MELIOIDOSIS IN SOUTHERN INDIA: EPIDEMIOLOGICAL AND CLINICAL PROFILE

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Abstract. Melioidosis, which is mainly prevalent in Thailand and Australia, has shown an increasing trend in India in the last few years. We carried out a retrospective study of 25 culture-proven adult cases of melioidosis who were admitted to a tertiary care hospital in southern India during June 2001 to September 2007. There was a six-fold increase in the number of cases in 2006 and 2007 as compared to 2001. Diabetes mellitus was the predisposing factor in 68% of cases, followed by alcoholism (28%). The clinical presentations were fever (80%), pneumonia and/or pleural effusion (48%), hepatomegaly (56%), joint involvement, and/or osteomyelitis (48%), splenomegaly (40%), splenic abscess (24%) and septicemia (28%). The organism, Burkholderia pseudomallei, was sensitive to co-amoxiclav, cotrimoxazole, ceftazidime, and carbapenem. The study suggests that melioidosis is an emerging infectious disease in the southwestern coastal belt of India, and it is likely to happen at much higher incidence.

Key words: melioidosis, epidemiology, clinical profile, India

INTRODUCTION

Melioidosis is endemic in Southeast Asia and northern Australia (Chaowagul et al, 1989; Hsueh et al, 2001; Currie et al, 2008). Melioidosis is an emerging infectious disease in India as is evident from case reports from different parts of India (John et al, 1996; Anuradha et al, 1997; Sengupta et al, 1998; Mathew et al, 1999; Rao and Shivananda, 1999; Jesudasan et al, 2003; Navaneethan et al, 2006; Vidyalakshmi et al, 2007; Saravu et al, 2008). Burkholderia pseudomallei, an environmental pathogen present in soil, infects individuals with predisposing factors like diabetes mellitus and alcoholism (Suputtamongkol et al, 1999; Currie et al, 2000b; Currie, 2003; White, 2003; Currie et al, 2004). It has a spectrum of manifestations that range from superficial skin abscesses to multiple visceral abscesses and presentations that vary from chronic debilitating illness to overwhelming septicemia.

The objective of this study was to identify the epidemiological and clinical profile of cases of melioidosis presenting to a tertiary care teaching hospital in Southern India. The research questions were as follows:
1) What are the risk factors associated with melioidosis, including occupation, 2) is there any seasonal trend in presentation of clinical cases, 3) what are the clinical and laboratory features at the time of presentation, 4) what is the antibiotic susceptibility pattern of *B. pseudomallei*, and 5) what are the outcomes of treatment?

**MATERIALS AND METHODS**

This study was carried out in a tertiary care institute in southern India. Twenty-five individuals with culture proven melioidosis in the previous seven years were studied retrospectively with special reference to clinical features, occupation, epidemiology, and treatment. Specific information was collected from patient’s medical records using a standardized format that included baseline demographic, laboratory, and microbiological data. Risk factors for melioidosis, such as occupation, chronic alcohol consumption, history of steroid intake, and concomitant diseases, were identified. In all individuals, the culture isolate was identified by the API ID 32 GN® commercial kit. Histopathology was done in a few patients by embedding the tissues in paraffin wax, and 5 µm sections were stained with hematoxylin and eosin.

Disseminated disease was defined as the one that affected more than one organ system. Septicemic melioidosis was defined as blood culture proven melioidosis with sepsis. Septic shock was described as sepsis with hypotension. Data analysis was done using Statistical Package for Social Sciences (SPSS®, version 10).

**Ethical considerations**

Ethical clearance was obtained from the University Ethics Committee, Manipal University (Ref No. UEC/30/2008, 2008/Oct/17).

**RESULTS**

Of the 25 patients, 80% were males, with an age range of 18-67 years (median: 45 years, IQR: 32-54). Fourteen (56%) were ≥45 years old. All patients were from the coastal regions of Kerala (3), Karnataka (18), and Goa (4). Seventeen (68%) patients presented during the monsoon season (Jun-Sep, Fig 1), and 14 (56%) patients had a history of heavy exposure to wet soil or surface water. In all, 3 cases were detected in 2001 and in 2005, but from 2006 to 2007; however, the number rose to 11 cases each year (Fig 2), which was approximately a six-fold increase by the end of the seven-year period.

