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Brief communication (Original)

Melioidosis: an underdiagnosed disease in India (epidemiology, clinical features, and outcomes)

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Background: Melioidosis is an emerging infectious disease in Southeast Asia. It is an under diagnosed and under reported disease in India mostly because of lack of awareness.
Objective: We studied the clinical profile and outcome of melioidosis.
Methods: A prospective observational study conducted at Kasturba Hospital, Manipal University from May 2007 to July 2009.
Results: There were 31 diagnosed patients in all. Diabetes mellitus was the most common risk factor (68%). Eighty-one percent of cases were detected in the rainy season. Male to female ratio was 3:1. The median age was 48 years. Fifty-two percent of patients were in the age group 41 to 60 years. Thirty-two of patients were agriculturists. Respiratory symptoms were the predominant presentations. The majority (87%) of patients had fever. The bacteria were sensitive to ceftazidime, cotrimoxazole, carbapenems, piperacillin, doxycycline, and chloramphenicol, and resistant to aminoglycosides. Forty-eight percent of patients had bacteremia. Forty-five percent of cases were cured. Twenty-percent of patients had septicemia and septic shock. Sixteen percent of patients died because of septic shock.
Conclusion: Melioidosis is very difficult disease to diagnose clinically and to treat; mostly because of varied presentations. Awareness of the existence of this disease in an endemic region with various underlying risk factors is essential for successful treatment. The early use of appropriate antibiotics and the efficient care of patients with sepsis improves outcomes dramatically. Patients with septicemia and septic shock still result in high mortality rates in spite of efficient critical care.

Keywords: *Burkholderia pseudomallei*, melioidosis, pneumonia, septicemia, septic shock, splenic abscess

Melioidosis is expanding gradually into previously considered nonendemic regions. This probably is partly because of increased recognition. It is caused by a gram-negative bacterium called *Burkholderia pseudomallei*, (previously called *Pseudomonas pseudomallei*), which is present in the soil and fresh water endemic areas [1]. Although several cases of melioidosis were reported in India over the last few years [2-7], still it is not widely recognized. Melioidosis has wide variety of manifestations ranging from an asymptomatic infection or, localized abscesses to overwhelming septicemia leading to death. Therefore, this study included the clinical profiles, epidemiology, treatment and the outcome of melioidosis.

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Materials and methods

A prospective observational study was conducted at Kasturba Hospital, Manipal, Karnataka, India; a tertiary care hospital, from May 2007 to July 2009. Thirty-one culture proven cases of melioidosis were included and all the patients with proven cases of melioidosis were more than 18 years old. Various aspects such as underlying diseases, seasonal variation; clinical features; occupation; risk factors; laboratory; microbiological and radiological data, treatment and outcome were studied. Cases were followed-up until death or completion of treatment. Data were analyzed with SPSS version 11.5. Descriptive analysis was done. Demographic data, clinical manifestations, treatment, and outcome are shown as percentages, mean and standard deviation as appropriate. We obtained approval for this study from our Institutional Ethics Review Board.

Results

Our study of 31 patients included 23 men. The age of the patients was from 18–80 years. The median age was 48 years, and the interquartile range was 39 to 55 years. Fifty-two percent (n = 16) of patients were in the age group of 41 to 60 years. Sixteen percent (n = 5) of patients were in the age group of 61 to 80 years, and 32% (n = 10) of patients were in the age group of 18-40 years. Thirty-nine percent (n = 12) of patients were from Udupi district; 19% (n = 6) of patients were from Shimoga district. Sixteen percent (n = 5) of patients were from Uttara Kannada district; 10% (n = 3) of patients were from Goa. Six percent (n = 2) of patients were from coastal Kerala; Six percent (n = 2) of patients were from Dakshina Kannada district, and 3% (n = 1) of patients were from Chitradurga district. Thirty-two percent (n=10) of patients were agriculturists; 16% (n = 5) of patients were housewives; 13% (n = 4) of patients were working in an office; 6% (n = 2) of patients were fishermen; 6% (n = 2) of patients were businessmen, and 10% (n = 3) of patients were factory laborers. Three percent (n = 1) of patients were each a driver, security guard, carpenter, retired officer, and a student. Seasonal distribution is indicated in **Figure 1**. Eighty percent of cases (25 out of 31) were reported from May to September.

