Original Article

Clinical characteristics and outcomes of bacteraemic melioidosis in a teaching hospital in a northeastern state of Malaysia: a five-year review

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Abstract

Background: Melioidosis is an important public health problem causing community acquired sepsis in the northeastern part of Malaysia.
Methodology: From January 2001 to December 2005, we reviewed case reports of all bacteraemic melioidosis admitted to a tertiary teaching hospital, Hospital Universiti Sains Malaysia.
Results: Thirty-five patients had positive blood culture for meliodosis and 27 case reports were traceable for further analysis. The mean age was 46.8 + 20.0 years. Twenty patients (74.1%) were male. The main clinical presentation was fever that occurred in 23 (85.2%) patients. Eighteen patients (66.7%) had lung involvement and three patients had liver abscess. Two patients presented with scrotal swelling, one of whom further developed Fournier's Gangrene. Nineteen (70.4%) patients had underlying diabetes, five of whom were newly diagnosed during the admission. Thirteen (48.1%) patients were treated with high-dose ceftazidime and six (22.2%) patients were treated with imipenem. Eight (29.6%) patients were not given anti-melioidosis therapy because the causative agents were not identified until after the patients died. The patients were admitted 16.8 days + 18.1. Seventeen patients (63.0%) died in this series, 13 patients of whom died within four days of admission.
Conclusions: The wide range of clinical presentations and the fatal outcomes of melioidosis require a high level of suspicion among physicians to develop an early appropriate therapy and reduce the mortality rate.

Key words: melioidosis, clinical features, Malaysia

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Introduction

Melioidosis is a tropical infectious disease caused by Gram-negative bacteria *Burkholderia pseudomallei*. This soil-borne disease is endemic in southeast Asia and northern Australia. Melioidosis has a diverse spectrum of clinical presentation and can affect any organ. It is important to define the demographic profiles, clinical characteristics, and outcomes of melioidosis because of the regional differences that have been described in the prevalence of organ involvement [1,2].

Kelantan State, which is located in the northeastern part of Malaysia, has a heavy monsoon season from November to March every year. This state is located in what is known as the Malaysian rice bowl and has more than 60,000 hectares of paddy fields [3]. Thousands of people are at risk of contracting *B. pseudomallei*, which is a great public health concern and an important cause of community acquired sepsis in the northeastern part of Malaysia. However, not many publications on meliodosis come from Malaysia. This study aimed to determine the demographic profiles, clinical characteristics, and outcome of patients with bacteraemic melioidosis who attended Hospital Universiti Sains Malaysia, Kelantan.

Materials and methods

A retrospective study was performed in Hospital Universiti Sains Malaysia (HUSM) by reviewing the blood culture results from the years 2001 to 2005 using the WHO-net program. HUSM is an 800-bed tertiary teaching hospital that is located in Kelantan, a northeastern state of Malaysia.

All confirmed cases of bacteraemic melioidosis were selected for the study Bacteraemic melioidosis is defined as any positive blood culture for *B. pseudomallei* with or without sepsis. The patients' records were reviewed accordingly to determine the demographic profiles, clinical characteristics, and

outcomes. Anti-melioidosis therapy for intensive phases used in HUSM during the study period was intravenous injection every eight hours of either 40 mg/kg ceftazidime or 20 mg/kg imipenem. The use of other antimicrobial agents or the use of ceftazidime or imipenem below these suggested doses without renal dose adjustment was not considered anti-melioidosis therapy. Death due to melioidosis was defined as a patient's death within 72 hours of blood culture positive for *B. pseudomallei* or a patient's clinical sepsis parameter that did not improve after the last blood culture positive for *B. pseudomallei*. Organ involvement of melioidosis was defined as present with clinical findings and/or investigative modalities of malfunctioning of that organ. The affected organ was probably the primary site of bacteraemia or its malfunction was a complication of bacteraemia. In HUSM, at least 5 ml of blood were collected aseptically and inoculated into BACTEC™ (Becton Dickinson, New Jersey, USA) blood culture bottles and incubated in the BACTEC™ automated blood culture system. *B. pseudomallei* was identified by the growth of silver-whitish colonies on blood agar, was Gram negative, oxidase positive, produced a neutral-alkaline reaction on triple sugar iron, was motile, grew on 42°C and was colistin-resistant which were also confirmed by API NE ® system (bioMérieux, France).

