

## Epidemiology and clinical spectrum of melioidosis: Analysis of cases from a tertiary care centre in southern Tamil Nadu

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### ABSTRACT

**Background.** We studied the clinical features and treatment outcome of patients with melioidosis in our hospital.

**Methods.** We did this retrospective observational chart review over a period of 7 years between December 2014 and February 2022.

**Results.** There were 59 cases and 23 deaths attributable to melioidosis over the study period. The age range was 5 to 74 years and 48 (81.3%) were men. The comorbid conditions included diabetes mellitus (68%), alcoholism (11.8%), pulmonary tuberculosis (6.7%) and chronic kidney disease (5%). Over three-fourths of patients (78%) presented during the rainy season (June to December) and were acute presentations (44 [75%]). The most common sites were liver and spleen, followed by the musculoskeletal system, skin, soft tissues, lungs and brain. Of the 21 (36%) patients with septic shock, 16 (76%) died. On the contrary, of 38 (64%) patients without septic shock, only 11% died. Of the 27 (47%) admitted to ICU, 11 (41%) died. In ICU, 18 (67%) were ventilated. Of the 23 (39%) deaths overall, median time from admission to death was 4 days. There were no relapses in the 42% patients followed up for 2–6 months.

**Conclusions.** The epidemiology of melioidosis is similar to other endemic areas with preponderance of men. There was a temporal association with the monsoon season and a higher number of acute cases. The differences included a higher proportion of deep visceral abscesses and musculoskeletal involvement compared to lung involvement.

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### INTRODUCTION

Melioidosis is an infectious disease caused by *Burkholderia pseudomallei*, an organism present in the rhizosphere and

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groundwater of tropical and subtropical regions affecting both humans and animals. The traditional melioidosis endemic regions include Southeast Asia and Australia. This belt has been expanding with recent reports from the Americas, Madagascar, Mauritius, India and other regions in south Asia. In 2022, 4 cases of melioidosis in the USA were linked to an aromatherapy spray imported from India, emphasizing the potential risk of transmission through commercial products.<sup>1</sup> In India, cases have been reported mainly from coastal regions of Karnataka, Kerala, Tamil Nadu, Puducherry and Odisha. Other risk drivers such as the growing diabetic population, climate change, high population densities and intensive agriculture can lead to an increasing incidence or the recognition of this emerging infection in new areas. It is uncertain whether these represent new hotspots or the unveiling of long-standing pre-existing endemic areas. We have recognized the presence of a previously hidden hotspot around Madurai, an area in the southcentral region of Tamil Nadu with an intensive agricultural background. Ever since the first report of melioidosis presenting with osteomyelitis in 2014, we have regularly identified cases of melioidosis.<sup>2,3</sup> We encountered 59 culture-confirmed cases of melioidosis over 7 years (December 2014 to February 2022). We present a detailed clinical and microbiological profile of these cases.

### METHODS

We did this retrospective observational chart review of patients of all ages diagnosed with culture-proven melioidosis. Fifty-nine patients with culture-proven melioidosis from December 2014 to February 2022 were included. Cases were identified from the hospital laboratory database. The patients' medical records were reviewed and the following information was extracted: demographic details, presentation, clinical diagnosis, risk factors, length of hospital stay, antibiotic susceptibility, choice and duration of antibiotic treatment, clinical outcome and the location at which the patient was staying at the time of laboratory confirmation. Radiology records, and biochemical and haematological data were retrieved from the hospital information system. Institutional ethics committee approval was obtained before analysis and publication.

