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RESEARCH

Clinico-epidemiological spectrum of melioidosis: a 2-year prospective study in the western coastal region of India

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Objective: To determine the geographical epidemiology, clinical presentations and risk factors associated with melioidosis.
Methods: A total of 28 confirmed cultures of *Burkholderia pseudomallei* were isolated and prospectively analysed with respect to clinico-demographic factors.
Results: Age groups ranged from neonate to 84 years of age. Five children were less than 12 years of age. There was a male predominance of 71.4%. There was a crude mortality of 25%; all deaths were due to septic shock, 42.8% of which occurred within 48 hours of admission. A strong linear association ($p = 0.01$) was found between intensity of rainfall and presentation of cases. Proportion of cases and mortality were greater among those with occupational or recreational exposure to soil (75%). Pneumonia (32.1%) was the most frequent primary clinical presentation and diabetes mellitus (64.3%) constituted a major risk factor for both development and death due to melioidosis. Higher occurrence of mortality was noted among patients with chronic kidney disease (CKD) than others (Fischer's exact test $p = 0.04$). One case of recurrence was noted.
Conclusion: Melioidosis is quite prevalent in the western coastal region of India and is strongly associated with intensity of rainfall. There is increased risk among diabetics and to those who are exposed to soil and surface water. Melioidotic lymphadenopathy may mimic tuberculosis, hence should be considered as a differential diagnosis. Patients with bacteraemia have a poorer prognosis; and, septic shock relates to imminent death.

Keywords: *Burkholderia pseudomallei*, India, lymphadenopathy, Mangalore, melioidosis, paediatric, relapse

Introduction

Melioidosis, a disease of public health importance, is caused by the soil dwelling Gram negative bacillus, *Burkholderia pseudomallei*. The disease is typically endemic to parts of North East Thailand and northern Australia; but, its global distribution has expanded owing to greater recognition, with recent reports of melioidosis coming from southern China, Hong Kong, Taiwan, the Indian subcontinent and parts of the Americas.[1] The disease is now believed to represent a serious global threat.

The clinical manifestations of the disease are protean, with a spectrum ranging from asymptomatic, or subclinical infection, to fatal fulminant pneumonia, or septic shock, with a mortality of up to 90%.[2] Melioidosis may occur as a result of activities leading to increased exposure to environments containing *B. pseudomallei*. Transmission of infection may occur through direct skin inoculation, contamination of wounds, inhalation or ingestion.[1] Diabetes is the most common risk factor associated with the disease.[1,2]

Burkholderia pseudomallei is an emerging infection in India, evident from numerous case reports from Karnataka, Kerala, Tamil Nadu, Maharashtra, Tripura, Assam, West Bengal and Orissa.[3–8] A higher incidence of cases has been reported from Western coastal regions as compared to the rest of India.[3] Recently, *B. pseudomallei* was isolated from soil in the eastern coastal region of India, thereby defining the geographical area in which humans and animals have an increased risk of melioidosis infection.[9] Studies have shown a positive correlation between the incidence of melioidosis and monsoon rains in endemic areas.[1] Environment studies have also found increased melioidosis cases among paddy workers.[10] The presence of environmental conditions such as temperature and precipitation, as well as a similar working conditions, provide ideal conditions for disease endemicity in the western region of India. Hence, a prospective study was carried out to determine the epidemiology, clinical presentation and risk factors of this disease.

Materials and methods

This prospective study was approved by the institutional ethics committee (FMMC/IEC/947/2012) and the data were analysed anonymously. The trial was registered at the Clinical Trial Registry, India (CTRI/2013/07/003834). All the patients with confirmed melioidosis cases who visited Father Muller Medical College and Hospital, Mangalore, between September 2012 and August 2014 were included in the study. Confirmation of melioidosis was carried out by specimen cultures and serological tests.

