ORIGINAL ARTICLE

A 5-year retrospective study of melioidosis cases treated in a district specialist hospital

Ray Yank Tang, MRCP[1], Soon Hooi Lim, MRCP[1], Jo Ee Lam, MBBS[1], Nurasykin Salim, Bsc (Hons) Biomed[2], Su-Sian Eileen Toh, MRCP[1], Yen Wen Chan, MRCP[1]

[1]Department of Medicine, Hospital Teluk Intan, Perak, Malaysia, [2]Department of Microbiology, Hospital Teluk Intan, Perak, Malaysia

ABSTRACT

INTRODUCTION: Melioidosis is caused by *Burkholderia pseudomallei*, a gram-negative aerobic bacillus, found in the soil and surface water. Treating melioidosis has been a challenge in district hospitals due to high usage of broad spectrum antibiotics and prolonged hospitalisation. This study is to review the patients' demography, clinical presentations and microbiological data.

METHODS: A 5-year retrospective study was carried out on patients admitted with culture positive for melioidosis from year 2013 to 2017 in Hospital Teluk Intan, Perak.

RESULTS: There were a total of 46 confirmed cases of melioidosis. Majority of the patients were working in the agricultural and farming (28.6%), and factories (25.7%). Thirty-one patients had diabetes mellitus (71.1%). Presentations of patients with melioidosis included pneumonia (54.3%), skin and soft tissue infection (19.6%), deep abscesses (15.2%) and bone and joint infections (13%). An average of 5.8 days was needed to confirm the diagnosis of melioidosis via positive culture. However, only 39.4% of these patients were started on ceftazidime or carbapenem as the empirical therapy. The intensive care unit (ICU) admission rate for melioidosis was 46% and the mortality rate was 52%. Our microbial cultures showed good sensitivity towards cotrimoxazole (97.1%), ceftazidime (100%) and carbapenem (100%).

CONCLUSION: Melioidosis carries high mortality rate, especially with lung involvement and bacteremia. Physicians should have high clinical suspicion for melioidosis cases to give appropriate antimelioidosis therapy early.

KEY WORDS:
melioidosis, abscess , pneumonia , antibiotic, Burkholderia pseudomallei, diabetes

INTRODUCTION

Melioidosis is a tropical infectious disease caused by *Burkholderia pseudomallei*, a gram negative bacillus found in soil and surface waters. It is endemic in Northern Australia, India, southern China and Southeast Asia including Malaysia.[1] Transmission can occur via inhalation, direct contact with contaminated soil or water through wound or skin abrasions and occasionally via aspiration or ingestion of contaminated water. The mortality of melioidosis varies considerably from 37.9 to 61 percent.[3] Reports from Malaysia showed the incidence rate of melioidosis in Sabah, Pahang and Kedah states were 2.57, 6.1 and 16.35 per 100,000 populations per year respectively.[2] There is insufficient data on the incidence rate in state of Perak as this is not a notifiable disease.

The clinical presentations of melioidosis vary greatly in terms of severity, systemic involvement and chronicity. Local clinical practice guidelines were developed to help clinicians to recognise melioidosis infections for better management of the cases. Acute melioidosis should be suspected in patients from endemic areas, with diabetes mellitus (DM), with history of exposure to contaminated environment, presenting with high grade fever or progressive pneumonia that does not respond to common antibiotics; or with hepatosplenomegaly.[4,5] Diagnosis of melioidosis is done via serological testing and microbial cultures. IgM ELISA has good sensitivity and specificity for melioidosis infection. High seroprevalence in endemic areas and cross reactions may result in false positive results.[6] Microbial cultures remain the gold standard diagnosis method for melioidosis infections.

Treatment of melioidosis consists of intensive therapy with intravenous ceftazidime or carbapenem for two weeks with consideration of prolonging antibiotic up till four to eight weeks in severe or deep focal infection.[7-9] Addition of trimethoprim/sulfamethoxazole during intensive phase can be considered if there are neurologic, prostatic, bone joint, cutaneous and soft tissue manifestations.[4,5,8,9] Eradication therapy for a minimum of three months with trimethoprim/sulfamethoxazole is required to prevent recurrence. Giving granulocyte-colony stimulating factor (G-CSF) in severe melioidosis is associated with a longer duration of survival but is not associated with a mortality benefit.10
In Teluk Intan Hospital (TIH), a government district hospital in Perak, we noticed an increase in the number of cases of melioidosis in our hospital in recent years. Thus a 5-year retrospective study was carried out to examine the patients' profiles, disease presentations and the outcomes.

