Pahang Melioidosis Registry

S H How, MMed*, T H Ng, MRCP*, A R Jamalludin, MPH*, H P Tee, MRCP, Y C Kuan, MRCP**, F Alex, M. Sc**, C A Aminudin, M S Ortho*, S Sapari, MMed**, M H Quazi, PhD***

*Kulliyyah of Medicine, International Islamic University Malaysia, P.O. Box 141, 27510, Kuantan, Pahang, Malaysia, **Hospital Tengku Ampuan Afzan, Kuantan, Malaysia

SUMMARY

Melioidosis has a high annual incidence and mortality rate in Pahang, Malaysia. We initiated the first melioidosis registry in the country on 1st July 2005 to improve the management of melioidosis in the state. Continuous medical education on melioidosis was carried out in all hospitals in the state to highlight the magnitude of the disease and to educate the doctors on the treatment of the disease. All culture confirmed cases were registered and analysed. During the one-year study period from 1st July 2005 till 30th June 2006, a total of 63 patients had positive culture for *Burkholderia pseudomallei*. The calculated annual incidence of melioidosis in Pahang state was 4.3 per 100,000 population per year (Adult, 6.0 per 100, 000 population per year and paediatric, 1.6 per 100,000 population per year). There were 55 Malays (87.3%), three Chinese (4.8%), four aborigines (6.3%) and one Indonesian. Nine (14.3%) were less than 18 years old. The median age was 49 years (range: 1 - 68 years). Only one patient (1.6%) had a previous history of confirmed melioidosis. With this programme, we had observed a decline in adult mortality from 54% to 44%, although this was not statistically significant. However, culture-confirmed relapses had dropped from 19% to nil. Several measures need to be taken to decrease mortality from melioidosis in endemic countries.

KEY WORDS:
Melioidosis, Burkholderia pseudomallei, Registry, Mortality

INTRODUCTION

Melioidosis is caused by the Gram-negative bacillus, *Burkholderia pseudomallei* which is endemic in Southeast Asia and Northern Australia. A retrospective review of culture-confirmed melioidosis from year 2000 to 2003 (by Medical Department, International Islamic University Malaysia) revealed a very high annual incidence of adult melioidosis in Pahang[1] (6.07 per 100,000 population per year). In that study, the mortality was 54% as compared to 19-39% in other endemic areas[2,3]. The likely reason for this high mortality rate in Pahang was inappropriate or inadequate treatment as only 32.7% of the patients received an appropriate antibiotic. Among the patients who survived, only 51.9% were given appropriate antibiotics for at least two weeks and most of the patients were not given eradication therapy. This was probably due to the lack of awareness among doctors regarding treatment of melioidosis. There were some differences in the clinical manifestation of melioidosis in Pahang as compared to other endemic countries. These include a lower incidence of localised melioidosis in Pahang (8%) as compared to 54% and 40% in Australia[2] and Thailand[3] respectively. No patient in Pahang presented with prostatic abscess as compared to 18% in Australia[2].

In view of the above findings, Medical Department, International Islamic University Malaysia in collaboration with Medical Department, Hospital Tengku Ampuan Afzan (HTAA) (with the assistance of the State Health Office) started the Pahang Melioidosis Registry. The aim of this registry was to create awareness among doctors in Pahang in the diagnosis and treatment of melioidosis and to reduce mortality in patients with melioidosis. It also allowed us to acquire more epidemiologic data on melioidosis in Pahang. We aim to analyse the data annually to assess if our objectives were achieved.

MATERIALS AND METHODS

A melioidosis questionnaire was designed to extract data on melioidosis cases confirmed by bacteriology investigations (of any clinical specimen) from 1st July 2005. The forms were filled by doctors involved in the management of the patients and were sent to the Head of Department of Medicine, HTAA. Queries arising from the data were verified by investigators by communicating with the doctor-in-charge or by going through the case record. Continuous Medical Education (CME) on melioidosis in the form of lectures were given to specialists, medical officers, paramedics and microbiologists of all general and district hospitals in Pahang by the investigators from time to time to ensure understanding of melioidosis among doctors in Pahang (at least once a year in each hospital). Guidelines on investigations and management of melioidosis were given to participants during the lecture.

