



Five Years Melioidosis Registry Data from 2011 to 2015 in Pahang, Malaysia: A Retrospective Study



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Abstract

Background: Melioidosis cases were conducted throughout the state of Pahang, Malaysia, from 2000 to 2004, and found that there were high annual incidences and mortality rates among melioidosis patients. A series of programs on medical education has since been introduced throughout Pahang, and a registry has been created to track the effects. **Objective:** We established and investigated the melioidosis registry with the aim of improving the state's melioidosis management **Methodology:** This comprehensive review of the 239 confirmed melioidosis cases from 1st January 2011 to 31st December 2015 was performed to trace the cultures from all microbiology laboratories in Pahang. Comparisons were made between these cases and previous records retrieved from the registry. Information was verified from the patient's case note when necessary. **Results:** The patients, aged from 1 to 84 years, were predominantly males (78.2%), Malays (82.0%), and had a median age of 51 years. The most common predisposing factor present in 165 (69.0%) patients was diabetes, while the most common clinical presentation observed in 109(45.6%) patients was pneumonia. With outcomes that were known within 209 patients, 106(50.7%) of them did not survive, and while the other 103(51.6%) were fully discharged. Patients who were fully discharged received appropriate antibiotics for both intensive and eradication therapies. Twenty patients (8.4%) had culture-confirmed relapses. **Conclusion:** Despite improvements in patient management, especially in treatment involving antibiotics, mortality rates remained high. Collectively, these research have found important relationships and insights that contribute for further management of the illness at the state level. [*Bangladesh Journal of Infectious Diseases, June 2022;9(1):7-14*]

Keywords: Melioidosis; *Burkholderia pseudomallei*; registry; mortality; awareness; Malaysia

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Introduction

The Gram-negative bacillus, *Burkholderia pseudomallei*, which is endemic in Southeast Asia and Northern Australia¹⁻⁵, is the cause of melioidosis. In Pahang, it had been previously reported in a review of culture-confirmed melioidosis that the annual incidence of melioidosis among adults was very high (6.1 per 100,000 population annually) from 2000 to 2003² and also (6.0 per 1000 000 population) from 2005 to 2006 as reported in Pahang Registry³. The mortality rate in Pahang was reported at 54% compared to other endemic areas where mortalities were between 19 to 39% cases^{1,5}. Inappropriate or inadequate treatment contributed to the high mortality rate, with only 32.7% of patients receiving the proper antibiotic. Of the remaining surviving patients, only 51.9% received suitable antibiotics for at least two weeks, and eradication therapy was not provided to most patients. This was probably because of the lack of awareness in treating melioidosis among the doctors.

The clinical manifestation of melioidosis in Pahang varied somewhat in comparison with the other endemic countries. In Australia¹ and Thailand⁵, the incidences of localized melioidosis were reported at 54.0% and 40.0%, respectively, but only 8.0% was reported in Pahang. This was probably due to the under usage of a selective medium to isolate *Burkholderia pseudomallei*.

The growing threats have led to the collaboration between the Medical Department of Islamic International University Malaysia and the state government of hospital in Pahang with the assistance of the State Health Office launching the Pahang Melioidosis Registry in 2004. In 2010, the registry was turned over to the State Health Office. The registry required all doctors to notify every melioidosis case and record their clinical presentation, progression, and treatment. In order to decrease the mortality rate in Pahang, the registry was initiated to improve doctors' knowledge on the diagnosis and management of melioidosis. Simultaneously, a series of programs on medical education was introduced in Pahang to educate the health personnel.

In this study, the culture-confirmed melioidosis cases occurring from 2011 to 2015 in all Pahang hospitals were reviewed and verified. The incidence rate, source of culture, the sensitivity of *Burkholderia pseudomallei*, and mortality rate were documented and compared to previous records in the registry.

These data demonstrated the impacts of the registry after initiation.