Results were expressed in terms of the number and percentage or the mean ± standard deviation. For categorical variables, the differences in patient characteristics and associated factors were tested by Chi-square and Fisher's exact test. For continuous variables, the independent t-test was used. The *p* value of ≤ 0.05 was considered significant. All analyses were done using SPSS software (SPSS, Chicago, Illinois, USA) in the Medical Informatics' Laboratory, School of Medical Sciences, Universiti Sains Malaysia.

Results

Out of 69,934 blood-culture request forms, 63 (0.09%) were positive for *B. pseudomallei* coming from 35 patients. We managed to trace the case folders of 27 cases for further analysis (Table 1). The mean age was 46.8 ± 20.0 years. The youngest was 15 days old and the eldest was 80 years old. Twenty patients (74.1%) were male. Fifteen (55.6%) patients presented during the northeast monsoon rainy season. Only one patient's work was directly related to gardening soil.

The main clinical presentation was fever that occurred in 23 (85.2%) patients. Eighteen patients (66.7%) had lung involvement and three patients had liver abscess. Two patients presented with scrotal swelling, one of whom further developed Fournier's Gangrene. The mean total white cell count during admission was 15.8 ± 7.5 $X10^3$ cell/mL. Seven patients had normal total white cell counts during presentation and five of them died.

Nineteen (70.4%) patients had underlying diabetes, five of whom were newly diagnosed during the admission. Four (14.8%) patients had chronic renal diseases, and five patients had no identified underlying disease. One patient had underlying systemic lupus erythematosus.

For anti-melioidosis therapy, thirteen (48.1%) patients were treated with high dose ceftazidime and six (22.2%) patients were treated with imipenem. Eight (29.6%) patients were not given anti-melioidosis therapy because identification of the causative agents was not made until after the patient died. The patients were admitted for 16.8 ± 18.1 days.

Seventeen patients (63.0%) died in this series of which 16 died directly due to bacteraemic melioidosis and 13 patients died within four days of admission. One of the patients (patient 11 in Table 1) was taken home against medical advice in an extremely ill state, failing to respond to imipenem. It is likely that this patient also died. This case was analyzed as death due to melioidosis.

In the association studies, death due to melioidosis among bacteraemic melioidosis was associated with shorter hospitalization, no identified underlying disease, and no anti-melioidosis therapy.

Discussion

There was no specific age for melioidosis. Neonatal melioidosis is not uncommon in Malaysia. The youngest case in this series was a 15-day-old boy who presented with abdominal distention and shock. Our centre had reported one case of neonatal meningitis due to *B. pseudomallei* in 1998 [4]. Another reported case of neonatal melioidosis in Malaysia was from the east coast state of Pahang in 2005 [5]. A case series of paediatric melioidosis in Kuala Lumpur reported one case of bacteraemic melioidosis in a neonate [6]. The baby was admitted for neonatal sepsis with fatal outcome.

We agree with the previous report from Kuala Lumpur that the correlation of melioidosis and rainfall is less strong in Malaysia compared to that in

Table 1. Summary of bacteraemic melioidosis cases in Hospital Universiti Sains Malaysia from January 2001-December 2005