Risk factors noted were that 68% (n = 21) of patients were diabetics. Twenty-five percent (n = 8) of patients had alcoholism as a risk factor; 13% (n = 4) of patients had chronic renal failure. Six percent (n = 2) of patients had a chronic obstructive pulmonary disease. Three percent (n = 1) of the patients had retrovirus positive status; 3% (n = 1) of patients had malignancy (acute myeloid leukemia m4 type), and 3% (n = 1) of patients had a history of near drowning as a risk factor.

Fever was the most common presenting complaint in 87% (n = 27) of patients followed by cough in 35% (n = 11); breathlessness in 29% (n = 9) and jaundice in 20% (n = 6) of patients. The other presenting complaints were, skin and soft tissue swelling in 20% (n = 6); joint pain-arthralgia in 16% (n = 5); oliguria in 13% (n = 4); abdominal pain in 13% (n = 4), and a discharging axillary sinus in 3% (n = 1) of patients. Sixteen percent of patients had fever of one-week duration; 55% of patients had fever duration of 7 to 30 days; 10% of patients had fever duration of 31 to 60 days, and 19% of patients had more than 60 days of fever. Thirty-five percent (n = 11) of patients had pneumonia; 20% (n = 6) of patients had pleural effusion; 3% (n = 1) of patients had a mediastinal mass and 3% (n = 1) of patients had a pyopneumothorax. Three percent (n = 1) of patients