MATERIALS AND METHODS

This is a 5-year retrospective study of melioidosis cases in TIH from January 2013 till December 2017. TIH is at 4.0035° N,

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Corresponding Author: Dr. Ray Yank Tang
Email: ryantang624@gmail.com

Table I: Characteristics of patients treated for melioidosis in Hospital Teluk Intan 2013-2017

Variables	Frequency, n (%) N=46
Age group (years)	
<35	5 (10.9)
35-50	9 (19.6)
51-65	26 (56.5)
>65	6 (13.0)
Gender	
Male	35 (76.1)
Female	11 (23.9)
Resident area	
Suburban	36 (78.3)
Urban	10 (21.7)
Occupation	
Agricultural/Farming	10 (28.6)
Factory/Industry	9 (25.7)
Professionals	3 (6.7)
Services	5 (11.1)
Unemployed	8 (22.9)
Unknown	11 (23.9)
Comorbidities*	
Diabetes mellitus	33 (71.7)
Hypertension	17 (37.8)
Ischemic heart disease	5 (11.1)
Chronic kidney disease	3 (6.7)
Congestive heart failure	1 (2.2)
Chronic liver disease	1 (2.2)
Chronic obstructive pulmonary disease	1 (2.2)
Bronchial asthma	3 (6.7)
Human immunodeficiency virus	1 (2.2)
No comorbidity	6 (13.0)

*some patients have more than one comorbid condition.

Table II: Clinical presentation and outcome for melioidosis patients in Hospital Teluk Intan 2013-2017

Variables	Frequency, n (%) N=46
Clinical presentations*	
Pneumonia	25 (54.3)
Deep abscesses	7 (15.2)
Bone and joint	6 (13.0)
Skin and soft tissue	9 (20.0)
Urinary tract	3 (6.5)
Gastrointestinal tract	5 (10.9)
Central nervous system	3 (6.5)
Requiring intensive care unit support	21 (45.7)
Requiring ventilator support	24 (52.2)
Requiring surgical intervention	7 (15.6)
Patients who received antimelioidosis therapy	13 (28.9)
Patients' outcomes	
Treated	17 (37)
Died	24 (52.2)
Discharged at own risk	5 (10.9)

*some patients have more than one system involvement.

Table III: Microbiology data for melioidosis patients in Hospital Teluk Intan 2013-2017

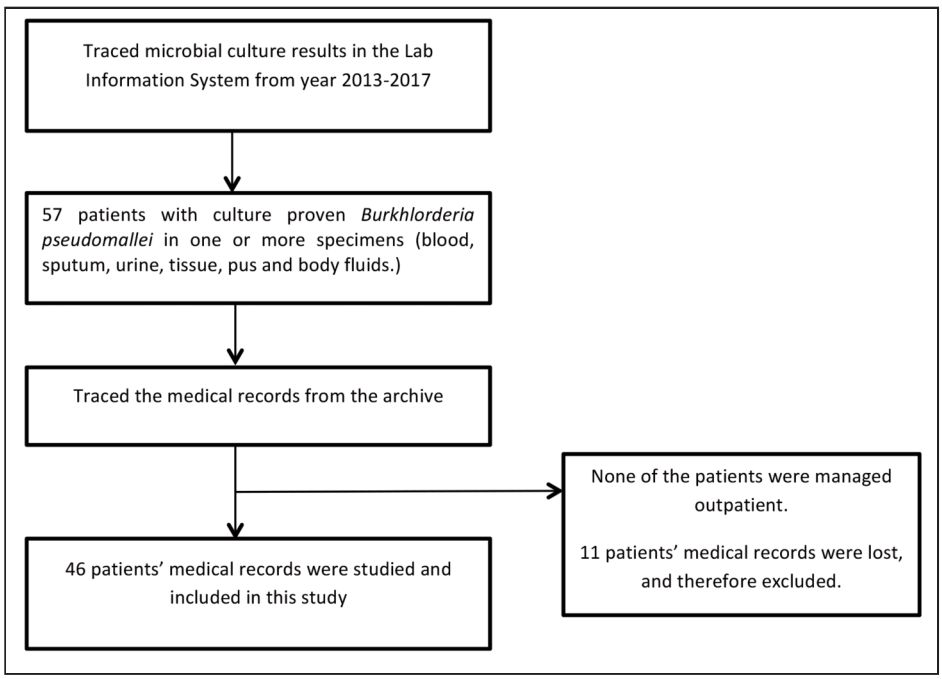
Variables	Frequency, n (%) N=46
Type of positive culture*	
Blood	42 (91.3%)
Sputum	4 (8.7%)
Tissue/pus	5 (10.9%)
Urine	5 (10.9%)
Average days to confirmation of melioidosis from first day of admission	
Minimum	3 days
Maximum	11 days
Mean	5.8 days (SD-2.03)
Antibiotic sensitivity pattern of *Burkholderia pseudomallei*	
Ceftazidime	100%
Imipenem	100%
Cotrimoxazole	97.1%