Methodology

Study Settings & Population: Pahang is the largest state in Peninsular Malaysia, covering a total area of 36,000km² with a population of more than 1.6 million in 2015. Following the establishment of the registry in 2004, the investigators gave a series of Continuous Medical Education (CME) in the form of lectures to improve awareness of melioidosis among specialists, medical officers, paramedics, and microbiologists from all tertiary and district hospitals in Pahang. A guidelines on investigations and management of melioidosis was developed and was distributed to the participants during the workshop and made readily accessible from the internet. The registry received notifications of melioidosis cases from all hospitals in Pahang. The patient's personal information, socio-demographic characteristics, clinical presentation, treatment given, and mortality status were recorded. This registry is not enforced by any act. Therefore, there were some missing data, and there were also records of patients with negative culture but positive serology.

Study Procedure: A retrospective review was performed for records on culture-confirmed cases from all microbiology laboratories in Pahang and matched with cases captured in the registry. Cases that were culture-negative but had positive serology were excluded from the analysis, and cases that were culture-positive but were not reported were retrospectively entered into the registry. Investigators checked for any mismatched information resulting from any data by tracing the case records. Following the initial infection, the second and any subsequent *Burkholderia pseudomallei* infections was defined as a "relapse". Appropriate intensive antibiotic therapy was defined as antibiotics treatment for at least two weeks with either ceftazidime, cefoperazone-sulbactam, amoxicillin-clavulanic acid, imipenem, meropenem, or any combination thereof. The definition of appropriate eradication therapy was antibiotics treatment for at least 20 weeks with either a combination of doxycycline and co-trimoxazole or only co-trimoxazole. In-hospital mortality rates were calculated based on the number of patients with known outcomes after excluding patients who were discharged against the advice of doctors, transferred to another hospital, or had an uncertain outcome. Pediatric patients were defined as those younger than 18 years old.

Laboratory Procedure: In Pahang, there are two government hospitals equipped with the facilities to isolate *Burkholderia pseudomallei*. Blood agar, Francis media⁶, and MacConkey agar were used to culture blood fluids at 37⁰ C, and preliminary identification was performed by observation of colony morphology on blood and MacConkey agar, the appearance of yellow haze on Francis media, oxidase test, motility, and antibiogram patterns. APITM 20NE (bioMérieux, France), a commercial bacteriological identification test kit that utilizes different biochemical tests, was used to confirm all isolates. Sensitivity testing was carried out using the disc diffusion method with BBLTM Sensi-DiscTM Antimicrobial Susceptibility Test Discs (Becton, Dickinson and Company, USA). The disc diffusion method is regulated by the Clinical and Laboratory Standards Institute Standard (CLSI). The E-test was used for sensitivity to trimethoprim-sulfamethoxazole. Blood samples were inoculated into the BactecTM 2940 automated continuous monitoring blood culture system (Becton Dickinson and Company, USA). All positive isolates were subsequently cultured in blood agar, Francis media, and MacConkey agar.

Statistical Analysis: Calculation of incidences was carried out by dividing the average number of patients per year over the average population from 2011 to 2015. Numerical data were described using the mean (standard deviation) or median (Inter-quartile range, IQR) depending on their distribution, and the categorical variable was described in proportion. Categorical variables were tested using the chi-square test. P value less than 0.05 was considered significant. IBM SPSS for Windows, Version 25.0 (IBM Corp. Released 2011. Armonk, NY) was used for data analysis.

Ethical Approval: This study has been registered in National Medical Research Register and approved by the Medical Review and Ethic Committee (MREC) of Malaysia with approval number: NMRR-10-290-5082

Results

During this five-year study period from 1 January 2011 to 31 December 2015, there were 239 patient with culture positive for *Burkholderia pseudomallei*. The annual incidence of melioidosis in Pahang was 2.79 per 100,000 people (4.04 per 100,000 among adult and 0.77 per 100,000 among pediatric). Most of the cases were presented from the tertiary hospitals in Temerloh (63.6%) and Kuantan (25.1%), while the other smaller district hospitals registered the remaining cases. In this study, the age range of the

patients was from 1 to 84 years with 23 (9.6%) pediatric patients were reported. The majority were males, (n=187, 78.2%), Malay population (n=196, 82.0%) and with a slight number of foreign workers (n=13, 5.4%) were also diagnosed with melioidosis. Only 20 patients (8.4%) had a history of possible melioidosis in the past with more than half with confirmed cultures. Occupational history was generally overlooked, with less than half of them being recorded. Out of the 84 working adults, 39(46.4%) of them were farmers (Table 1).