"Relapse" was defined as second and subsequent infections with *Burkholderia pseudomallei* after the introduction of the registry or during the registry period. Patients with a culture-proven infection before the study period were considered to have a positive history of past infection. Appropriate intensive antibiotic therapy was defined as antibiotic treatment with either ceftazidime, cefoperazone-sulbactam, amoxicillin-clavulanic acid, imipenem, meropenem or the combination of any of these drugs for at least two weeks. Appropriate eradication therapy was defined as antibiotic treatment with either doxycycline and co-trimoxazole or co-trimoxazole alone for at least 20 weeks. In-hospital mortality was calculated based on patients with a known outcome, after

This article was accepted: 6 January 2009
Corresponding Author: How Soon Hin, Kulliyyah of Medicine, International Islamic University, P.O. Box 141, 27510, Kuantan, Pahang, Malaysia
Email: how_sh@yahoo.com

excluding patients who were discharged against the advice of doctors, transferred to another hospital or had an uncertain outcome. Paediatric patients were defined as patients less than 18 years old. Three hospitals in Pahang had the facilities to isolate B. *pseudomallei*. They were HTAA, Hospital Sultan Haji Ahmad Shah, Temerloh (HoSHAS) and Hospital Raub (HR). Body fluids were cultured in blood agar, Francis media[4] and MacConkey agar at 37^{0}C and preliminary identification was done by observing the colony morphology on blood and MacConkey agar, appearance of yellow haze on Francis media, oxidase test, motility and antibiogram pattern. All isolates were then confirmed by API ™ 20NE(bioMérieux, France), a commercial bacteriological identification test kit which utilises various biochemical tests. Sensitivity testing was performed by disc diffusion method using BBL ™ Sensi-Disc ™ Antimicrobial Susceptibility Test Discs (Becton, Dickinson and Company, USA). The disc diffusion method was standardised to Clinical and Laboratory Standards Institute Standard (CLSI). Blood samples were inoculated into Bactec™ 2940 automated continuous monitoring blood culture system (Becton Dickinson and Company, USA). All positive isolates were subsequently cultured onto blood agar, Francis media and MacConkey agar.

Statistical Analysis

The data was analysed using SPSS for Windows version 10 (SPSS Inc., Chicago, Illinois). The incidence was calculated by dividing the number of patients with melioidosis over the estimated population in the same year. The differences in the management and the outcome of the disease between the retrospective study[1] (January 2000 to June 2003) and first year of Pahang Melioidosis Registry (July 2005 to June 2006) were tested using chi-square taking two-tailed significance level < 0.05. Methods and definitions used for the retrospective study and Pahang melioidosis Registry were almost similar except the earlier study was retrospective. Francis media and API ™ 20NE were not used at that time.

RESULTS

During the one-year study period from 1st July 2005 till 30th June 2006, a total of 63 patients had positive culture for B. *pseudomallei*. Most of the cases presented to the two largest hospitals namely HTAA (57.1%) and HoSHAS (33.3%); the remaining cases were from other smaller district hospitals. The calculated annual incidence of melioidosis in Pahang state was 4.3 per 100, 000 population per year (Adult, 6.0 per 100, 000 population per year and paediatric, 1.6 per 100, 000 population per year). There were 55 Malays (87.3%), three Chinese (4.8%), four aborigines (6.3%) and one Indonesian. Nine (14.3%) were 18 years of age or below. The median age was 49 years (range: 1 - 68 years). Only one patient (1.6%) had a previous history of confirmed melioidosis.

B. pseudomallei were isolated from blood in 59 patients (93.7%). Among patients with positive blood cultures, three patients had positive pus cultures, one pleural fluid and one urine culture as well. Only four patients (6.3%) had localised melioidosis and they were all adults. Overall, thirty two patients (50.8%) were discharged well and 27 patients (42.9%) died in the hospital. The remaining four patients were either transferred to another hospital or discharged against medical advice.