Blood cultures were performed using the BACTEC 9120 Automated blood system (Fluroscent series, Beckton Dickinson, USA). All other specimens were cultured on 5% sheep blood agar (Himedia, India) and MacConkey Agar (HiMedia, India). Isolates were identified by standard microbiological procedures.[11] Positive identification encompassed: oxidase positive; motile; Gram negative bacilli with bipolar staining; wrinkled colonies with a metallic sheen on blood agar; oxidative utilisation of glucose, lactose and maltose; positive for arginine dihydrolase; reduced nitrate to nitrites; positive gelatin liquefaction; growth at 42 °C; resistant to gentamicin (10 µg/disk) and colistin (30 µg/disk); sensitive to amoxicillin-clavulanate (20/10 µg/disk); and, growth on Ashdown agar, with formation of purple, rugose, cauliflower head colonies.[12] All the isolates were confirmed by slide latex agglutination using 4B11 monoclonal antibody (99.1% sensitivity).[13]

Investigation, treatment and follow up of cases was carried out. All the melioidosis cases were followed for a minimum of 12 weeks after discharge until eradication therapy was completed or death. All the risk factors and underlying comorbidities, including demographic details such as age, sex, location and occupation were noted. To determine the correlation of rainfall with melioidosis, the month of clinical presentation was noted. Average monthly rainfall data from 2012 to 2014 were obtained from the India Meteorological Department.[14]

Melioidosis was classified as bacteraemic (a positive blood culture with single or no focus of infection) or non bacteraemic (a single or more focus of infection and negative blood culture). Clinical presentations were defined as acute (symptoms present less than 2 months) or chronic (symptoms present over 2 months) in nature.[15]

Diabetes mellitus was defined as a fasting blood glucose level of 126 mg/dl or post-parandial blood glucose level of 200 mg/dl.[16] Excessive alcohol consumption was defined as 14 drinks per week, or 4 drinks per occasion, for men and more than seven drinks per week, or three drinks per occasion, for women.[17] Chronic kidney disease was defined as kidney damage or glomerular filtration < 60 ml/min/1.73 m^2 for ≥ 3 months.[18] Chronic lung disease defined as documented diagnosis of chronic airway obstruction disease.[15]

Statistical analysis

The data obtained were analysed using SPSS Software version 13. Association between categorical variables were analysed using Fischer's exact test. A p value of < 0.05 was considered significant. Binomial test and chi-square tests were used to analyse the significance among the categorical variables.

Results

A total of 28 cases of melioidosis were confirmed during the two year study period.

All the patients who presented to the hospital came from the western coastal belt of India, extending from Karwar in northern Karnataka to Kannur in Kerala. Majority of these patients hailed from Mangalore in Karnataka, Kannur and Kasargod in Kerala. (Figure 1)

The age of presentation ranged from a pre-term neonate to 84 years (median age: 48 years). Majority (64.3%) of the patients were aged ≥ 40 years. Five cases were children (≤ 12 years); among them was a pre-term neonate. Male preponderance was seen (71.4%; $p = 0.03$).

Figure 1: Geographical distribution of 28 melioidosis cases.

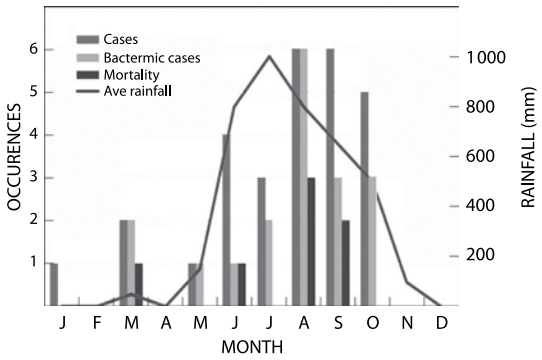

Figure 2: Relationship between average monthly rainfall, occurrence of cases, bacteraemia and deaths.

Out of 28 cases, 18 (64.3%) presented with bacteraemic melioidosis. A total of seven fatal cases were recorded, of which five (71.4%) were bacteraemic. One case of death was due to paediatric melioidosis, which is a rare finding. All deaths occurred due to septic shock.

Overall, twenty four patients (85.7%) presented during the monsoon months (June to October, southwest monsoon). Figure 2 shows the average monthly rainfall,[19] occurrence of melioidosis, incidence of bacteraemia and the number of deaths resulting from melioidosis. A strong linear association was found between intensity of rainfall and occurrence of cases (p = 0.001). In the study, an adjusted relative risk of 4.67 for bacteraemic cases and 5.0 for deaths were noted among melioidotic cases during monsoons as compared to rest of the seasons.