### Microbiological data

Clinical specimens were processed as per the standard local microbiological culture techniques. For blood culture, at least 10 ml of blood was collected aseptically and inoculated into BACTEC (BD) blood culture bottles and incubated in the BACTEC FX40 automated blood culture system. Exudates and respiratory specimens were plated on blood, chocolate and MacConkey agar media. *B. pseudomallei* was identified by the growth of silver white colonies with a metallic sheen on blood agar. No selective media such as Ashdown agar or broth were routinely used for processing of non-sterile specimens. Pus from deep abscesses and respiratory samples were also processed for acid-fast stain and mycobacterial polymerase chain reaction (PCR), anaerobic bacterial and fungal culture. Phenotypic identification of *B. pseudomallei* was done by a combination of the following tests: characteristic metallic sheen and wrinkled appearance of colonies, oxidase positive, motile, Gram-negative bacilli with bipolar staining with a 'safety-pin' appearance, and resistance to polymyxin antibiotics (colistin 10 µg and polymyxin B 300 U disks) along with a positive arginine dihydrolase reaction.<sup>4</sup> The identification of isolates was also confirmed by the VITEK 2 system. Some antibiotics—ceftazidime,

meropenem, trimethoprim–sulphamethoxazole and doxycycline–were tested by microbroth dilution in the VITEK 2 system.

### Definitions

Patients were classified on the basis of duration of symptoms: acute ( $\leq 2$  months) or chronic ( $> 2$  months).<sup>5</sup> Multifocal disease was defined as involvement of two or more organs and disseminated disease as involvement of one organ plus bacteraemia.<sup>6</sup> Patients were classified as having bacteraemic or non-bacteraemic melioidosis, depending on whether their blood cultures were positive or negative for *B. pseudomallei*. Children included all individuals  $\leq 18$  years in accordance with the UN Convention on the Rights of the Child.<sup>7</sup> Excessive alcohol consumption was defined as  $> 14$  drinks per week or 4 drinks per occasion for men, and as  $> 7$  drinks per week or 3 drinks per occasion for women, in accordance with the criteria established by the US National Institute on Alcohol Abuse and Alcoholism.<sup>8</sup>

### Statistical analysis

Statistical analyses were performed using SPSS software version 22.0 (IBM, Armonk, NY, USA) and MedCalc program for Windows. Continuous variables were reported as mean and range, and categorical variables were compared using chi-square test. A value of  $p < 0.05$  was considered as statistically significant.

## RESULTS

There were 59 cases and 23 deaths attributable to melioidosis over the study period. The age range was 5 to 74 years. There were two children (3.3%) and 48 (81.3%) were men. Most of the

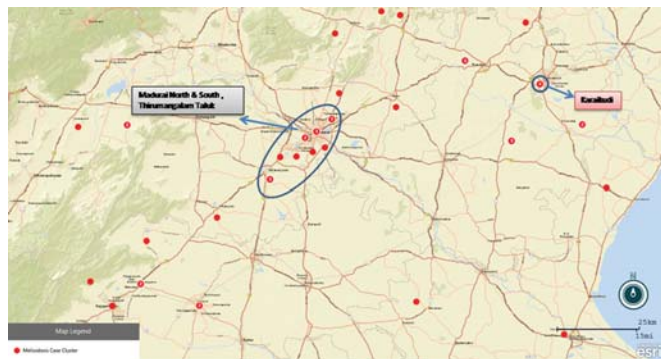


FIG 1. Spot map distribution of melioidosis cases based on residential address

cases were reported from Madurai and neighbouring Sivagangai and Virudhunagar districts (Fig. 1). The underlying conditions included diabetes mellitus (68%), excessive alcohol consumption (11.8%), pulmonary tuberculosis (6.7% confirmed by microscopy/PCR) and coronary artery disease (6.7%). None of the patients were HIV-seropositive. One patient with a chronic splenic abscess presented following recent Covid-19 infection. However, the absence of a demonstrable immunodeficient state did not rule out melioidosis, as 17 patients (29%) had no evidence of underlying immune deficit.

Thirty (50.8%) cases had direct exposure through occupational activities such as farmer (37%), plumber (11.8%), road construction (1.6%) and 28 (47.4%) had no evident environmental or recreational exposure. In one case there was a specific exposure scenario that was considered the likely infecting event: disseminated melioidosis occurred in a young healthy immunocompetent man who was involved in a road traffic accident few days before the onset of septicaemia. Seventy-eight per cent presented during the wet season (June to December), and the mortality rate was higher in patients presenting in the months between October and January (44.4%; 16 of 36 cases died) compared to the rest of the months (30.4%; 7 of 23 cases) but was not statistically significant ( $p=0.41$ ).