Paediatric melioidosis

Among nine patients with culture-confirmed melioidosis, five patients (55.6%) had underlying medical illnesses (Three had diabetes mellitus, one chronic renal failure and one Thallassemia major with post-splenectomy). More than half of them had pneumonia (66.7%) and one each had septic arthritis, liver abscess and urinary tract infection. All patients had positive blood cultures and one patient each had positive cultures from pleural fluid and joint fluid. Five patients (55.6%) died in the hospital and others were discharged home.

Adult melioidosis

In contrast to paediatric patients, the majority of adult patients (90.7%) had underlying illnesses that predisposed them to melioidosis. Diabetes mellitus, which was the commonest underlying illness, was present in 88.9% of all adult melioidosis patients. Occupations were recorded in 41 patients and only 19.5% were farmers. 51.2% were non-farmers and 29.3% were unemployed at presentation.

Pneumonia was the commonest presentation (57.7%) and 25% of the patients had multiple organ involvement. Four patients had localised melioidosis of whom two had lymphadenitis, one had septic arthritis and another had left leg abscess. Among patients who were discharged well, 27 (96.4%) were given appropriate intensive therapy for at least two weeks or more as compared to 52% in the retrospective study (p=0.02). Almost all patients (93%) were given appropriate eradication therapy for 20 weeks as compared to 38% previously (p=0.001). During our one-year registry period, 22 adult patients (44%) died in the hospital as compared to 54% in our retrospective study (p=0.2). The comparison with the previous retrospective study is shown in Table I.

DISCUSSION

Melioidosis is endemic in both Northern Australia[2] and Southeast Asian countries particularly Malaysia [1,5], Thailand [3] and Singapore [6], and had been reported as sporadic cases in other parts of the world. Comparing with our previous retrospective study, we found almost similar incidence, median age and male to female ratio. However, there were more paediatric cases (14.2%) as compared to the last study (7.6%). This was probably due to an increased awareness of melioidosis among paediatricians. Our bacteraemic melioidosis (93%) remained higher than other regions (39-60%)[2,3,6]. This may be due to a more virulent strain of *Burkholderia pseudomallei* in Pahang or late presentation of our patients. Furthermore, most of our patients were diabetic (89%) as compared to other regions (20-57%) [2, 3, 6]. Diabetes mellitus is a risk factor for severe Gram-negative sepsis. Currently, we are conducting a study to determine the relationship between the strain of *Burkholderia pseudomallei* and disease severity.

Table I: Adult Melioidosis in Pahang

	January 2000-June 2003	July 2005-June 2006
No of cases	135	54
Incidence*	6.1	6.0
Median age (year)	51	50
Male: female ratio	3.6:1	3.9:1
Paediatric patients (%)	7.6	14.2
Bacteraemia (%)	92	93
Mortality rate (%):		
Overall	54	44
Bacteraemic cases	54	47
Underlying disease (% of cases)		
At least one	85	91
Diabetes mellitus	74	89
Antibiotics after diagnosis		
Appropriate intensive therapy >2 weeks	52	38
Maintenance therapy	97	93
Relapse	19	0

* Per 100000 populations per year

In our previous study, we did not find any patients with prostatic abscess. However, since August 2005, we performed routine Computed Tomography (CT) of abdomen and pelvis in all male patients with culture-confirmed melioidosis in HTAA. Three cases of melioidotic prostatic abscess were detected by CT abdomen and pelvis but not on ultrasonographic study. This shows that CT pelvis is more sensitive than ultrasound in detecting prostatic abscess. All three patients had multiple prostatic abscesses. Two of them had liver and/or splenic abscesses. None of them required surgery and all were treated with one month of intensive antibiotic followed by five months of eradication therapy. They remained well during follow up.

In our retrospective study, we found that only half of the patients were given appropriate intensive therapy and only 38% were given eradication therapy. This resulted in a high mortality rate in this region (54%) as compared to other regions (19-44%)[1-3, 6]. The Pahang Melioidosis Registry, which is the first of its kind in Malaysia, included an extensive programme of education and data collection. Every district hospital in the state was visited and talks were given to the doctors, laboratory staff and supporting personnel with regards to the disease. The previous high mortality rate in the retrospective study was highlighted. The melioidosis guideline, which includes the recognition of the disease and appropriate treatment guideline, was introduced. With this programme, we observed a decline in mortality from 54% to 44%, although this was not statistically significant. This is probably due to the small number of patients in the present study. However, there was no culture-confirmed relapse a year after the study period. This is most likely due to improvement in the treatment of melioidosis, even though the follow up period is shorter when compared to the retrospective study.