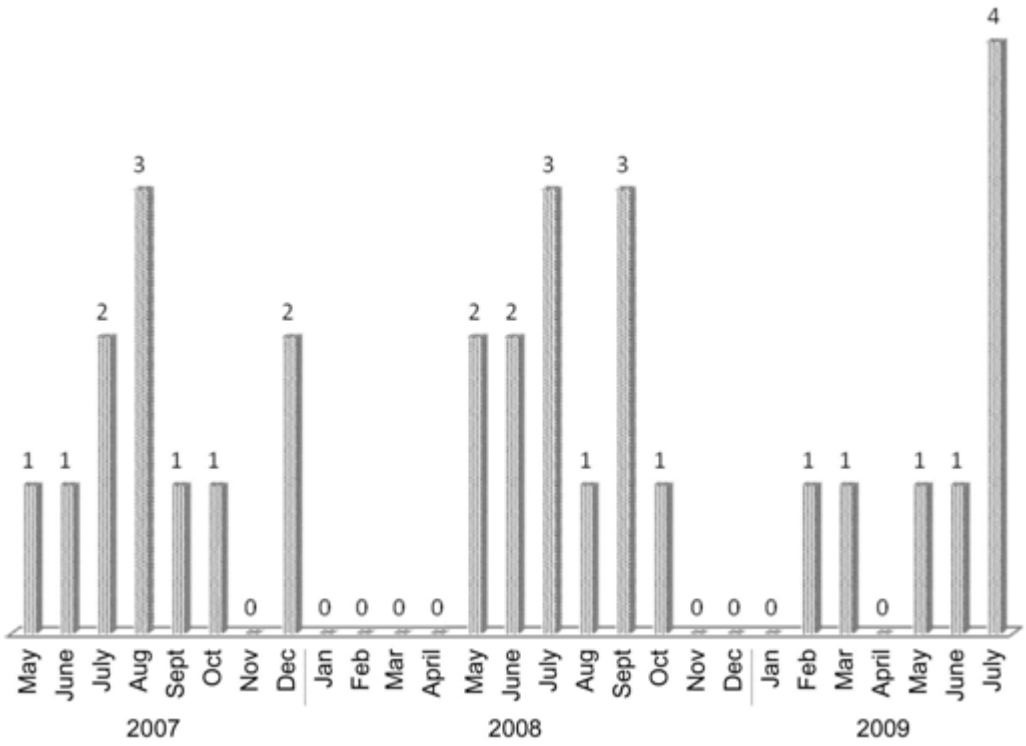

Figure 1. Seasonal distribution of melioidosis cases

had multiple liver abscesses; 6% (n = 2) of patients had splenic abscess, and 6% (n = 2) of patients had osteomyelitis. Six percent (n = 2) of patients had septic arthritis; 6% (n = 2) of patients had cervical lymphadenopathy; 10% (n = 3) of patients had submandibular lymph node abscess, and 3% (n = 1) of patients had parotid abscess. Three percent of patients had subcutaneous abscess in the back, and 3% (n = 1) patients had discharging axillary sinus as clinical presentation. Twenty percent (n = 6) of patients had septicemia with septic shock. In 23% of patients, a chest X-ray image showed consolidation. Eleven percent of patients had consolidation with pleural effusion. In 3% of patients, a chest X-ray image showed hydropneumothorax; 3% of patients had an anterior mediastinal mass. In 15% of patients chest X-ray images showed ARDS (acute respiratory distress syndrome) features, and 32% of patients had a normal chest X-ray. Forty-three percent of patients had hepatomegaly; 14% of patients had splenomegaly; 33% of patients had hepatosplenomegaly. Ten percent of patients had splenomegaly with abscess, and 5% of patients had liver abscess on an ultrasonogram of the abdomen.

Laboratory investigation

Table 1 shows the mean and standard deviations laboratory variables showing anemia, elevated ESR, and total leukocyte count (TLC), glycosylated hemoglobin (Glyco Hb), and elevated blood sugar levels. Nine (29%) patients had hemoglobin of less than 10 gm/dl; seven (22%) patients had high ESR (100mm/one hour); 19 patients (61%) had total leucocyte count of more than 11,000 (cells/mm^3). In 39% of patients, the blood culture was positive for *B. pseudomallei*. In 35.5% of patients, pus culture, and in 7% of patients endotracheal tube aspirate culture showed growth of *B. pseudomallei*. In 7% of patients both blood and pus culture were positive for *B. pseudomallei.* In 3% of patients, the bone marrow aspirate culture, and in another 3% of patients, both bone marrow and blood culture was positive for *B. pseudomallei*. FNAC (fine needle aspiration cytology) of lung tissue culture was positive in one patient (3%).

Table 1. Mean and SD of laboratory variables

Parameter	Mean	SD
Hemoglobin (gm/dl)	10.8	±2.5
ESR (mm/1 hour)	87.4	±31.1
TLC (cells/cumm)	13,248	±7256
FBS (mg/dl)	180.4	±84.0
PPBS (mg/dl)	263.2	±84.1
GlycoHb (%)	12.5	±2.9

Figure 2 indicates antibiotic sensitivity patterns. *B. pseudomallei* were sensitive to imipenem, meropenem, piperacillin-tazobactam, cotrimoxazole, chloramphenicol, and tetracycline in 100% of patients. They were also sensitive to doxycycline, ceftazidime, cefoperazone-sulbactam, amoxicillin-clavulanate and, fluoroquinolones in 96%, 96%, 94%, 85%, and 44% of patients respectively. *B. pseudomallei* was 100% resistant to aminoglycosides and resistant to fluoroquinolones in 56% of patients.

Treatment

Intensive phase

In the intensive phase, ten patients (32%) received amoxicillin-clavulanic acid empirically. Eight patients (26%) received piperacillin-tazobactam and four patients (12.8%) received ceftriaxone. Cefoperazone-sulbactam and cefotaxime was given to two patients (6.4%) each empirically. They survived the intensive phase. After a culture report, 20 (64%) patients received ceftazidime, 4 patients (12.8%) received meropenem; 3 (10%) patients received piperacillin-tazobactam. Amoxicillin-clavulanic acid was given to 2 (6%) patients. Cefoperazone-sulbactam and cefotaxime therapy was given to one (3%) patient each. Achieving an afebrile state and clinical stability were the main criteria for transition from intensive to eradication phase.

Eradication therapy

Forty-five percent (n = 14) of patients received cotrimoxazole and doxycycline; 10% (n = 3) of patients received cotrimoxazole, doxycycline, and amoxicillin-clavulanic acid in the eradication phase.