Overall, 44 (75%) presentations were acute and 15 (25%) were chronic. Reactivation of disease from a latent focus could not be ascertained due to the lack of previous radiological reports to assess any long-standing abnormalities and a lack of melioidosis serology to look for long-standing positive serology.

Thirty-seven (63%) patients were bacteraemic. Fever was the most common symptom (71%). Fifteen patients in whom blood cultures were not sent were classified as non-bacteraemic due to localized involvement without signs and symptoms of bacteraemia. There were 14 (23.7%) patients with liver and/or splenic abscess, 9 (15.2%) presenting with septic arthritis and/or osteomyelitis and 1 with spondylodiscitis, 7 (11.8%) with cellulitis, 7 (11.8%) with pneumonia, 6 (10.2%) with subcutaneous abscess, 5 (8.4%) with neurological melioidosis that included acute transverse myelitis, intracranial and intraspinal phlebitis, cortical venous thrombosis, brachial plexitis and scalp abscess with subgaleal haematoma, and 3 (5.1%) with suppurative lymphadenitis. Bacteraemia without an evident clinical focus was also a common presentation (5 cases; 8.4%; Table I).

Examples of some interesting cases include a 48-year-old man with diabetes who presented with fever, breathlessness and headache of one week duration. On examination, there was scalp abscess with subgaleal collection, culture of which grew

TABLE I. Demography, clinical course and outcome of bacteraemic and non-bacteraemic cases

Characteristic	Bacteraemic cases (n=37)	Non-bacteraemic cases (n=22)	p value
Mean age in years (range)	49 (5–74)	46 (15–70)	0.41
Gender (men:women)	29:8	19:3	
Duration of hospitalization in days (range)	12 (1–74)	14 (4–29)	0.53
Focus of infection, n (%)	Liver and/or spleen abscesses: 10 Arthritis and/or osteomyelitis: 6 Skin and soft tissue: 5 Neurological: 4 Lung: 5 Parotid abscess: 1 Pericardium: 1 Unknown site: 5	Soft tissue infection: 8 Liver and/or spleen abscesses: 4 Arthritis and/or osteomyelitis: 4 Spondylodiscitis: 1 Suppurative cervical lymphadenitis: 2 Salivary gland abscess: 1 Pneumonia: 1 Scalp abscess with subgaleal haematoma: 1	
Case fatality rate, n (%)	21 (57)	2 (9)	0.0003

*B. pseudomallei*. Sputum culture also grew *B. pseudomallei* and sputum PCR was positive for tuberculosis. The patient was concurrently treated for both conditions and recovered. Another 60-year-old man with diabetes had fever for one month and was admitted with breathing difficulty and altered sensorium. Blood culture grew *B. pseudomallei* and SARS-CoV-2 was detected by reverse transcriptase-PCR in a nasopharyngeal swab. Unfortunately, the patient developed acute respiratory distress and succumbed to the infection. Another 64-year-old man with uncontrolled diabetes presented with liver and spleen abscesses and concurrent acute pancreatitis, and another with massive pericardial tamponade requiring pericardiocentesis.

Of the 21 (36%) patients with septic shock, 16 (76%) died of acute fulminant melioidosis and 5 recovered. In contrast, the mortality rate was only 11% in the 38 (64%) patients without septic shock. Even among 18 patients with bacteraemia without septic shock, only 3 (17%) died (Table II).

Drug susceptibility to meropenem, ceftazidime, cotrimoxazole and doxycycline was 98.3% (one isolate with intermediate susceptibility, confirmed by repeat testing with VITEK 2), 100%, 90% and 100%, respectively. After receipt of sensitivity reports, intravenous meropenem was administered at the recommended dose of 25 mg/kg body weight 8-hourly in 23 patients with bacteraemia for 2 weeks, and in all other patients, ceftazidime was administered at the recommended dose of 50 mg/kg body weight, 8-hourly for 2 weeks. Doxycycline or cotrimoxazole were given for 12 weeks for the eradication phase in most patients.