The treatment of melioidosis infection is rather challenging in view of a long period of eradication therapy and the relapse rate is high if it is not treated adequately. A study by Chaowagal *et al*[7] found that 23% of their patients had culture-proven relapse with a yearly rate of 15%. The mortality rate associated with relapse was 27%. In the Australian study[8], 13% of patients had bacteriologically confirmed relapses with a mortality rate of 11%. Half of the relapses were due to poor adherence to the eradication therapy and another 37% of the relapses were related to doxycycline monotherapy. Therefore, patients with melioidosis must be told about the importance of eradication therapy and possible relapses associated with poor adherence to treatment. Directly observed therapy (DOT) is defined as observation of the patient by a health care provider or other responsible person as the patient ingests the medication. DOT has been shown to be effective in sustaining and ensuring compliance in patients taking anti-tuberculosis medication. A report from Texas illustrated the effectiveness of DOT[9] and the community based DOT program in Baltimore, Maryland, for example, clearly illustrated the benefits of DOT therapy[10] in tuberculosis treatment. Therefore, implementation of DOT in melioidosis may improve compliance, reduce relapse and improve survival.

In addition to that, public health personnel should also be actively involved in creating awareness of this disease among the residents in their respective areas. For instance, giving health talks regarding the nature and source of the disease, preventive measures such as wearing gloves whenever dealing with soil and work in plantations especially among diabetics. This will ultimately improve our health care service and reduce the mortality rate related to melioidosis.

In conclusion, several measures need to be implemented to reduce the mortality of melioidosis in endemic countries.

ACKNOWLEDGEMENT

We would like to acknowledge the assistance of the Director of Health in Pahang, all directors in district hospitals in Pahang, medical officers, nurses and other supporting staff who made the registry successful.

REFERENCES

1. How SH, Ng KH, Jamalludin AR, Shah A, Rathor Y. Melioidosis in Pahang. Malaysia Med J 2005; 60: 606-13.
2. Currie BJ, Fisher DA, Howard DM, *et al*. Endemic meliodosis in tropical Northern Australia: a 10 year prospective study and review of the literature. Clin Infect Dis 2000; 31: 981-86.

3. Suputtamongkol Y, Hall AJ, Dance DAB, *et al*. The epidemiology of melioidosis in Ubon Ratchatani, northeast Thailand. Int J Epidemiol. 1994; 23: 1082-90.
4. Francis A, Aivar S, Yean CY, Naing L, Ravichandran M. An improved selective and differential medium for the isolation of Burkholderia pseudomallei from clinical specimens. Diagn Microbiol Infect Dis 2006; 55: 95-9.
5. Puthucheary SD,Parasakthi N, Lee MK. Septicaemic meliodosis: a review of 50 cases from Malaysia. Trans R Soc Med Hyg 1992; 86: 683-85.
6. Heng BH, Goh KT, Yap EH, Loh H, Yeo M. Epidemiological surveillance of meliodosis in Singapore. Ann Acad Med Singapore 1998; 27: 478-84.
7. Chaowagul W, Suputtamongkol Y, Dance DA, Rajchanuvong A, Pattara-arechachai J, White NJ. Relapse in melioidosis: incidence and risk factors. J Infect Dis 1993; 168: 1181-5.
8. Currie BJ, Fisfer DA, Anstey NM, Jacups SP. Melioidosis: Acute and chronic, relapse and reactivation. Trans R Soc Trop Med Hyg 2000; 94: 301-4.
9. Weis SE, Slocum PC, Blais FX, *et al*. The effect of directly observed therapy on rates of drug resistance and relapse in tuberculosis. N Engl J Med 1994; 330: 1179-84.
10. Chaulk CP, Moore-Rice K, Rizzo R, Chaisson RE. Eleven years of community based directly observed therapy for tuberculosis. JAMA 1995; 274: 945-51.