Table 1: Social-Demographic Characteristics of All Patients

Characteristics	Values
Age (Years) Median (IQR)	51(37-59)
Gender	
• Male	187(78.2%)
• Female	52(21.8%)
Race	
• Malay	196(82.0%)
• Chinese	12(5.0%)
• Indian	6(2.5%)
• Orang Asli	12(5.0%)
• Others	13(5.4%)
Nationality	
• Malaysian	226(94.6%)
• Non-Malaysian	13(5.4%)
Occupation*	
• Managerial/Professional	2 (0.8%)
• Technical/Sales/Administrative	12(5.0%)
• Farmers/Forestry/Fishing	39(16.3%)
• Other service occupations	10(4.2%)
• Industrial worker	21(8.8%)
• Housewife	11(4.6%)
• Student/Children	22(9.2%)
• Unemployed	24(9.6%)

*Percentage reported based on total cases (n=239) as denominator, missing data was reported 41.4%

Diabetes was the most common predisposing factor (n=165, 69.0%), while pneumonia was the most common clinical presentation (n=109, 45.6%). *Burkholderia pseudomallei* was isolated most commonly from blood (n=207, 86.6%) followed by sputum (n=36, 15.1%), urine (n=17, 7.1%), and subcutaneous pus (n=19, 7.9%). The rest were uncommon specimens, including bronchoalveolar lavage, endotracheal tube, pleural fluid, peritoneal fluid, urethra discharge, pus from bone, septic joint and liver abscess. Considering pediatric melioidosis None of the paediatric patients had any history of previous infections. Two patient had diabetes mellitus, and another had chronic rheumatic heart

disease. The most common presentation was pneumonia which was seen in 10 (43.5%). This was followed by 7(30.4%) patients who had subcutaneous abscess. Three (13.0%) patients had splenic abscess, 3(13.0%) had meningoencephalitis, and the others had a urinary tract infection. There was one patient who had multiple hornet stings, causing skin cellulitis, which led to the growth of *Burkholderia pseudomallei*. There were positive cases in blood cultures of 15 patients. The other positive cultures were from pus (7), sputum (5), urine (1), and tissue (1). Among 23 patients with known

outcomes, 68.2% of them were fully discharged, and 31.8% died in the hospital. In case of adult melioidosis, the median age among adult patients was 53 years old (age range from 20 to 84 years, IQR: 18 years) with a male to female ratio of 4:1. Diabetes mellitus was the most common predisposing factor for melioidosis among adult patients (Table 3). Twenty (9.3%) of them had underlying chronic renal failure. Other predisposing factors that were documented include chronic lung infection, HIV infection, thalassemia, underlying malignancy and urinary calculi (Table 2).