Outcome

Mean duration before diagnosis was 6.7 days (SD 2.7) after admission to the hospital. Mean duration for defervescence was 9.9 days (SD 2.1). Mean duration of intensive phase of therapy was 10.9 days (SD 4.80); Mean duration of eradication phase of therapy was 4.8 months (SD 1.04). Forty-five percent (n = 14) of patients improved clinically and symptomatically during the intensive phase of treatment; 23% (n = 7) of patients did not come for

follow up in the eradication phase of therapy. Twenty percent (n = 6) had septicemia and septic shock and 16% (n = 5) of the patients expired; 10% (n = 3) of patients were still under follow-up, and 6% (n = 2) of the patients were discharged against medical advice in critical conditions. **Table 2** shows the overall outcomes. **Table 3** shows details of the treatment of septicemic patients and their outcomes. Among the two patients, who were discharged against medical advice, one was a 39-year-old male from Austria who had been residing in Goa. He had chronic alcoholism and acute myeloid leukemia as risk factors. He also had unknown substance abuse, severe weight loss and anemia, and left lower lobe pneumonia. He was receiving i.v. piperacillin-tazobactam and other supportive treatments. He later became delirious, refused treatment left in a critical condition against advice. The culture reports of blood and marrow aspirates were positive for *B. pseudomallei*, and had been received after he left the hospital. His final fate is not known. All patients who died of melioidosis had severe refractory septic shock and received advanced critical life support. This in spite of the fact that all organisms were susceptible to the empirical antibiotics started initially. Among 7 patients (22%) who survived, 2 to 3 days of ICU unit care was required, although they did not have septic shock.

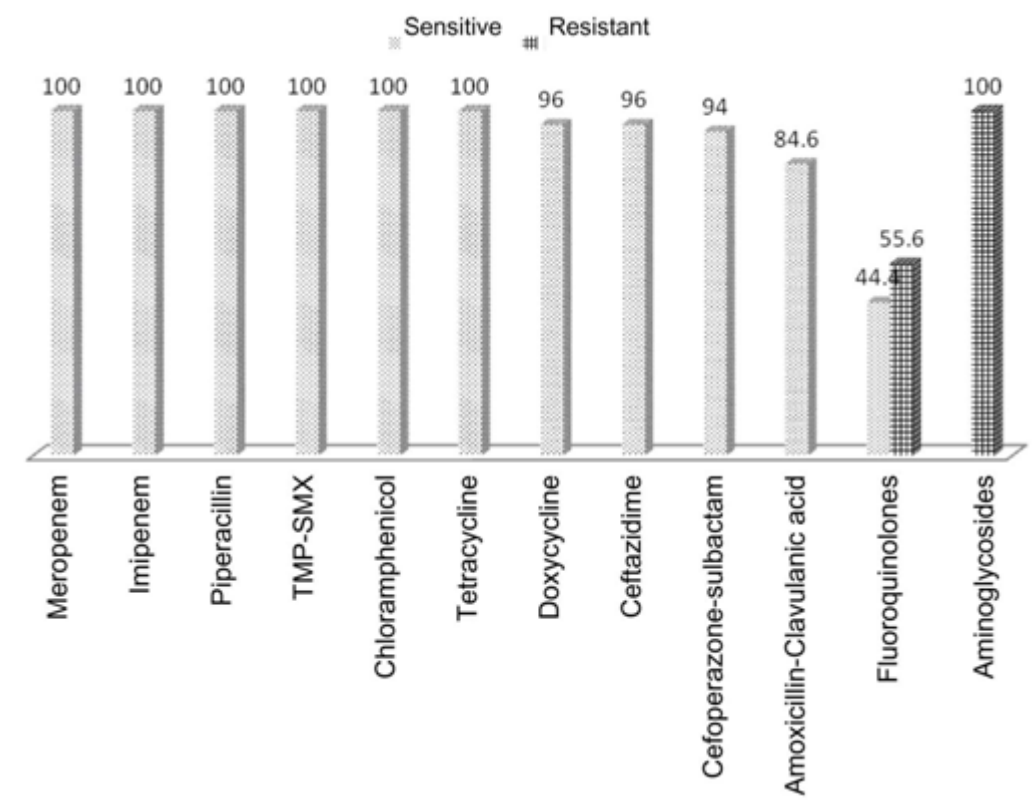

Figure 2. Antibiotic sensitivity pattern

Table 2. Indicates the overall outcome

Total number of patients	31
Number of patients who survived	14 (45%)
Number of patients who did not come to follow-up in the eradication phase	7 (23%)
Number of patients who were still under follow-up in the eradication phase	3 (10%)
Number of patients who were discharged against advice in the intensive phase (This includes one female patient who had septic shock)	2 (6%)
Number of patients who had septicemia and septic shock	6 (20%)
Number of patients who died because of septic shock	5 (16%)