A higher number of melioidosis cases (21; 75%, p = 0.01) were identified among those who had history of exposure to soil and surface water either due to occupational (farming, fishing, forest guard, etc.) or recreational activities when compared to other cases of melioidosis.

Clinical presentation

Pneumonia (9; 32.1%) was the most common presentation on admission, followed by bacteraemia with no evident focus (6; 21.4%), lymphadenopathy (3; 10.7%), septic arthritis (3; 10.7%) and genitourinary infection (3; 10.7%). (Table 1)

All the cases of pneumonia presented during the monsoon months (June to October); however the presentation was more common during the peak of monsoon (July–August) than to other months. Pneumonia was the most common presentation and was responsible for the highest mortality (71.4%) seen among the bacteraemic cases.

Of the three cases of melioidotic lymphadenopathy, one was bacteraemic and involved the submandibular lymph nodes. The other two cases involved the upper deep cervical lymph nodes, one of which was seen in a 2-year-old child. In fine needle aspiration cytology, lymph nodes in all cases showed granulomatous reactions mimicking tuberculous lymphadenitis.

Melioidotic septic arthritis affects mainly the large joints, such as the knee, elbow and shoulder joints.[3] In our study, all three cases presented with septic arthritis of the knee joints.

All the cases of genitourinary melioidosis were seen in males. Two presented with prostatitis and one presented with severe dysuria and fever. Two of these cases died: one within 48 hours of admission and the second after 48 hours. Both patients were already in septic shock during admission and succumbed to death due to multi organ failure. Two cases of superficial abscess presented: one as an anterior chest wall abscess and the other was a neck abscess. Both were treated with a local incision and drainage, followed by antibiotics.

One case was confirmed as recurrent melioidosis following completion of antibiotic therapy; and, clinical improvement has been isolated. The case had presented as hepatomegaly, initially with right lobe liver abscess, but no culture was done. Thereafter, the patient presented twice, once as pericardial effusion and the other as an anterior chest wall abscess. In both, melioidosis was proven by culture and treated. Differentiation of relapse from reinfection can be proven only by DNA sequencing which was not performed.

Predisposing factors were present in 27 cases (96.4%). Eighteen (64.3%) cases were either newly diagnosed or uncontrolled

Table 1: Clinical presentation in melioidosis cases

Clinical presentation	Number of cases (*n*)	Septic shock cases (%)	Deaths (%)
Bacteraemic melioidosis	**18**	**05**	**05**
Pneumonia	08	03 (37.5)	03 (37.5)
Septic arthritis	01	-	-
Lymphadenopathy	01	-	-
No evident focus	06	01 (16.7)	01 (16.7)
Genitourinary	01	01 (100.0)	01 (100.0)
Cellulitis	01	-	-
Non Bacteraemic melioidosis	**10**	**02**	**02**
Pneumonia	01	01 (100.0)	01 (100.0)
Septic arthritis	02	-	-
Lymphadenopathy	02	-	-
Genitourinary	02	01(50.0)	01(50.0)
Splenic Abscess	01	-	-
Soft tissue abscess	02	-	-
Total	**28**	**07**	**07**

Table 2: Risk factors in melioidosis

	Risk factor	Number (% total cases)	Died (% mortality)	*p* - value[a] (Fischer's exact test)
1	Exposure to soil	21 (75.0)	5 (23.8)	0.58
2	Diabetes	18 (64.3)	6 (33.3)	0.18
3	Age ≥ 40 years	18 (64.3)	6 (33.3)	0.36
4	Alcoholism	06 (21.4)	3 (50)	0.14
5	Chronic kidney disease	04 (14.3)	3 (75)	0.04
6	Chronic lung disease	03 (10.7)	1 (33.3)	0.59
7	Immunocompromised state[b]	03 (10.8)		
8	No defined risk factor	01 (3.6)		

[a]Risk factors present versus mortality in culture positive.
[b]One case of preterm, steroid therapy and malnutrition.

diabetics and 18 (64.3%) cases were aged over 40 years. Alcoholism, chronic kidney disease and chronic lung disease were other risk factors. There was a statistically higher occurrence of mortality among patients with chronic kidney disease (CKD) than those without CKD (Fischer's exact test $p = 0.04$).One case had no defined risk factor. (Table 2)

Three of the cases had co-existing infections (1 case of dengue, 1 case of leptospirosis and 1 case of hepatitis B).