Table 2: Clinical Characteristics of Melioidosis Patients in Pahang

Variables	Overall	Pediatric	Adult
Had Previous Infection	20 (100.0%)	0(0.0%)	20 (100.0%)
Risk Factors			
• Diabetes	165 (69.3%)	2(8.7%)	163 (75.8%)
• Chronic renal failure	20 (9.3%)	0 (0.0%)	20 (9.3%)
• Chronic lung disease	7 (2.9%)	0 (0.0%)	7 (2.9%)
• Human Immunodeficiency Virus (HIV)	1(100.0%)	0 (0.0%)	1(100.0%)
Clinical Presentation / Predisposing factors			
• Pneumonia	109 (45.8%)	10(43.5%)	99 (46.0%)
• Septic Arthritis	16 (6.7%)	0(0.0%)	16 (6.7%)
• Osteomyelitis	2 (0.8%)	0(0.0%)	2 (0.8%)
• Soft Tissue Abscess	34 (14.3%)	7(30.4%)	27 (12.6%)
• Prostatic Abscess	3 (1.3%)	0(0.0%)	3 (1.3%)
• Liver Abscess	26(10.9%)	1(4.3%)	25 (11.6%)
• Splenic Abscess	49(20.6%)	3(13.0%)	46 (21.4%)
• Meningoencephalitis	12 (5.0%)	3(13.0%)	9 (4.2%)
• Brain Abscess	1(0.4%)	0(0.0%)	1(0.4%)
• Pyelonephritis / UTI /Perinephric abscess	20 (9.3%)	0(0.0%)	20 (9.3%)
• Thalassemia	1(0.4%)	0(0.0%)	1(0.5%)
• Malignancy	1(0.4%)	0(0.0%)	1(0.5%)
• Urinary calculi	1(0.4%)	0(0.0%)	1(0.5%)
Site of Culture Positive			
• Blood	207 (86.6%)	15 (65.2%)	192 (88.9%)
• Tissue	17 (7.1%)	1(4.3%)	16 (7.4%)
• Urine	17 (7.1%)	1(4.3%)	16 (7.4%)
• Subcutaneous abscess	19 (7.9%)	7 (30.4%)	12 (5.6%)
• Sputum	36 (15.1%)	5 (21.7%)	31 (14.4%)
Serology Test - Positive	90/190 samples sent (47.3%)		
Outcomes			
• Discharge	103 (43.1%)	14 (60.9%)	89(41.2%)
• AOR* discharge	9 (3.8%)	2 (3.2%)	7 (3.2%)
• Death	106 (44.4%)	7 (30.4%)	99 (45.8%)
• Transfer to other hospital	21 (8.8%)	0 (0.0%)	21 (8.8%)

*AOR- at own risk

Table 3: Adult Melioidosis in Pahang

Variables	January2000- June 2003 ¹	July 2005 – June 2006 ²	January2010 – December2015
No of cases	135	54	216
Incidence*	6.1	6.0	4.0
Median age (year)	51	50	53
Male: female ratio	3.6:1	3.9:1	4.0:1
Bacteraemia (%)	92	93	86.6
Mortality rate (%):			
• Overall	54	44	44
• Bacteraemic cases	54	47	93.4
Underlying disease (% of cases)			
• At least one	85	91	88.5
• Diabetes mellitus	74	89	75.5
Relapse	19	0	20

*Per 100,000 populations per year

The most common presentation was pneumonia 99 (45.8%) followed by splenic abscess 46 (21.3%), soft tissue abscess 27 (12.5%), liver abscess 25 (11.6%), urinary tract infection 20(9.3%), septic arthritis 16(7.4%), meningoencephalitis 9 (4.2%), osteomyelitis 2 (0.9%), prostatic abscess 3 (1.4%), and brain abscess 1 (0.5%). Some of the patients had multiple organs involved. Other uncommon infections were pancreatic abscess, peritonitis, psoas abscess, vulva abscess, infected prosthesis, infective endocarditis, and pan-ophthalmitis. Blood culture was the most common method used to isolate *Burkholderia pseudomallei*, which was positive in 192 (88.9%) of cultures, followed by sputum culture 31(14.4%), urine culture 16(7.4%), and subcutaneous pus culture 12(5.6%). Other specimens were pus from liver abscess, pleural fluid, synovial fluid, etc. Samples from 119 patients were sent for serology tests, and 90 patients of the results show positive (Table 2).

Table 4: Sensitivity Tests of *Burkholderia pseudomallei* on Various Antibiotics

Antibiotic	Sensitive
Ceftazidime	229(99.2%)
Amoxicillin-Clavulanic acid	206(96.3%)
Gentamycin	1(5.6%)
Trimethoprim-Sulfamethoxazole	206(90.4%)
Tetracycline	208(97.7%)
Imipenem/meropenam	218(96.5%)
Ciprofloxacin	27(60.0%)

Overall, 103 (43.1%) patients were fully discharged from the hospital, and 106 (44.4%) patients died. The remaining patients, whose outcomes were unknown, were either transferred to other hospitals or discharged against medical advice (Table 2).

