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Melioidosis: distinctive clinico-epidemiological characteristics in southern India

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Abstract

As it is increasingly being reported from India, we carried out a prospective study of patients with culture-proven melioidosis from south India, examining clinical, laboratory features, epidemiological data, risk factors, treatments, outcomes at three and six months, and factors associated with mortality.

Between 2014 and 2018, 31 cases were identified. Diabetes (83.9%) and alcohol abuse (58.1%) were common risk factors. Musculoskeletal, skin and soft tissue manifestations together constituted 48.4% of presentations, while 29% had pneumonia. During the intensive phase, 74.2% received one of three recommended antibiotic regimes, but 51.6% did not receive continuation treatment. Pneumonia and lack of continuation treatment were independently associated with a high mortality of 25.8%. Hot spots for melioidosis exist in India, and there is considerable diversity of presentation, including skin, soft tissue, musculoskeletal and neurological involvement. High rates of bacteraemia are shown.

Keywords

Burkholderia pseudomallei, pneumonia, epidemiology, mortality

Introduction

Burkholderia pseudomallei has been known to microbiologists for nearly a century; however, its pathological significance in humans became evident during the Vietnam War when it was increasingly recognised as a cause of serious infections among soldiers.[1] Subsequent research led to identification of large endemic areas in Southeast Asia and Australia.[2] According to the estimates based on recent statistical modelling studies, at least 165,000 melioidosis cases occur every year, of whom 89,000 die.[3] It is also suggested that the infection is underreported from current endemic areas and that endemicity exists in approximately 34 countries that have not yet reported cases. The findings of the Darwin study, the largest series on melioidosis to date, threw light on the varied presentation of the disease and the risk factors associated with it; however, data were entirely collected from the Australian continent, a traditional 'hotspot' of melioidosis.[4] Various investigators have reported series of cases from endemic pockets in Southeast Asia, albeit not comparable to the Darwin study in numbers.[5–7] The majority of cases in India have been reported from Mangalore, a coastal town in the southwestern part.[8,9] The clinical and epidemiological features in all these studies are remarkably similar, despite diversity in the number of cases described. Pneumonia was the commonest presentation and diabetes the commonest risk factor; high mortality rates were recorded.[8] Since 2013, an increasing number of cases have been detected in and around Pondicherry, a small town, formerly a French colony, located on the south-eastern coast of India. Preliminary data

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suggested that the clinical and epidemiological features of our cases were different from those reported elsewhere.

Materials and methods

We conducted a prospective study after obtaining approval from our Institute Research and Ethics committees. We included adults admitted to our hospital between January 2014 and March 2018 with proven isolation of *B. pseudomallei* from blood or other body fluids (urine, cerebrospinal fluid [CSF]), aspirated material (from abscesses, bone marrow) or sputum. Specimens were processed according to standard microbiological procedures.[10] Organisms were further confirmed by *VITEK*® 2 compact instrument (Bio Merieux). Isolates were tested against the antibiotics ceftazidime, piperacillin tazobactam, imipenem, meropenem and cotrimoxazole.

Patient data consisted of demographic information including age, gender, place of residence, occupation and any habits such as alcohol abuse, and disease-related information including duration of chief symptom(s) before seeking medical care, clinical presentation (pulmonary symptoms or signs, musculoskeletal, neurological, skin and soft tissue manifestations, deep-seated abscess, sepsis without foci and genitourinary manifestations). Infection was considered acute if symptoms were present for <2 months and chronic if duration was >2 months.[4] Relevant laboratory parameters at admission including complete blood counts, erythrocyte sedimentation rate, liver function tests, renal function tests and electrolytes, blood, urine and sputum cultures were recorded on all patients. Depending on the clinical picture, cultures were also performed on synovial fluid, CSF, pus from aspirates and bone marrow aspirates. A chest radiograph was done for all patients while selected patients underwent an abdominal ultrasound and/or computed tomography (CT) scan at the discretion of the treating clinician, on a case-by-case basis. We reviewed the treatment given to patients with reference to the choice of empiric and definitive antibiotics, duration of intensive therapy and duration of maintenance therapy. We documented the outcomes at the end of hospital stay as well as at three and six months of treatment to determine complete cure, partial cure (with residual functional deficit), death, loss to follow-up and recurrent melioidosis.

Descriptive statistics were used to represent clinical and epidemiological characteristics of patients. Survival patterns were obtained by Kaplan–Meier method and Log Rank test was performed to identify significant factors. Risk factors were determined using Cox hazard analysis.

Written informed consent was obtained from all patients (or relatives when this was not possible). All data have been maintained confidentially and the study was approved by the Institute Ethics Committee (RC/16/74).