Predisposing factors (Table 1) were present in 21 (84%) patients, which included diabetes mellitus (17, 68%) and alcoholism (7, 28%). Other predisposing factors included AIDS (1), chronic lung disease (1), chronic kidney disease (1), and on chemotherapy for malignancy (1). Four patients (16%) had no predisposing factors. By occupation, 4 were farmers, 7 were doing office jobs, and others were a manual laborer (1), civil contractor (1), electrician (1) and fisherman (1) who also had exposure to soil/surface water.

Patients had varying presentations (Table 2). Seventeen (68%) patients had disseminated melioidosis, 7 (28%) patients had septicemic melioidosis, and 4 (16%) had only skin abscesses. Fever was the most common complaint and was present in 20 (80%) patients. Six patients (24%) had chronic presentation with fever of >60 days, and 7 (28%) patients presented with fever of 15 days or less. Seven (28%) patients with septicemic melioidosis had fever ranging from 1 to 60 days. Three of them had skin and soft tissue involvement; one had chronic osteomyelitis, and another, mediastinal lymphadenopathy.
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Five (20%) patients had pneumonia, and 9 (36%) patients had mild pleural effusion, one of which was loculated empyema. Four patients (16%) with hepatomegaly had multiple liver abscesses, and 6 (24%) patients with splenomegaly had splenic abscesses. Four (16%) had soft tissue swellings as the only clinical manifestation. We had patients with rarer presentations, such as ascites (16%), prostatic abscess (8%), pericardial effusion (4%), subdural collection (4%), and mediastinal lymphadenopathy (4%). No clinical focus was found in 4 (16%) patients, and they presented only with septicemia. A CT scan of the abdomen and pelvis to look for hidden abscesses was not done in all patients because of financial considerations. Seven (28%) patients had septic shock. Three (12%) patients had received empirical antitubercular therapy either in our hospital or elsewhere prior to admission. Mantoux test was positive in 2 (8%) out of 5 patients who had the procedure. Chest x-rays

Table 1
Predisposing factors for melioidosis.

<table>
<thead>
<tr>
<th>Predisposing factor</th>
<th>% (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>68</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>28</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>4</td>
</tr>
<tr>
<td>HIV</td>
<td>4</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>8</td>
</tr>
<tr>
<td>Chemotherapy for malignancy</td>
<td>4</td>
</tr>
<tr>
<td>Exposure to soil/farming</td>
<td>32</td>
</tr>
<tr>
<td>No predisposing factor</td>
<td>16</td>
</tr>
</tbody>
</table>

Table 2
Different clinical features in the study subjects.

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>% (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>80</td>
</tr>
<tr>
<td>Pneumonia and/or pleural effusion</td>
<td>48</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>56</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>40</td>
</tr>
<tr>
<td>Skin and soft tissue involvement</td>
<td>32</td>
</tr>
<tr>
<td>Joint involvement</td>
<td>28</td>
</tr>
<tr>
<td>Septicemia</td>
<td>28</td>
</tr>
<tr>
<td>Splenic abscess</td>
<td>24</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>20</td>
</tr>
<tr>
<td>Ascitis</td>
<td>16</td>
</tr>
<tr>
<td>Prostatic abscess</td>
<td>8</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>4</td>
</tr>
<tr>
<td>Subdural collection</td>
<td>4</td>
</tr>
<tr>
<td>Mediastinal lymphadenopathy</td>
<td>4</td>
</tr>
<tr>
<td>No clinical focus found</td>
<td>16</td>
</tr>
<tr>
<td>(only septicemia)</td>
<td></td>
</tr>
</tbody>
</table>

Fig 1–Seasonal distribution of melioidosis and rain fall.

Fig 2–Annual distribution of cases, 2001-2007.
showed pneumonia in 5 (20%) patients, pleural effusion in 9 (36%) patients, and bilateral nodular opacity and mediastinal widening in one (4%) patient each, and was normal in 13 (52%) patients. In 3 (12%) patients, it presented like tuberculosis and empirically ATT was administered.

Hemoglobin less than 10g/dl and ESR more than 100 mm at the end of 1 hour were seen in 16 (64%) patients, and leukocytosis was seen in 14 (56%) patients. Serum CRP and ferritin were elevated in 6 (24%) and 8 (32%) patients, respectively. Liver functions revealed significantly elevated alkaline phosphatase of more than 300U/l in 12 (48%) patients, and only 2 (8%) patients had transaminases of more than 150 U/l. Acute onset renal function abnormality was present in 5 (20%) patients.