*Note: some patients have more than one sample with positive growth

Table IV: Selected associated factors of mortality among melioidosis patients

Variables	Treated (N=17) Frequency, n (%)	Died during admission (N=24) Frequency, n (%)	p value
Gender			
Male	13 (76.5)	17 (70.8)	0.736
Female	4 (23.5)	7 (29.2)	
Age			
<34	3 (17.6)	2 (8.3)	0.720
35-50	2 (11.8)	6 (25.0)	
51-64	11 (64.7)	12 (50.0)	
>65	1 (5.9)	4 (16.7)	
Diabetes mellitus	13 (76.5)	17 (70.8)	0.736
Comorbidity			
None	2 (11.8)	4 (16.7)	1.000
At least one	15 (88.2)	20 (83.3)	
Pneumonia	8 (47.1)	14 (58.3)	0.537
Bacteremia	15 (88.2)	23 (95.8)	0.560
Antimelioidosis therapy given upon admission	5 (15.4)	8 (33.3)	1.000
Amoxicillin-clavulinate given*	3 (17.6)	3 (12.5)	1.000

*amoxicillin-clavulinate given as empirical therapy upon admission among those who were not given first line antimelioidosis therapy.



101.0402° E on the west coast of Peninsular Malaysia, located at Teluk Intan town, south of Perak state. We went through the microbial culture results in the hospital Laboratory Information System and performed universal sampling of all patients with culture proven *B.pseudomallei*. Each case was studied by reviewing the written medical records from the hospital archive to determine the sociodemographic profiles, clinical characteristics, and outcomes.

We included all patients who were admitted to the hospital with culture proven *B.pseudomallei* infection in at least one specimen, including blood, sputum, urine, tissue, pus or body fluids, obtained during hospital admission. Patients with missing medical records were excluded.

Suburban was defined as region outside Teluk Intan town. Anti-melioidosis treatment meant giving first line antibiotics, for patients with the intention of treating melioidosis before the confirmative culture result is ready. Anti-melioidosis therapy in TIH was intravenous ceftazidime 100-200mg/kg/24h in 3-4 divided doses or intravenous meropenem 25mg/kg/day in three divided doses. Bacteraemia is defined by blood culture positive for *B.pseudomallei*. Mortality was defined as death of patients with confirmed culture of melioidosis during the admission.

Statistical analysis

A descriptive statistical analysis was conducted using Statistical Package for the Social Sciences (SPSS 23.0, IBM, USA). Chi-square test and Fisher Exact test were used to study the association of the patients' characteristics and clinical presentations with the patients' outcomes. The p-value of less than 0.05 is considered statistically significant.

RESULTS

Demographics

The number of melioidosis cases increased over the years, especially a marked surge in numbers of cases in 2017 (Figure 1). The majority of our patients were 51-65 years old (56.5%) with a male predominance (76.1%) (Table I). Ten patients were involved in agricultural and farming industry (28.6%), including workers in palm oil plantation, paddy field farmers and fishery. There was 25.7 percent who are factory and construction workers. Majority of patients lived in suburban areas (78.2%).

Clinical Presentations

There were 71.1% of melioidosis patients with underlying DM. Other comorbidities include ischemic heart disease, congestive heart failure, hypertension, chronic obstructive pulmonary disease, bronchial asthma, chronic liver disease and chronic kidney disease. Six patients did not have any comorbidity (13.3%). One of them was HIV positive (Table I). Table II shows the initial clinical presentations. Most of them presented with pneumonia (54.3%), followed by skin and soft tissue infections (19.6%), visceral abscesses (15.2%) and bone and joint infections (13.0%). Total of 91.3% of melioidosis patients presented with bacteraemia. There were 45.7% of patients requiring intensive care unit support and 52.2% requiring ventilation for respiratory failure. Fifteen percent of the patients required surgical debridement as part of the treatment process.

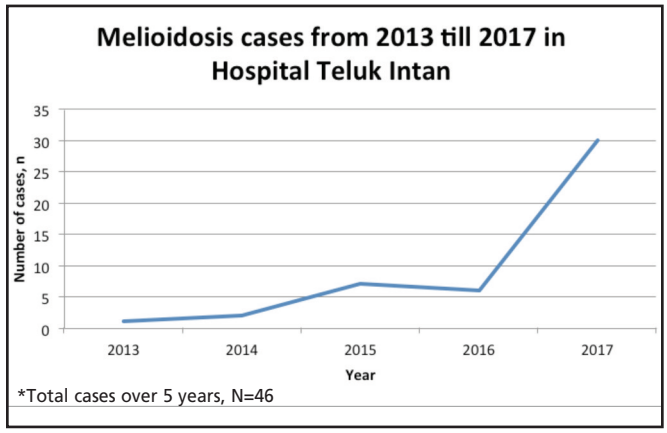


Fig. 1: Number of melioidosis cases from year 2013 till 2017.