Twenty-seven (47%) patients were admitted to the ICU and of these, 11 (41%) died. In ICU, 18 (67%) were ventilated. Of the 23 (39%) deaths overall, the median time from admission to death was 4 days; 42% patients were followed for 2 to 6 months with no recurrence.

## DISCUSSION

In our population as elsewhere, melioidosis predominantly affected middle-aged men suggesting possible occupational exposure. The increased incidence of acute melioidosis during the wet season concurs with other studies that have shown a correlation between rainfall intensity and disease.<sup>9,10</sup> The high proportion of patients with diabetes (68%) is in keeping with

other studies.<sup>9,10</sup> Specific defects in neutrophil function have been well described in diabetes, alcohol excess and renal disease and are probably involved. Excess alcohol also decreases ciliary beat frequency, impairs alveolar macrophage phagocytosis and inhibits cytokine responses.<sup>11</sup> There is insufficient evidence to support an association of melioidosis with HIV infection. Tuberculosis–melioidosis co-infection is not unusual probably reflecting overlapping risk factors and interferon-mediated host response.<sup>12</sup> In our study, a middle-aged man with diabetes and with melioidosis (pulmonary and scalp abscess) and concurrent pulmonary tuberculosis was treated successfully with appropriate regimens. Concurrent melioidosis and Covid-19 infection has been reported previously.<sup>13</sup> An elderly man with diabetes and acute melioidosis presented with acute respiratory distress syndrome and had melioidosis and Covid-19. It is not clear if this was a coincidence or whether SARS-CoV-2 precipitated his acute decompensation. We speculate that immunocompromising effects of Covid-19, such as lymphopaenia, might make patients with melioidosis prone to severe manifestations. Also, the absence of an immunodeficient state does not rule out melioidosis, as we observed 6 cases of head and neck infections, including suppurative cervical lymphadenitis and parotid abscess in immunocompetent individuals.

The association between melioidosis and rainfall is well established.<sup>9</sup> An increase in cases was identified in the months during and after the rainy season (September to January). There has been a steady increase in the cases identified over the years. Percutaneous exposure is another well recognized route of transmission when wounded skin is exposed to contaminated soil or water, often during occupational exposure, in addition to inhalation of water particles or dust contaminated with the organism.<sup>14</sup> An example was disseminated melioidosis occurring in a young healthy immunocompetent man who was involved in a road traffic accident a few days before the onset of septicaemia. Some noteworthy aspects of this case were the acute onset of bacteraemic melioidosis following a short incubation period, the lack of risk factors and occurrence outside the rainy season (March 2019). We believe the most probable source was from the soil at the site of the accident, when a large load of organisms could have been inoculated in the wounded area.

TABLE II. Clinical presentations and outcome of 59 cases of melioidosis

Presentation	Total		Bacteraemic cases		Non-bacteraemic cases	
	n (%)	Deaths (%)	n (%)	Deaths (%)	n (%)	Deaths (%)
<i>Septic shock</i>	21 (36)	16 (76)	19	15 (79)	2	1 (50)
Liver and/or spleen abscesses	5	3	5	3	0	0
Arthritis and/or osteomyelitis	4	2	3	1	1	1
Skin and soft tissue	2	1	1	1	1	0
Lung	5	5	4	4	0	0
Pericardium	1	1	1	1	0	0
Unknown site	5	5	5	5	0	0
<i>No septic shock</i>	38 (64)	4 (11)	18	3 (17)	20	1 (5)
Liver and/or spleen abscesses	9	0	5	0	4	0
Arthritis and/or osteomyelitis	6	1	3	0	3	1
Skin and soft tissue	11	1	4	1	7	0
Lung	2	0	1	0	1	0
Neurological	5	0	4	0	1	0
Lymphadenitis	2	0	0	0	2	0
Salivary gland	2	0	1	0	1	0
Unknown focus	3	2	3	2	0	0