*B. pseudomallei* was grown in all patients in pus cultures aspirated from the liver, spleen, mediastinal lymph node, ascites, subcutaneous swellings, or joint effusions. Blood cultures were positive in 9 (36%) patients. Median duration prior to diagnosis was 10 days (IQR 5-17) after presenting to us. Bone marrow showed granuloma in one (4%) patient. Aspirated material from liver abscess showed caseating granuloma in another (4%).
The isolate from the patients was sensitive to amoxiclav, cotrimoxazole, chloramphenicol, piperacillin, cefotaxime, ceftazidime and meropenem and resistant to gentamicin. Patients were treated according to their sensitivity patterns. Fifteen (60%) patients were given multidrug therapy. Empirical therapy usually included parenteral co-amoxiclav. However, once the diagnosis was confirmed, patients received parenteral ceftazidime or carbapenem initially, followed by oral combination of co-amoxiclav and cotrimoxazole, or cotrimoxazole and doxycycline. Parenteral antibiotics were given for a mean duration of 14 days (SD ± 4 days). Mean time for defervescence was 8.5 days (SD ± 2.5 days). Mean duration of treatment was 5 months (SD ± 1.2 months). One patient underwent splenectomy because of persisting splenic abscesses, following which the patient was cured. Histopathology of the spleen revealed stellate granulomas. *B. pseudomallei* was cultured from the splenic tissue. Two (8%) patients died; one with HIV infection who succumbed to septicemic melioidosis and the other to candidal sepsis. Three patients were discharged against medical advice, and at the time of discharge, they were ill and could not afford further treatment. Twenty patients were discharged on oral medications, out of which, 16 were available for follow-up. Nine (36%) patients have completely improved with the treatment and are well with mean duration of follow-up of 8 months. Seven (28%) patients were receiving eradication phase treatment.

**DISCUSSION**

The hospital where the study was conducted is located on the western coast of Karnataka, a South Indian state. The hospital is a 1,400-bed tertiary-care teaching hospital that caters to a population of over 1 million and receives referred cases from the adjoining states of Kerala and Goa. The center is a tertiary referral center, and hence there may be a referral bias. Most of the secondary hospitals do not have the facilities to culture nor the expertise to identify *B. pseudomallei*. Melioidosis has been increasingly detected in our hospital since 2006. Cases have come from three southern states of India, mainly from the western coast. There was a male preponderance as was found in other studies, probably related to outdoor work (Puthucheary et al., 1992; Heng et al., 1998; Currie et al., 2000b). An age of >45 years was present in majority and has been documented as an independent risk factor (Currie et al., 2004). In our study, the cases were clustered during the rainy season, from May to September. *B. pseudomallei* is present in soil and surface water in endemic regions. Humans are infected by percutaneous inoculation, inhalation, and ingestion (White, 2003). In Thailand and northern Australia, 75-85% of the cases occur in rainy season (Currie et al., 2000b). Bacteria that move to the surface with the rising water table during the rainy season are responsible for the increase in the transmission rate (Thomas et al., 1979). In our study, 32% of the patients with melioidosis were farmers or had exposure to soil. Diabetes and excessive alcohol consumption were documented as the main predisposing factors that corroborate with other studies (Currie et al., 2004; Chan et al., 2005). The rate of diabetes in our study (68%) was higher when compared to the rates of other studies, which range from 23 to 60% (Chaowagul et al., 1989; Punyagupta et al., 1989; Suputtamongkol et al., 1999; Currie et al., 2004). Excess alcohol consumption has
been documented in 12-37% of melioidosis cases as compared to 28% in our study (Suputtamongkol et al, 1999; Currie et al, 2004). Although melioidosis does not seem to be associated with HIV infection (Dance, 2000; Chierakul et al, 2004), we had one individual presenting with the septicemic form. In an Australian study, chronic renal disease, chronic lung disease, and age >45 were independent risk factors for melioidosis (Currie et al, 2004). In our study, chronic lung disease and chronic renal disease were predisposing factors in 4% and 8%, respectively, which is less when compared to findings of 27% and 10%, respectively, in another study (Currie et al, 2000b). No predisposing conditions were identified in 13-36% cases in other studies (Suputtamongkol et al, 1999; Currie et al, 2004) as compared to 16% in the our study.