No	Age (year)	Gender	Occupation	Month of admission	Presentation	Organ Involvement	Associated illness	TWC on admission	Antibiotic therapy for intensive phase	Outcome
1	45	Male	Working at rice mill	October	Fever Abdominal distention Jaundice	Lung	DM Renal failure	8.0	Ceftazidime	Died due to melioidosis
2	44	Male	NA	July	Fever Neck cellulitis after dental extraction	Soft tissue	DM	18.2	Ceftazidime	Recover
3	63	Female	Retired teacher	July	Fever	Lung	DM	12.8	Imipenem	Recovered with relapse
4	54	Female	Housewife	January	Admitted in shock	NA	DM Severe heart valve problem	16.2	No anti-melioid therapy	Died due to melioidosis
5	80	Male	Retired teacher	December	Fever Weakness	Lung	No	10.9	No anti-melioid therapy	Died due to melioidosis
6	61	Male	Odd job	January	Fever Urinary retention	Lung Urinary tract	DM	13.4	No anti-melioid therapy	Died due to melioidosis
7	61	Male	Retired staff	November	Fever Scrotum swelling	Lung	DM	20.8	Imipenam	Recovered
8	52	Male	Policeman	December	Fever Cough	Lung	DM	15.0	Ceftazidime	Died due to melioidosis
9	56	Female	Retired staff	December	Fever Cough	Lung	Chronic liver disease	16.8	No anti-melioid therapy	Died due to meliodosis
10	38	Male	Policeman	June	Seizures	Lung	DM – newly diagnosed	28.2	Ceftazidime	Recovered
11	25	Female	Gardener	June	Fever	NA	No	40.7	Imipenem	Died due to melioidosis*
12	12	Female	Student	January	Fever Seizures	Brain	SLE Lupus nephritis	7.7	Imipenem	Died due to melioidosis
13	62	Male	NA	September	Fever Cough	Lung	DM	5.6	No anti-melioid therapy	Died due to melioidosis
14	75	Female	NA	March	Lethargy Vomiting	Lung	DM CRF	4.3	Caftazidime	Died due to upper gastro-intestinal bleed and nosocomial sepsis
15	46	Male	NA	February	Fever Abdominal pain	Lung	DM	25.3	Ceftazidime	Died due to melioidosis
16	60	Male	NA	September	Fever Cough Diarrhea Abdominal pain	Lung	DM - newly diagnosed	18.1	Ceftazidime	Died due to melioidosis

Table 1. Continued

No	Age (year)	Gender	Occupation	Month of admission	Presentation	Organ Involvement	Associated illness	TWC on admission	Antibiotic therapy for intensive phase	Outcome
17	70	Male	Retired staff	August	Fever Scrotal swelling	Soft tissue	DM	19.5	Ceftazidime	Recovered
18	1#	Male	-	December	Abdominal distention Shock	NA	No	15.7	No antimelioid therapy	Died due to melioidosis
19	49	Male	Retired army	June	Fever Epigastric pain Jaundice	Lung Liver	DM – newly diagnosed	12.8	Imipenem	Died due to melioidosis
20	62	Female	NA	October	Fever Cough	Lung	No	12.4	No anti-melioid therapy	Died due to melioidosis
21	56	Male	NA	November	Fever Left leg swelling Multiple skin abscess	Lung Skin	DM	16.7	Ceftazidime	Recovered with relapse
22	5	Male	-	November	Fever Diarrhoea Vomiting	NA	No	20.2	No anti-melioid therapy	Died due to melioidosis
23	41	Male	NA	October	Fever	Liver Soft tissue Skin	DM – newly diagnosed	14.6	Ceftazidime	Recovered
24	34	Male	Sea diver instructor	November	Fever	Liver Spleen	DM – newly diagnosed	8.6	Ceftazidime	Recovered
25	40	Male	Laborer	March	Fever Nausea Vomiting Jaundice	Lung Right hip joint	DM CRF	19.9	Ceftazidime	Died due to melioidosis
26	48	Male	NA	April	Fever Cough	Lung	DM	10.8	Imipenem	Recovered
27	24	Male	Assistant engineer	November	Fever Nausea Vomiting	Lung	CRF	13.6	Ceftazidime	Recovered

15 day-old;
* This patient was taken home against medical advice in an extremely ill state. It is likely that this patient also died and was analyzed as died due to melioidosis.
DM – Diabetes mellitus; CRF – Chronic renal failure; SLE – Systemic lupus erymathosus; NA – not available

Thailand and in northern Australia [7]. We found that months of presentation were not significant association of mortality due to melioidosis. We also found that the occupation of bacteraemic melioidosis patients was not necessarily related to soil. Only one patient was working as a gardener. One other patient worked in a rice mill. This is in contrast with a previous study in Thailand that found that more than half of melioidosis patients were paddy farmers [8,9]. As in other studies on melioidosis [2,6,8-10], men were predominantly affected, perhaps because they were more frequently exposed to soil and water.

Fever was the most common clinical presentation; however, absence of fever during presentation was observed in four patients. High total white cell counts were present in many bacterial infections but we observed normal total white cell counts in seven patients although they had severe sepsis; nevertheless, these two factors were not significantly associated with mortality in associated studies. Other presentations included cough, scrotal swelling, Fournier's Gangrene, urinary retention, neck cellulitis, abdominal distention, jaundice, vomiting, and seizures. The wide diversity of clinical syndromes are known phenomena in melioidosis [11].