Table 3. Details of septicemic patients-treatment and outcome

Age Sex	Risk factors	Initial symptoms	CXR	Empirical antibiotics	Diagnostic specimen/Culture and sensitivity pattern	Appropriate antibiotics	Outcome
55 F	An episode of near drowning in freshwater 6 days previously	High grade fever, breathlessness, cough, chest pain of 6 days duration.	ARDS	Piperacillin-tazobactam, metronidazole	Blood culture after 3 days. Organism was sensitive to piperacillin and meropenem		Died within 24 hours of hospital admission
80 M	COPD, male	Fever, breathlessness of 3 days duration, respiratory failure	Right side upper, midzone opacity, midzone opacity on left side	Piperacillin-tazobactam, meropenem and azithromycin for 5 days	ET tube aspirates culture. Bacterium was sensitive to piperacillin and meropenem	Ceftazidime and meropenem were continued	Died 2 weeks after admission
70 F	Type 2 DM	One year h/o intermittent fever, cough, which worsened since 15 days	Right lower lobe pneumonia with effusion	Piperacillin-tazobactam and amoxicillin-clavulanic acid for 6 days	Blood culture. Bacterium was sensitive to piperacillin and ceftazidime	Ceftazidime for 3 days	Died 9 days after admission
56 M	Type 2DM, male	Intermittent fever of 10 days duration, cough, breathlessness of 3 days duration	ARDS	Piperacillin-tazobactam, doxycycline and levo-floxacillin for 5 days	ET tube aspirates culture after 5 days Bacterium was sensitive to piperacillin, doxycycline, and meropenem	Meropenem started and doxycycline continued	Died 7 days after admission
48 F	CKD-FSGS	Intermittent fever and cough of 3 weeks duration.	Right lower lobe pneumonia	Oral roxithromycin before admission. After admission meropenem, vancomycin for 3 days	Blood culture was positive after 3 days. Bacterium was sensitive to meropenem		Died within 3 days
62 F	Type2DM, agriculturist COPD	Intermittent fever, pain abdomen, vomiting of 1 month duration and cough with scanty sputum of 1 week duration	ARDS	Piperacillin-tazobactam for 5 days	Blood culture, bacterium was sensitive topiperacillin and meropenem	Meropenem for 2 days	Discharged against medical advice in a very critical condition

COPD = chronic obstructive pulmonary disease, CKD = chronic kidney disease, FSGS = focal segmental glomerulosclerosis, ARDS = acute respiratory distress syndrome, ET Tube = endotracheal tube

Discussion

A male preponderance is evident in all melioidosis case series published, but proportions differ significantly. This likely reflects the outdoor work and occupational exposure to soil and water through activities like agricultural work, fishing, gardening and water sports [1, 8-10]. *B. pseudomallei* from the soil and surface water enters the body through existing skin lesions like minute wounds, abrasions, ulcers, or by inhalation of dust particles and water droplets in aerosol; most commonly during the rainy season, or by aspiration of contaminated water during near-drowning episodes [1,2,9,11,12]. About 75 to 85% of cases of melioidosis in northeastern Thailand and northern Australia have been reported occurring during the wet season [11, 13]. During monsoon rains, the bacteria move to the surface with the rising water table and multiply in the surface water and wet soil. This, in turn, is responsible for increasing exposure to persons with larger inoculating doses [13-15]. The intense monsoon rainfall, which is often associated with heavy winds, leads to aerosolization of bacteria. The