Melioidosis can present acutely or may follow chronic indolent course; it may present in disseminated or localized forms with or without septicemia. In our study, pneumonia, pleural effusion, skin and soft tissue swellings, and liver and splenic abscesses were the common presentations. Various studies have shown that pneumonia is the commonest clinical presentation (Chan et al, 2005). Neurological involvement, though less common, can be seen in 4% of cases. They can have brain stem encephalitis, cerebral abscess, cranial nerve palsies, and paraparesis (White, 2003). One (4%) of our patients had subdural collection and presented with hemiplegia and altered sensorium.

Melioidosis is a great masquerader, and it is often confused with staphylococcal abscesses in acute form or tuberculosis in chronic presentations. Mantoux test results may be positive, as it was in two of our patients. Aspirated pus may be confused with caseous material of tuberculosis. Tissue biopsy may show granuloma. In our series, granuloma was demonstrated in bone marrow, liver aspirate, and the spleen. Three of our patients had received empiric anti-tubercular therapy (ATT). In the present series, 36% were bacteremic. The incidence of bacteremic melioidosis has been 46% to 60% in different series (Currie et al, 2000b).

Mortality rate in our series was 8%, and it was 22% in patients with bacteremic melioidosis. In previously reported studies, overall mortality ranged from 19 to 46% (Suputtamongkol et al, 1999; Currie, 2003), while in septicemic form it went up to 65% (Puthucheary et al, 1992). Rate of relapse is around 10% and can be more if antibiotic therapy is shortened to eight weeks or less (Currie et al, 2000a).

The sensitivity to third generation cephalosporins, especially ceftazidime, doxycycline, pipéracillin, cotrimoxazole, and co-amoxiclav and resistance to aminoglycosides, first- and second-generation cephalosporins, macrolides, and rifampicin is unusual and unique to this bacillus. Fluoroquinolones are also weakly sensitive. Growth of pseudomonas species with sensitivity to ceftazidime, amoxicillin clavulanic acid, and cotrimoxazole, and resistant to gentamicin should prompt us to specifically look for this species.

The recommended antibiotic regimens are a) co-trimoxazole at 8/40 mg/kg (≤320/1,600 mg) every 12 hours and ceftazidime at 50 mg/kg (≤2 g) intravenously every 6 hours, or b) meropenem at 25mg/kg (≤1 g) intravenously every 8 hours. The duration of therapy for intensive phase is at least 14 days, and a longer duration of 4-8 weeks for deep-seated infection, osteomyelitis, or septic arthritis.
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(Cheng and Currie, 2005). The other recommended regimen are imipenem at 20 mg/kg intravenously every 8 hours or ampicillin-clavulanate at 20/4 mg/kg intravenously every 4 hours (White, 2003).

The subsequent eradication phase antibiotic regimens are a) co-trimoxazole at 8/40 mg/kg, every 12 hours for 3-6 months (Cheng and Currie, 2005); b) chloramphenicol 10 mg/kg orally every 6 hourly for 8 weeks, doxycycline at 2 mg/kg orally twice a day for at least 20 weeks, and co-trimoxazole at 5/25 mg/kg orally twice a day for at least 20 weeks, or c) amoxicillin-clavulanate at 30/15 mg/kg orally (tds) for 20 weeks and amoxicillin at 30 mg/kg orally (tds) for 20 weeks (White, 2003).

Melioidosis in India has been reported since 1991 (Table 3), when it was detected in a child (Raghavan et al, 1991). A series of 28 patients of septicemic melioidosis over 10 years has been reported from Vellore (Jesudasan et al, 2003). The same center had reported this infection in 6 patients in 1996, where patients were from Tamil Nadu, Maharashtra, Kerala, Orissa, West Bengal, and Tripura (John et al, 1996). Recently 25 cases of melioidosis were reported from Karnataka, which included patients from Kerala (Vidyalakshmi et al, 2007). Thus, melioidosis and the causative organism are being recognized gradually in various centers in India. However, it is mostly under-recognized and under-reported. In the present study, it is interesting to note that there has been a drastic increase in number of positive cases since 2006, which may be partly attributed to the increasing detection rate due to a higher-index of suspicion.

The majority of the Indian population eats rice, and consequently, there are vast paddy fields. Being a tropical country, one-third of a year will have monsoons with heavy rains in most places. However, melioidosis is diagnosed increasingly only from the southern coastal part of India. The diagnosis of melioidosis requires clinical vigilance and an intensive microbiological workup. With this study, we hope to raise the awareness of clinicians to the existence of melioidosis in India. To recommend prophylactic measures, environmental studies are required to know the prevalence of the etiological organism in the environment.

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