Melioidosis has been reported in all sites of the body, but most commonly skin, soft tissues, musculoskeletal system, liver, spleen, lungs, prostate and kidneys. It has less frequently been reported from the brain, breast, mediastinum, scrotum, cornea and lymph node, and rarely in a mycotic aneurysm and pericarditis.<sup>9</sup> We found the most common sites to be the liver and spleen, followed by the musculoskeletal system, skin, soft tissues, lungs, brain and less frequently lymph node, salivary gland, pericardium and pancreas. CT scan of the abdomen and pelvis was done in most patients with suspected melioidosis to rule out diverse internal organ abscess. Liver and spleen abscesses often responded to treatment without requiring drainage. Cases that presented with multiple deep visceral abscess were provisionally diagnosed as melioidosis. The lower proportion of patients with pneumonia in our study compared to others might partly relate to the difficulty of isolating *B. pseudomallei* from respiratory samples without selective media such as Ashdown agar. In addition, blood cultures were not done in all patients with pneumonia, so cases of pneumonic melioidosis could have been overlooked.

Other cases were initially clinically diagnosed as having pyogenic arthritis/osteomyelitis, tuberculous lymphadenitis/spondylodiscitis/pericarditis/meningitis. In this modern era of improved healthcare facilities, any illness of unknown cause should not be attributed to tuberculosis. A meticulous attempt to identify the aetiology by radiological and microbiological work-up should be made.

Drug susceptibility patterns in our study are in concurrence with other Indian studies and the global literature. In a retrospective analysis of 114 patients at Christian Medical College, Vellore, between January 2008 and December 2014, susceptibility of *B. pseudomallei* to carbapenems and ceftazidime was 100%, while resistance to trimethoprim-sulphamethoxazole and doxycycline was found in 5.9% and 2.6%, respectively.<sup>10</sup> In our series, investigation of mechanisms of antimicrobial resistance was not attempted despite finding an unusual isolate with decreased susceptibility to meropenem, confirmed by repeat testing. A relatively high resistance rate (10%) to trimethoprim-sulphamethoxazole was also observed by microbroth dilution in the VITEK 2 system. However, this combination is known to be difficult to test against *B. pseudomallei* and we were unable to confirm these results by an alternative method such as gradient diffusion (e.g. Etest). It remains to be established whether the results we observed translate into clinically relevant resistance.

The higher mortality rate among patients presenting between October and January (44.4%) than those presenting during the rest of the year (30.4%) was not statistically significant. A similar association was seen in a study from Manipal, with statistically significant number of cases and higher mortality during monsoon months. 71.6%, 75.7%, 81.8% and 66.6% of melioidosis cases, bacteraemia, septic shock and deaths due to melioidosis, respectively occurred during the monsoon months.<sup>16</sup> It has been speculated that moist, humid conditions during the monsoon result in an increase in the environmental load and a switch to inhalation as the most frequent route of infection might account for such a difference.<sup>15</sup>

In conclusion, the epidemiology of melioidosis in Madurai is similar to that in other endemic areas in respect of middle age, preponderance of men, diabetes, alcoholism, chronic renal disease, lack of association with HIV and an association of incidence and mortality with the monsoon season. Differences

include the higher proportion of deep visceral abscesses and musculoskeletal compared with lung involvement. Invariably, septic shock is a strong predictor of mortality. In relation to surveillance systems, reporting and diagnostic facilities, India is at least 30 years behind other endemic areas such as Thailand and Australia, where health authorities have taken the condition seriously and appropriate measures are in place. Efforts should be made in India to establish enhanced surveillance for melioidosis, either voluntary or mandatory. However, for melioidosis to be included under the surveillance programme of the National Centre for Disease Control, a greater number of cases would have to be detected. We believe that there are likely to be many places within India yet to be unveiled as melioidosis-endemic. It is possible for any laboratory with a culture facility to make a presumptive identification of *B. pseudomallei* using the three antibiotic disc test (resistance to gentamicin and colistin/polymyxin and susceptibility to co-amoxiclav), which was recently shown to be 100% specific in Vietnam.<sup>17</sup> India could become the first South Asian country to classify melioidosis as a notifiable disease. With an environment hospitable to the bacterium, a large number of people with diabetes, many from a rural background, and an unevenly developed healthcare system, melioidosis is a neglected tropical disease which should be better known within India.

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