inhalation of bacteria in droplet form increases the risk of transmission of *B. pseudomallei* leading to septicemic pneumonia [13, 16]. In this study, 74% of patients were male and 81% of cases were reported in the rainy season, which is in accordance with the previous reports from Thailand and other Asian regions [1, 2, 5-9, 12, 13]. Male gender, age more than 45 years and diabetes mellitus are the individual risk factors for melioidosis [17]. Diabetes mellitus is the strongest well-established risk factor [1]. In this study, out of 31 patients, 21 (68%) had diabetes mellitus. Alcohol consumption, chronic renal disease, and obstructive lung diseases are other significant risk factors. The most likely reason for this predisposition is the known impairment of neutrophil function, i.e., impaired chemotaxis, opsonization, and phagocytic functions [1, 9, 12 18]. Other underlying risk factors are heart failure, solid tumors, hematologic malignancies, steroid therapy, thalassemia, and cirrhosis [12, 18]. Melioidosis was detected only in 1.5% HIV-infected patients in northeast Thailand [19]. Though HIV is not an established risk factor for melioidosis, there are reports of 2.4% to 4% of patients with melioidosis and HIV coinfection [2, 20]. Like tuberculosis, HIV infection does not alter the natural course or outcome of melioidosis [1, 12, 19]. Melioidosis acquired after near drowning episodes in fresh water, are said to have more severe disease and shorter incubation periods and are associated with higher fatality rates compared to melioidosis acquired after near drowning in sea water. The higher concentration of the organism in the aspirated fresh surface water and osmotic factors are probable explanations for this difference [21].

Respiratory disease is the predominant manifestation in melioidosis with pneumonia as a major manifestation in this study. This is in accordance with previous studies [22-24]. The pneumonia may present as acute or chronic [25]. Acute pneumonia is characterized by fever, cough, pleuritic pain or is seen in a patient who is severely ill, with multiorgan dysfunction and septic shock [24, 25]. Acute pneumonia may be associated with the formation of abscesses in various organs, including the lung. The rupture of these abscesses leads to empyema and pneumothorax [9]. Chest X-ray images may reveal numerous nodules or consolidation involving one or more lobes [9, 26]. In the chronic form of lung involvement, there is a prolonged history of fever, loss of weight, productive cough, with or without hemoptysis. There may be a sudden worsening leading to septicemia [24]. The radiological findings are nonspecific and include the mixed nodular or patchy pulmonary infiltrates [26], pleural effusion and cavity formation in the upper lobe has been reported [24, 25]. The subacute and chronic forms of pulmonary melioidosis may mimic tuberculosis with cavity formation in the lung apex [25].

One of our patients had a mediastinal mass with a submandibular lymph node abscess on one side. Chest X-ray imaging and CT reports were suggestive of malignancy. Lymph node biopsy showed granuloma, suggestive of tuberculosis. The culture reports from a bone marrow aspirate and pus from the abscess revealed *B. pseudomallei*. During treatment, the patient developed submandibular lymphadenopathy on the contralateral side and an increase in the size of the mediastinal mass. However, the mediastinal mass resolved completely with continuation of treatment. In the first week of treatment, an increase in the size of an abscess, which is already present, or appearance of new abscesses, can disseminate bacteria to various joints, muscles or visceral organs, and it should not be interpreted as treatment failure [8].

The clinical manifestations of musculoskeletal melioidosis are nonspecific [5, 6]. Clinical features can mimic acute or chronic arthritis [6]. Involvement of any bone has been reported [6]. Commonly, large joints like knees, ankles, shoulders, and elbows are involved [5, 6]. Often, soft-tissue abscess is associated with osteomyelitis. Orthopedic manifestations can be of localized disease only or a part of dissemination [5, 26, 27]. Orthopedic manifestations present with fever, pain, swelling, and restriction of motion of the involved joints [5, 6]. Surgical treatment is usually required along with antibiotics [1, 5, 6]. In this study, melioidosis in the form of femoral and tibia osteomyelitis were seen, as well as involvement of ankle and elbow joints. These patients received successful surgical and antibiotic therapy.