Antibiotic susceptibility was determined by means of the agar disk diffusion (Hi Media, India) as per the manufacturer's guidelines. The clinical isolates from all the 28 cases were sensitive to ceftazidime (30mcg, HiMedia India), trimethoprim sulfamethoxazole (1.25 / 23.75 mcg, HiMedia India), doxycycline (30 mcg, HiMedia India), imipenem (10 mcg, HiMedia India) and meropenem (10 mcg, HiMedia India). Based on the laboratory reports patients were treated, as recommended, with intravenous ceftazidime during the acute phase (2 weeks) and trimethoprim–sulfamethoxazole alone or in combination with doxycycline, during the eradication phase (12–20 weeks).

Discussion

Although numerous melioidotic cases have been reported from the western coastal region of India, lack of awareness could be a hindering factor in identification of such versatile bacteria.

Under the Köppen climate classification, Mangalore has a tropical monsoon climate and is under the direct influence of the Arabian Sea branch of the southwest monsoon. It receives about 95% of its total annual rainfall within a period of about six months from May to October, while remaining extremely dry from December to March.[14] The association of occurrence of melioidotic cases with intensity of rainfall is well documented among multiple studies carried out in endemic regions of northern Australia and Thailand.[19,20] In our study, a strong association of disease presentation to climate was noted where 85.7% of patients presented during the monsoon ($p = 0.001$).

Burkholderia pseudomallei is a soil saprophyte in endemic regions, which spreads through inoculation or inhalation.[21] In a recent publication, it was been isolated from soil in the eastern coastal part of India.[9] In an unpublished study, *B. pseudomallei* has also been isolated from soil in Mangalore. The intensity of rainfall has shown to be an independent risk factor for pneumonia, septic shock and death.[20] In our study, a similar association was seen where 85.7% of melioidosis cases, 83.3% of bacteraemic cases, and 85.7% of septic shock and death cases occurred during the monsoon months. Multiple possible explanations have been suggested through different studies for the increased severity of cases following rainfall, including: aerosolisation from soil and surface water during heavy winds and rain; and, larger doses of inoculation as seen in drowning cases and more virulent bacteria.[20]

The overall mortality rate (25%) was high in our study. Development of septic shock appears to be a mortality indicator as all the cases that developed septic shock in our study died. Out of seven, two presented with septic shock at admission and one developed septic shock within 24 hours of admission. All three of these cases died within 48 hours before identification could be made and appropriate treatment initiated. The rest of the mortality occurred after treatment with appropriate standard antibiotics (intravenous ceftazidime 50 mg/kg Three times a day) were started, thereby highlighting the vicious nature of infection once it is established. Persistence of a high bacterial load in the presence of appropriate antibiotic treatment raises questions on whether or not different mechanisms of virulence could be responsible for the refractoriness.

Various studies have demonstrated that melioidosis is more common among adults than children. [22] This concurs with the finding in our study (23; 82.1% of the total cases). Overall, paediatric melioidosis constitutes for 5 – 15% of the total melioidosis cases; and, the mortality in paediatric cases is 35%, compared to 50% in adults. In our study, similar results (7 fatal cases; 25% of total) were obtained. A single death was reported in the paediatric age group: the patient had grade II malnutrition as a risk factor on presentation.[23]

Males formed the higher proportion of cases (71.4%). Male predominance has been documented in studies from endemic regions. Males accounted for 66.7, 69.0 and 61.8% of cases in India,[3] Australia[15] and Thailand,[19] respectively. This can be explained as males have a higher exposure to outdoor activities, either in occupational or recreational form, than females.

Exposure to soil or surface water has been documented and identified as a risk factor for melioidosis acquisition.[21] In a Thailand study, diabetic rice farmers had a six to nine time higher risk at contracting melioidosis as compared to non-diabetic and non-rice farmers. In northern Australia, 75% of cases had exposure through recreational activities and 18% by occupational activities.[15] In our study, overall 75% had such exposures, which was comparable to studies from endemic areas; most of which had occupational exposure.