Results

During the study period, 31 patients (27 men, 87.1%) were diagnosed with melioidosis (mean age = 47.4 ± 13.9 years) and 20/31 (64.5%) patients were farmers. The majority (64.5%) of cases presented during the cooler months of the year (November to February), which corresponds with the Indian north-eastern monsoons, although the disease was present throughout the year. The median duration of symptoms before presentation was 14 days (range = 5–180 days). Alcohol consumption was identified in 18 (58.1%) patients, while diabetes was present in 26 (83.9%) patients. Two patients were taking immunosuppressive medication.

Presentations varied: musculoskeletal and dermatological predominated in 15 (48.4%) cases; pulmonary in 9 (29.0%); deep-seated abscess in 7 (22.6%); neurological in 4 (12.9%); genitourinary in 2 (6,5%); and sepsis with unknown focus in 3 (9.7%) cases. Only three had chronic infection.

Blood culture was positive in 28 (90.3%) patients while the organism was cultured from bone marrow in one patient and from sputum in 3 (9.7%) patients. Major laboratory abnormalities identified are summarised in Table 1. A notable finding was a consistent elevation of alkaline phosphatase levels disproportionate to a mild rise in liver transaminase levels.

Table 1. Significant laboratory derangements in patients with melioidosis (n = 31).

Parameter	Mean ± SD	Proportion of patients with abnormal values (%)
Total leucocyte count ($\times 10^3$)	11.2 ± 4.6	41.9
ESR (mm/h)	64.1 ± 36.4	74.2
Alkaline phosphatase (IU/L)	201.4 ± 136.5	58
SGOT (IU/L)	84.8 ± 143.6	48
SGPT (IU/L)	66.7 ± 66.6	51.6
Serum albumin (g/dL)	2.8 ± 0.7	83.8*
Serum sodium (mmol/L)	128.2 ± 6.8	66.7*

*Abnormally lower than reference range values. All others are abnormally high values.
ESR, erythrocyte sedimentation rate; SD, standard deviation.

Hypoalbuminemia was very common and detected in 83.8% and hyponatremia in 66.7%.

One of the three recommended first line agents was received by 23 (74.2%) patients as intensive treatment, but 16 (51.6%) did not receive any continuation phase treatment. Among the 15 patients who were initiated on continuation phase treatment, 11 (35.5%) received trimethoprim-sulfamethoxazole, 3 (9.7%) received doxycycline with trimethoprim-sulfamethoxazole and 1 (3.2%) received only doxycycline. A total of 8 (25.8%) patients died in hospital; two of these patients had culture-proven recurrence (at three and five months), both of whom succumbed to illness. Nine (29.0%) patients were lost to follow-up, but 14 (45.1%) were known to have been completely cured at the end of the six months of follow-up.

Cox Regression analysis showed that neither age, gender, duration of symptoms before presentation, use of alcohol, diabetes mellitus, specific organ involvement nor abnormal laboratory tests had significant association with mortality. Only pulmonary manifestations and lack of continuation therapy were independently associated with mortality.

Discussion

While most studies have identified pneumonia as the most common manifestation of melioidosis,[4,8,11] we found a composite of skin, soft tissue and musculoskeletal involvement as predominant presentations (48.4%). This parallels recent reports from south India[12] and Bangladesh.[13] Unusual skin and soft tissue presentations such as lid abscess have previously been reported from our centre.[14]

Although inhalation and inoculation have been identified as the common routes of transmission of melioidosis, the relative contribution of each to the development of specific clinical manifestations remain unknown. It is logical to believe that pneumonia is probably a reflection of inhalational transmission, while skin, soft tissue and musculoskeletal involvement suggest inoculation. This implies contact with contaminated soil and surface water.

Microbiological confirmation of *B. pseudomallei* is a key element in the diagnosis of melioidosis. Bacteraemic melioidosis was remarkably high in our study, in contrast to most other series.[4,8,12,13] This is significant given that the organism is often misidentified as *Burkholedria cepacia*, an emerging cause of hospital-acquired infections. The two may be differentiated by simple biochemical tests in the laboratory but may require confirmation by automated systems.

Awareness regarding melioidosis is still low leading to undertreatment and improper antibiotic choice. The lack of continuation phase treatment was independently associated with mortality at six months. While improper/inadequate continuation phase antibiotics have been associated with recurrence in previous studies, it has not previously been linked to mortality.[4,8,12,13] Although infrequent in our study, it was fatal.

Our study had some limitations, with fewer cases than the series from Mangalore. A significant number of patients were lost to follow-up; some of these patients may have died. We conclude that south India is yet another potential hot spot, where the clinical presentation appears different from other endemic areas.

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