Only 20 patients (8.4%) had a culture-confirmed relapse (Table 3).

Table 5: Mortality Outcomes in Patients with Pneumonia

Outcomes	Pneumonia		P Value
	Present	Absent	
Discharge well	27(23.9%)	86(76.1%)	0.0001
Death	73(69.5)	32(30.5%)	
AOR discharge	3(33.3%)	6(66.7%)	
Transfer to other hospital	9(42.9%)	12(57.1%)	

Resistance to ceftazidime and carbapenem was rare, observed in 2(0.8%) and 4(1.7%) patients respectively (Table 4).

Table 6: Intensive and eradication therapies in well discharged adult patients

Antibiotics	Intensive Therapy	Maintenance Therapy
Ceftazidime	71(79.8%)	
Carbapenem	14(15.7%)	
Amoxicillin-Clavulanic Acid	1 (1.1%)	5(5.1%)
Cefoperazone	1 (1.1%)	
Trimethoprim-Sulfamethoxazole	23(25.8%)	6(6.1%)
Ciprofloxacin		1 (1.1%)
Trimethoprim-Sulfamethoxazole & Doxycycline		62 (63.3%)

The mortality rate was as high as 50.7% among the patients with known outcomes. Patients with pneumonia had higher mortality rates than those who did not have pneumonia (69.5% cases vs 30.5% cases; $p < 0.0001$). (Table 5).

Of the 188 patients with known outcomes, 89 (47.3%) were fully discharged, and 99 (52.7%) died. Some patients were discharged against medical advice or transferred to other hospitals, with their outcomes unknown. Among the 89 patients who were fully discharged, 71 (79.8%) received ceftazidime, 14 (15.7%) received carbapenem, 1 (1.1%) patients received amoxicillin-clavulanic acid, and 1 (1.1%) patient was given cefoperazone. These antibiotics were given as intensive therapy for the patients. Trimethoprim-sulfamethoxazole was given to 23 (25.8%) of the patients as a combination therapy. For maintenance therapy, 6 (6.1%) of patients were discharged with Trimethoprim-sulfamethoxazole, and the majority of the patients who receive combinations of Trimethoprim-sulfamethoxazole and doxycycline were given to others 62 (63.3%). The other antibiotics that were used for maintenance were amoxicillin-clavulanic acid 5 (5.1%) patients and ciprofloxacin 1 (1.1%) patient. (Table 6).

Discussion

Melioidosis is endemic in Northern Australia and Southeast Asian countries, in particular, Malaysia²⁻³, Thailand⁵ and Singapore⁷, compared to other parts of the world where there are only sporadic cases. The incidence is slightly reduced while the median age, and male to female ratio in our adult patients were similar in comparison to the previous studies by How et al²⁻³. The bacteremic melioidosis (86.6%) cases in this study remained higher than those of other regions (39 to 60%)^{1,5}. This was probably due to the majority of the adult patients in this study had diabetes (69.0%), which was more than other regions (20 to 57%)^{1,5}. In addition, late presentation of our patients was also one of the probable causes and further research is needed to further analyse our *Burkholderia pseudomallei* strain to determine the virulent characteristic of organism. Besides that, there was an increase in localized melioidosis cases in recent years, especially with more *Burkholderia pseudomallei* isolated from wound, urine, and sputum compared to the previous study²⁻³. This could be explained by educating doctors on the use of the selective Francis medium⁶, especially when culture specimens were taken from a non-sterile site.

No patients with prostatic abscess were found in the previous study². This was in contrast to a small

prospective study done on male patients who have routinely undergone Computed Tomography (CT) of abdomen and pelvis, where it was found that prostatic abscess was present in about one-third of the male patients⁸. In this study, a prostatic abscess was detected in 3 patients using ultrasound abdomen rather than CT pelvis. Therefore, a higher incidence of prostatic abscess in Australia¹ was likely due to the routine use of CT scan in melioidosis patients there rather than the differences in presentation among different countries.