Visceral and soft-tissue abscesses result from hematogenous dissemination [1]. Splenic abscess is the most common, followed by liver and kidney abscesses [26]. The liver abscess is characteristically described to contain numerous small abscess cavities or multiloculated lesions giving rise to a “Swiss cheese” or “honey comb” appearance on CT images [5]. Presence of both splenic and liver abscesses is usually because of melioidosis [26]. In this study, two patients had splenic abscess, and one patient had multiple liver abscesses.

A parotid abscess is seen in 40% of children in Thailand, but is rare in Australia [1]. A middle-aged woman, who had newly detected Type 2 diabetes mellitus, presented with parotid abscess in this study. In the current study, melioidosis mimicked tuberculosis as cervical lymph node abscess, chronic axillary discharging sinus, tibia and femoral osteomyelitis, splenic abscess, and mediastinal mass. Lymph node biopsy and histopathology reports were first suggestive of tuberculosis in the form of granuloma formation [5].

In this study, 48% of patients were bacteremic, and the mortality rate in this group was 16%. This is consistent with previous reports of rates of bacteremia of 46% to 60%, and a mortality rate of 19% to 46% respectively in previous studies [23]. Five out of six patients who had severe septicemia with septic shock (84%) died. Mortality rates of 86%–90% because of septicemia are reported [28]. Melioidosis is a great mimicker of other diseases [1]. The clinical manifestations and the radiological features are not specific [9, 26]. In endemic areas with underlying risk factors, if a patient has a fever with acute respiratory distress syndrome, pyrexia of an unknown cause, multiple skin and visceral abscesses, sepsis with pneumonia, in suspected cases of tuberculosis where acid-fast bacilli are not demonstrable, melioidosis should be considered [9]. In nonendemic regions, a detailed history of previous travel and occupation of the patient is very important. Melioidosis acquired through occupational exposure may remain latent for many years to decades, which later manifests as acute severe recrudescent fulminating disease mimicking chronic infections like tuberculosis or hidden abscesses. Various reports of soldiers during the Vietnam war, or persons who worked in endemic southeast Asian countries, who became critically ill, many years to decades after return to their homeland, have been published in the medical literature [29, 30].

Culture of blood, bone marrow aspirate, pus, cerebrospinal fluid, urine, sputum and the other appropriate clinical specimens is the criterion standard for the diagnosis of melioidosis and the organism can usually readily be cultured and identified [1, 5]. *B. pseudomallei* is sensitive to various antibiotics like, ceftazidime, imipenem, meropenem, piperacillin, cotrimoxazole, tetracycline, doxycycline, chloramphenicol, and amoxicillin-clavulanate. It can be resistant to many antibiotics, including penicillin, first-and second-generation cephalosporins, macrolides, aminoglycosides, and rifampicin [1, 9]. At present, the drug of choice for melioidosis is intravenous ceftazidime 2 g intravenously every 8 hours and in combination with oral cotrimoxazole (8/40 mg/kg/day up to 320/1600 mg/day) in divided doses every 12th hour for 10 to 14 days. In simple bacteremic melioidosis, ceftazidime alone can be given in the intensive phase for 10 to14 days. The other option is meropenem (25 mg/kg up to 1000 mg three times daily) used in the intensive therapy [9, 24, 32]. Severe infections such as the involvement of the central nervous system, skeletal system, during the intensive phase, may be extended for up to 4 weeks [1, 31, 32]. In the eradication phase of therapy, doxycycline (4 mg/kg/day in a divided dose) along with cotrimoxazole (8/40 mg/kg/day up to 320/1600mg twice daily) should be given for 12 to 20 weeks [9, 24, 32]. In severe infections, prolonged treatment is required and late recurrences are not uncommon [9, 32]. Age >50years is an independent risk factor and a predictor of increased mortality [12]. In this study, 4 out of 5 patients who were above the age of 50 years died.

Conclusion

Melioidosis is a very difficult disease to diagnose clinically because of varied presentations and lack of awareness. Melioidosis is known to recur; occasionally decades later. A high index of suspicion, early use of appropriate antibiotics and efficient clinical support will improve outcome. Extended term treatment is usually required. Patients with septicemia and septic shock have a very higher mortality rate in spite of appropriate care. This is a hospital-based study where the sample size is small. In this study, the amount alcohol consumption was not determined exactly.

The authors have no conflicts of interest to declare.

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