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Pediatric melioidosis in Pahang, Malaysia

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Melioidosis is much less common in children than in adults. This study investigated the incidence, demographic characteristics, presenting symptoms and outcome of pediatric melioidosis in Pahang, Malaysia. This retrospective study included patients ≤18 years old with positive body fluid cultures for *Burkholderia pseudomallei* from January 2000 to June 2003. Data on culture results were obtained from 2 referral hospitals. The incidence of pediatric melioidosis was 0.68/100,000 population per year. Of the 13 patients identified during the study period, 10 were male; 9 were Malays, 2 were Indians and 2 were aborigines. The mean age of these patients was 9.5 ± 5.4 years. None of the patients had a previous history of confirmed melioidosis or predisposing factors for infection. Localized melioidosis was the most common presentation (46.2%) followed by melioidosis with septic shock (38.4%). Among patients with localized melioidosis, head and neck involvement (83.3%) was the most common presentation (2 patients with cervical abscesses, 1 with submandibular abscesses and 2 with acute suppurative parotitis) and another patient had right axillary abscess. All of the patients with septic shock had pneumonia and 2 of them had multi-organ involvement. The mortality among patients with septic shock was 80% and death occurred within 24 h of admission in all cases. In contrast, no complications or death occurred among patients with localized melioidosis. Melioidosis with septic shock is less common than localized melioidosis in pediatric patients, but is associated with very high mortality.

Key words: Incidence, melioidosis, mortality, retrospective studies, signs and symptoms

Melioidosis, an infection caused by the Gram-negative bacillus *Burkholderia pseudomallei*, is endemic in Southeast Asia and Northern Australia [1] and has been reported sporadically in other parts of the world, especially among travellers who return from endemic areas. Pneumonia is the most common presentation in adults and is associated with high mortality [1]. High-dose ceftazidime, imipenem, amoxicillin-clavulanate or cefoperazone-sulbactam therapy for 2-4 weeks followed by maintenance therapy is generally recommended for severe cases. Maintenance therapy usually consists of 8 weeks of chloramphenicol combined with doxycycline and trimethoprim-sulfamethoxazole (co-trimoxazole) for 20 weeks [1].

Melioidosis is less common in children compared to adults and the clinical presentations are different [2-4]. Data on pediatric melioidosis are limited and its incidence is unknown in most endemic areas. There are also differences in clinical manifestations of pediatric melioidosis among different regions [2-4]. This study retrospectively reviewed cases of pediatric melioidosis in Pahang, Malaysia to determine the incidence, demographic features, clinical presentation and outcome in this group of patients.

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Materials and Methods

Pahang is 1 of the 14 states in Malaysia. It has an area of 35,965 km^2 and a total population of 1.28 million with 11 districts (583,000 people were aged less than 18 years in 2002 according to the Department of Statistics). The major economic activity is agriculture, mainly rubber and oil palm cultivation, especially in Temerloh and Jerantut districts. A retrospective study was conducted to identify cases of pediatric melioidosis (aged ≤18 years) in Pahang during the period from January 2000 to June 2003. In Pahang, there are 9 hospitals (1 general hospital and 8 district hospitals); however, only Hospital Mentakab (HM) and Hospital Tengku Ampuan Afzan (HTAA) in Kuantan have facilities to perform culture and sensitivity tests for *B. pseudomallei*. Therefore, cases with a positive culture

for *B. pseudomallei* from blood, pus, cerebrospinal fluid or other body fluids were identified from the database of the microbiology departments of these 2 hospitals. Case records were reviewed and relevant data was extracted, including demographic characteristics, clinical presentations, physical findings, laboratory and radiologic findings and clinical outcome. Patients with positive blood culture were classified as having septicemic melioidosis and those patients with positive culture from other sources were classified as having localized melioidosis. Shock was defined as a blood pressure of less than 90/60 mm Hg which failed to respond after fluid resuscitation.

