Melioidosis in Sri Lanka is related to the outdoor, agricultural, barefoot lifestyle practiced by the majority.

Public health issues

Melioidosis may be considered a highly neglected tropical disease with a high (and as yet unknown) morbidity and mortality in the economically most disadvantaged communities. The burden of disease is likely to increase due to steep population growth and the rising prevalence of diabetes in such regions. Climate change has increased the likelihood of severe weather events, such as storms and flooding, that are associated with case clusters with increased mortality [20].

Steps that should be taken to address this situation include raising awareness of this infection in global public health organizations such as the World Health Organisation, making melioidosis notifiable in all countries where it is likely to be endemic, improving access to health care in poor rural communities, devising and distributing inexpensive point of care tests for melioidosis to hospitals in such areas and making effective antibiotics affordable in these populations. Exposure mitigating practices such as use of mechanical agriculture and protective clothing when coming into contact with mud and water may reduce infection [20] but may not be practical. As melioidosis is caused by a soil and water saprophyte that infects both animals and humans it is an ideal candidate for the 'One Health' approach to control. This demands the involvement of a multidisciplinary team of physicians, veterinarians, microbiologists and public health personnel.

Conflict of interest

There are no conflicts of interest.

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