Microbiology data

The average number of days to confirm melioidosis by positive culture from first day of hospital admission was 5.8 days and maximum up to 11 days. Mean inhibitory concentration (MIC) of antibiotic testing for *B.pseudomallei* showed very good sensitivity towards cotrimoxazole (97.1%), ceftazidime (100%) and carbapenems (100%) (Table III). The laboratory did not provide antibiotic testing for amoxicillin-clavulanate or other cephalosporins, due to limitation of local resource.

Treatment and outcomes

Only 28.9% of patients were given empirical therapy upon admission. The common antibiotics used before confirmed diagnosis were ampicillin-sulbactam, amoxicillin-clavulanate, cefuroxime, ceftriaxone and macrolides. Overall mortality rate for melioidosis treated was 52.2%. Our study did not show any significant association of higher mortality rate with gender, age group, diabetes mellitus, presence of any comorbidity, pneumonia, bacteraemia and not giving anti-melioidosis therapy (Table IV).

DISCUSSION

The exact reason behind the surge in incidence of melioidosis in the year 2017 is unknown. Possible reasons like change in the pattern of referrals from community clinics/other hospitals and increasing prevalence of diabetes mellitus were described in other study.[11]

Melioidosis can be difficult to distinguish from common diseases based only on clinical grounds, such as community acquired pneumonia, urinary tract infections, leptospirosis and cellulitis.[12-14] Patients with diabetes mellitus and workers in agriculture or factories have increased risk of contracting melioidosis. What was different from the melioidosis case definition is that there was a significant proportion of patients who worked as professionals, in services or being unemployed (28.3%). In our study, two melioidosis cases were diagnosed as a result of drowning in freshwater in motor vehicle accidents, in which these patients did not have any comorbidity. One of them was transferred to a private health facility; the other one died due to severe aspiration pneumonia.

We did not perform serological tests routinely for these patients due to limited resources and difficulty in interpreting the result in absence of seroprevalence data in Teluk Intan. Mean inhibitory concentration (MIC) method is more accurate in determining antibiotic susceptibility compared to disc diffusion test.[15] In our study, disc diffusion tests for antibiotic susceptibility showed almost 100 percent resistance rate to cotrimoxazole, in contrast with MIC results.

Pulmonary involvement and bacteraemia were shown to be associated with higher mortality rate in melioidosis patients.[9,15,16] Our study showed higher mortality rate among melioidosis patients with pneumonia and bacteraemia, but there was no statistical significance. We also found that the outcome among patients without comorbid is not significantly different from those who had at least one comorbid disease, including DM. Although DM is a strong risk factor for contracting melioidosis infection, it was not found to be significantly associated with higher mortality of melioidosis patients in other studies.[15,16]

Lack of clinical suspicion for melioidosis caused the delay in giving anti-melioidosis therapy was shown to be the contributing factor of mortality.[12] Our study noted only 28.9 percent of our patients were initiated on appropriate antibiotic for melioidosis upon admission. The lack of statistical significance in the association with mortality rate was thought to be due to small sample size and presence of other confounding factors. The empirical therapy was mainly targeting community acquired pneumonia, urosepsis, gastroenteritis and leptospirosis, which used ceftriaxone or penicillins mostly. Aminoglycosides, fluoroquinolones and ceftriaxone have shown high failure rate in melioidosis treatment.[3,17] Among the group of patients who were not given antimelioidosis therapy upon presentation, the usage of amoxicillin-clavulanate in our study was 13.0 percent. Although studies showed that *B.pseudomallei* is mostly sensitive to amoxicillin-clavulanate,[3,17] our study showed no significant difference in mortality rate by starting amoxicillin-clavulanate. Amoxicillin-clavulanate is only a second-line intensive therapy as higher dose of clavulanic acid is required,[3] compared to the usual regime for other infections.

CONCLUSION

Melioidosis can present in a wide spectrum of severity. Physicians must have high clinical suspicion of melioidosis to provide early antimelioidosis antibiotic and improve the patients' outcomes. Gram staining for early identification of gram negative bacilli can be considered to guide clinicians in initiations of antibiotic for melioidosis. Local antibiotic resistance data against melioidosis needs to be considered when deciding the choice of antibiotic.

ETHICS APPROVAL

This work was approved under the National Health Institute, Ministry of Health, Malaysia, NMRR No. 17-3517-37438 on 17th Disember 2018.

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