Both HTAA and HM used the same method for isolation of *B. pseudomallei.* Body fluids were cultured in blood agar and MacConkey agar at 37°C and confirmation was done by colony morphology, staining reaction, motility and biochemical tests (indole, triple sugar iron, citrate, phenyl deaminase, oxidase fermentative 1% glucose, urease, oxidase and DNAse). Sensitivity testing was performed by agar dilution method using BBL™ Sensi-Disc™ antimicrobial susceptibility test discs (Becton Dickinson and Co., Sparks, MD, USA). Blood samples were incubated in a tryptic soy broth bottle (Roche) in the BACTEC system (Becton Dickinson) and cultured in blood agar and MacConkey agar if positive growth was detected. Confirmation and sensitivity testing were done as described above.

Statistical analysis

All data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 10 software package. Mann Whitney *U* test was used to compare the blood results of different groups and chi-squared test was used for the comparison of proportions. A p value of <0.05 was considered as statistically significant.

Results

During the period of study, a total of 14 patients were identified from the microbiology departments of the 2 hospitals. The calculated incidence of pediatric melioidosis in Pahang state was 0.68 per 100,000 population per year. Only 13 patients' case records could be traced and analyzed. Among them, 10 patients (76.9%) were male. Nine of the 13 patients were Malays (69.2%), 2 were Indians (15.4%) and 2 were aborigines (15.4%). The mean age was 9.5 ± 5.4 years (range, 2-18 years). Nine of the 13 patients (76.9%) were admitted to HM, 2 (15.4%) to HTAA, and 1 each to Kuala Lipis and Jerantut hospitals. Most patients were from the Temerloh (30.8%) and Jerantut (23.1%) districts. None of the patients had a previous history of confirmed melioidosis, underlying medical illness or predisposing factors for infection. One of the patients had a history of right axillary abscess in 1998. Incision and drainage was done but pus culture was negative. He returned to the hospital in 2001 with similar symptoms and pus culture was positive for *B. pseudomallei*. Most patients presented in the months of April (23.1%) and June (23.1%).

Physical examination on admission revealed hepatomegaly in 4 patients (30.8%), but none had splenomegaly. Jaundice was noted in only 1 patient. Localized melioidosis was found in 6 patients (46.2%) and the remaining patients were classified as having septicemic melioidosis. Among the patients with septicemic melioidosis, 1 had hypotension at admission and another 4 developed hypotension after admission. All patients with septic shock had fever of 1 weeks' duration or less. One of the patients developed renal impairment and another patient had an abnormal coagulation profile on admission. All patients had pneumonia and 2 had involvement of multiple organs (Table 1, case number 1 to 5). The mortality rate among patients with septic shock was 80% and death occurred within 24 h of admission in all cases. All patients who died were given cephalosporin on admission but only 1 of them was treated with ceftazidime. The remaining 2 patients who had septicemia without shock (Table 1, case number 6 and 7) presented with fever and cough. Physical examination revealed acute pharyngitis without any evidence of pneumonia in both of these patients. Chest radiographs did not show any consolidation or abscess but blood cultures were positive for *B. pseudomallei*. One of these 2 patients developed thrombocytopenia later during hospitalization but both patients were discharged following recovery after antibiotic therapy.

Among patients with localized melioidosis (negative blood culture), head and neck involvement (83.3%) was the most common presentation (2 patients had cervical abscesses, 1 patient had submandibular abscess and 2 patients had acute suppurative parotitis) and 1 patient had right axillary abscess (Table 1, case number 8 to 13). Fever was absent in 2 cases. Incision and drainage were done in all patients but only 2 patients were given ceftazidime for at least 2 weeks. No death occurred among patients with localized melioidosis, in

Table 1. Case summaries of pediatric melioidosis in Pahang (January 2000 to June 2003)