Pneumonia as the most common clinical presentation (32.1%) correlates with other studies being carried out. The incidence was similar to the Indian study[3] (34.7%) but less than that seen in other endemic regions. In a study from Darwin, northern Australia,[15] pneumonia accounted for 51% of cases while in Thailand[21] it accounted for 45% of total cases. Inhalation is believed to be the mode of acquisition of pulmonary melioidosis, especially during extreme weather like cyclones and heavy rainfall. In our study, all the acute pneumonia presented during monsoon.

There were differences in clinical presentations in the study, with a higher number of melioidotic lymphadenopathy and musculoskeletal melioidosis and lower proportion of genitourinary melioidosis, as compared to studies from Australia[15] and Thailand.[21] The presentation in this study was similar to an Indian study[3] carried out in the same population, except that genitourinary cases were isolated in this study but were not reported in the Indian study.

Lymph node involvement by *B. pseudomallei* is a rare phenomenon. In various studies, suppurative involvement of mediastinal, inguinal and lymph nodes from the head and neck have been reported.[24] In our study, involvement of lymph nodes from the upper deep cervical nodes and submandibular nodes were reported on. All were suspected to be tuberculous in nature and Fine Needle Aspiration cytology (FNAC) was carried out. The lymph nodes had the histopathological picture of granulomatous inflammation mimicking tuberculous lymphadenitis but smears for acid fast bacilli were negative.[3] In a study of 100 suspected lymphadenitis cases undergoing FNAC in our institution, microbiological work-up showed growth of *Mycobacterium tuberculosis* complex in 46 specimens with *Burkholderia pseudomallei* in 3 cases (unpublished data). Hence, melioidosis should be considered as a differential diagnosis for all granulomatous lymphadenitis that is acid fast bacilli negative in a high tuberculosis burdened country like India.

Musculoskeletal melioidosis is a well-recognised manifestation but rarely presents in endemic areas. In the studies from Darwin, Australia and the Infectious Diseases Association of Thailand series, musculoskeletal infection accounted for 3.75% and 5% of the total cases respectively.[15,21] In contrast, in our study all such cases presented as septic arthritis involving knee joints and accounted for 10.7% of the total cases.

Melioidotic abscesses may either serve as a source of systemic infection or result from hematogenous spread.[21] On presentation of abscesses at unusual sites such as the spleen, prostate and parotid,[25] a differential diagnosis of melioidosis should be considered. In Thailand, 95% of splenic abscesses were due to *B. pseudomallei*. In our study, internal organ abscesses were uncommon, except for one case of splenic abscess. This may have been either due to lack of awareness among clinicians to carry out investigations, such as ultrasound, to find secondary foci or failure to send an abscess sample for microbiological work-up.

Recurrent melioidosis after an apparent cure is well documented in endemic areas. Reported rates of recurrences are 16% in Thailand[26] and 6% in northern Australia.[15] A Thailand study showed 75% were due to relapses, while the rest were due to reinfection. The most important determinants were the choice and duration of oral eradication therapy, bacteraemia on admission, multifocal distribution and diabetes mellitus. In our study, only one recurrence was identified, which was in a non-diabetic patient who had bacteraemia on initial presentation.

Diabetes is well known to be an important risk factor and the rate of newly diagnosed or uncontrolled diabetes in our study (64.3% of the total melioidotic cases) compares well with the rates obtained in endemic regions. It has been established that incompetent neutrophil function reduces phagocytosis, which increases the risk among the diabetics.[27] According to the International Diabetes federation, India is presently home to 65.1 million diabetics; ranking second in the world with 52% of them unaware or undiagnosed. It has been forecast that there will be 100 million diabetics in India by 2030. Therefore, it is quite apparent that if the rising diabetic trend goes unchecked, melioidosis might soon emerge as a common and major infectious disease in this country.

Conclusion

India is an agro-based economy, where around 70% of the population earns its livelihood from agriculture. Rice is a staple crop and paddy fields are present all over the country. The southern coastal region of India receives monsoons almost one third of the year, with Mangalore being among the wettest places in India. An increased number of melioidosis cases have been reported from this part of India; and, is strongly associated with the intensity of rainfall. An increased clinical vigilance with good microbial work-ups would help with improved, accurate and rapid diagnosis. A soil study to determine environmental presence of the bacteria in the region showed positive results and will be published. Hence, through this study we hope to contribute to the understanding of melioidosis epidemiology in this region and increase awareness among clinicians of its presence.

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Competing interests – Authors have declared that no competing interests exist.

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