Previous study showed that the isolated organisms were typically susceptible to ceftazidime (99.2%), tetracycline (87.2%), and amoxicillin-clavulanic acid (81.9%), which was quite similar to the current study. As the resistance to commonly used antibiotics for melioidosis was not increased, this suggested that the routine use of antibiotics did not interfere with the antibiogram of *Burkholderia pseudomallei* in the environment. However, there was an increase in resistance to meropenem and ciprofloxacin. Resistance to trimethoprim-sulfamethoxazole was lower in this recent study, possibly due to more widespread use of the E-test than the disc diffusion test.

It was discovered in the previous study that only half of the patients received suitable intensive therapy and only 38.0% cases received eradication therapy². Nevertheless, almost all patients from this study were given the appropriate antibiotics sufficiently for both intensive and eradication therapies. The majority of patients were given a combination of doxycycline and trimethoprim-sulfamethoxazole as eradication therapy after a randomized controlled trial showed a reduction in relapse⁹. Only a few patients were given antibiotics that have not been recommended as eradication therapy. Despite this, 20 (8.4%) patients had documented relapse which was much lower than the 19% reported in the previous study and other studies^{2,10-11}. Despite the better use of intensive therapy, the mortality rate was not reduced. This was possibly due to the delay in presentation to hospitals and likely due to severe presentation of bacteremia.

The Pahang Melioidosis Registry, Malaysia's first of its kind, provided an extensive education program for doctors to improve patient care. However, it failed to reduce the mortality rate significantly. This contrasts with data from Darwin¹², which showed that the overall mortality rate was reduced to 14%. In the same study, patients presented with septic shock had a 44.0% mortality rate. This study did not include data on septic shock, but the majority of patients had severe sepsis, as bacteremia was noticed

in nearly 93.4% of them. In the Darwin study, patients with an underlying risk factor and older age had higher mortality rates. This may explain the higher mortality rate of patients in this study as there was at least one risk factor present in the majority of adult patients and also late presentation to the hospital.

The incidence and mortality rate of melioidosis are slightly reduced in this study suggested that public health effort is significant to reduce the number of deaths due to melioidosis. Public health personnel should play a key role in actively raising awareness of melioidosis among residents in endemic areas, especially farmers. Efforts including providing health talks regarding the mode of transmission, nature, and source of the disease, preventive measures such as wearing gloves while dealing with soil and working in plantations should be carried out. Susceptible groups, such as diabetes patients, should be more thoroughly educated. Patients who are suspected of having melioidosis are advised to come to the hospital sooner. This will ultimately decrease the melioidosis-related mortality rate.

Conclusion

The mortality rate of melioidosis has remained high in Pahang after nearly a decade. There was only a significant reduction of relapse cases after the introduction of the guidelines and management to the health personnel. In order to decrease the mortality rate of melioidosis, the implementation of more public health measures is required.

Acknowledgements

The authors would like to thank the participants who made this study possible.

Conflict of Interest

We declare that we have no conflict of interest.

Financial Disclosure

The author(s) received no specific funding for this work.

Contribution to authors:

HSH designed the overall study. HSS, VKF, TCL and MRS were responsible for data collection. KKBS involved in data cleaning. HSH, UAZ, MSMI, FM conducted data analysis and interpretation. HSH and UAZ drafted the first manuscript. UAZ, MSMI, FM and BCL revised the manuscript. All authors read and approved the final manuscript.

Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author and are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

Ethical approval for the study was obtained from the Institutional Review Board. As this was a retrospective study

the written informed consent was not obtained from all study participants. All methods were performed in accordance with the relevant guidelines and regulations.

How to cite this article: Hin HS, Zainulabid UA, Ibrahim MSM, Mahmud F, Chiu LB, Singh KKB, Chee LT, Fong KV, Sulong MR. Five Years Melioidosis Registry Data from 2011-2015 in Pahang, Malaysia: A Retrospective Study. *Bangladesh J Infect Dis* 2022;9(1):7-14

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Article Info

Received on: 7 October 2021

Accepted on: 24 December 2021

Published on: 1 June 2022

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