Nineteen patients (70.4%) had underlying diabetes in this series, five of whom were newly diagnosed during the admission. Puthucheary *et al.* reported only 28% of the patients in their study with diabetes [12]. Undiagnosed diabetes mellitus is an occult risk factor of melioidosis and the patient might

Table 2. Selected associated factors of mortality among bacteraemic melioidosis patient

Variable	Died due to bacteraemic melioidosis N = 16 Mean (sd)* / Freq (%)	Recovered or died due to other causes N = 11 Mean (sd)* / Freq (%)	*p* value#
Gender			
Male	11 (68.8)	9 (81.8)	0.446[a]
Female	5 (31.3)	2 (18.2)	
Age (years)	44.4 (22.5)	50.1 (16.0)	0.455[b]
Month of presentation			
Dry	6 (37.5)	6 (55.5)	0.381[a]
Rainy	10 (62.5)	5 (45.5)	
Length of hospital stay (days)	3.1 (2.3)	36.7 (10.4)	<0.001[b]
Fever during presentation	14 (87.5)	9 (81.8)	0.683[a]
Total white count during admission	16.2 (8.3)	15.3 (6.5)	0.769[b]
Lung involvement	11 (68.8)	7 (63.6)	0.782[a]
Underlying disease identify	11 (68.8)	11 (100.0)	0.014[c]
Anti-melioidosis therapy given	8 (50.0)	11 (100.0)	0.001[c]

p value significant at 0.05
[a] Pearson chi square
[b] Independent t-test
[c] Fisher's exact test

present very severe sepsis. In the present study, two out of five patients with newly diagnosed diabetes mellitus died. Renal disease was another risk factor identified in four patients with bacteraemic melioidosis. Five patients had no identified underlying disease.

The pulmonary involvement in this study (66.7%) was higher than that in previous cases from Kuala Lumpur (58%) [12]. Another series from Australia reported 60% of pulmonary involvement among bacteraemic melioidosis patients [13]. The liver and spleen were also common sites for abscess formation. Liver and/or spleen abscess were also reported as the most common sites for extrapulmonary infection in Thailand [9]. In this series, we found three cases of liver abscess and one case of splenic abscess. Involvement of the brain is in the form of brain abscess [14,15]. We found one case of possible cerebral melioidosis, but the patient died before proper diagnostic work was commenced.

The mortality rate was very high. There was not much difference in the mortality rate in this series when compared to the previous report in 1992 (65%) [12]. Thirteen of the deaths occurred within four days of admission. The patients died before the laboratory was able to confirm the causative organism. This condition was significantly associated with mortality in this series.

From the results of this study, we suggest that, in an endemic area such as our region, melioidosis should always be included as a working diagnosis in cases presenting with community-acquired infection even if the patient has no underlying medical illness. Low index of suspicion in cases with unidentified underlying diseases puts the patient at risk of not getting proper anti-melioidosis treatment. This study found that anti-melioidosis therapy was given to only one of the patients who had no identified underlying diseases.

Lack of clinical suspicion leading to delay in treatment is well described in other studies. Only one out of seven (14.3%) paediatric bacteraemic melioidosis patients was treated empirically with active drugs for melioidosis in Pahang, Malaysia [16]. There were better findings in Singapore where 43.3% bacteraemic melioidosis patients had initial empiric antibiotic therapy that was appropriate for melioidosis [13]. This is in contrast with the study in Australia that found no fatal cases among patients with no identified underlying illness [10] who were treated empirically with active drugs for melioidosis.

As stated above, thirteen patients died within four days of admission. We were able to identify five cases of newly diagnosed diabetes mellitus presenting with melioidosis. It was unfortunate that these patients died before a proper, full laboratory

investigation was done, and as a result, these cases were categorized as having no identified medical illness. The bottom line is that a higher index of suspicion of melioidosis among physicians is very important, even in patients with no identified underlying diseases.

In this study, 20.0% of the surviving patients suffered a relapse. Currie *et al.* reported a 13.0% relapse in a greater number of patients with 2.4% of patients relapsing twice [17]. Relapse can be due to poor compliance with eradication therapy, failure of eradication therapy, inadequate intensive therapy, re-inoculation from bone flap re-implant, chronic *B. pseudomallei* carriage, and new infection [17].

In conclusion, this review shows the importance of a high index of suspicion among physicians in order to provide early therapy and reduce the mortality rate among melioidosis patients.

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