Case no.	Age (years)	Month of diagnosis	Clinical presentation	Fever duration (days)	Organ involvement	Source of positive culture
1	6	Jan	Fever, cough, headache	4	Pneumonia, liver abscess and meningitis	Blood, CSF
2	18	Apr	Fever, cough breathlessness	4	Lung abscesses with pneumonia	Blood
3	2	Oct	Fever and fits	3	Pneumonia	Blood (CSF: normal)
4	15	Jun	Fever and cough	4	Lung abscesses with pneumonia	Blood, trachea aspirate
5	2	Jun	Fever, cough	7	Pneumonia, liver and subcutaneous abscess	Blood
6	11	Jul	Vomiting	0	Acute pharyngitis	Blood
7	4	Jul	Fever and cough	5	Acute pharyngitis	Blood
8	15	Jun	Right parotid and submandibular abscess	0	Parotid gland and lymph node	Pus
9	12	Apr	Right axillary abscess	30	Lymph node	Pus
10	8	Mar	Left submandibular abscess	7	Lymph node	Pus
11	5	Dec	Left parotid abscess with submandibular lymph nodes enlargement	14	Parotid gland and lymph node	Pus
12	15	Oct	Left cervical abscess	0	Lymph node	Pus
13	10	Apr	Right cervical abscess	7	Lymph node	Pus

Abbreviations: EM = empirical; DE = definite; CSF = cerebrospinal fluid; I&D = incision and drainage

contrast to the 80% mortality rate in patients with septic shock (p=0.006). There was no clear documentation of maintenance therapy and most of these patients were lost to follow-up. Two of these patients were contacted by phone more than 3 years after the diagnosis and both of them were well with no relapse.

Only 1 patient with localized melioidosis had a high white blood cell (WBC) count whereas all patients with septicemia had either a WBC count of less than 4×10^3/mL (29%) or more than 11×10^3/mL (71%). Platelet count on admission was less than 150×10^6/mL in 3 patients (23.1%); 2 of them had septic shock and 1 had localized melioidosis. There were no significant differences in blood cell counts or blood urea level between patients with localized and septicemic melioidosis (p ranging from 0.295 to 0.731).

Fifteen specimens were sent for sensitivity testing. Two patients had positive cultures from more than 1 type of body fluid with no difference in antibiotic sensitivities. All *B. pseudomallei* isolates were sensitive to ceftazidime, imipenem and ciprofloxacin (Table 2). None of the isolates was sensitive to gentamicin; 83% of isolates were sensitive to tetracycline. Resistance to co-trimoxazole was found in 46.2% of isolates.

Discussion

Melioidosis has long been considered to be a rare disease in children, representing 5-13% of total cases of melioidosis [3,5]. In this study, we identified 14 cases of pediatric melioidosis from January 2000 to June 2003 and 157 adult cases, resulting in an average incidence of pediatric melioidosis of 0.68/100,000

Table 2. Sensitivity test results for *Burkholderia pseudomallei*

Antibiotic	No. sensitive (%)	No. resistant (%)
Ceftazidime (n = 13)	13 (100)	0 (0)
Amoxicillin-clavulanate (n = 3)	3 (100)	0 (0)
Gentamicin (n = 13)	0 (0)	13 (100)
Sulfamethoxazole-trimethoprim (n = 13)	7 (53.8)	6 (46.2)
Tetracycline (n = 12)	10 (83.3)	2 (16.7)
Imipenem (n = 12)	12 (100)	0 (0)
Ciprofloxacin (n = 12)	12 (100)	0 (0)

Treatment: EM and DE (after culture result)	Complications	Outcome
EM: ceftazidime, amikacin, acyclovir	Shock	Died within 24 h of admission
EM: cefuroxime, cloxacillin	Shock	Died within 24 h of admission
EM: cefuroxime, penicillin	Shock	Died within 24 h of admission
EM: cefoperazone	Shock and renal impairment	Died within 24 h of admission
EM: ampicillin, gentamicin DE: ceftazidime and imipenem for 2 weeks followed by co-trimoxazole for 3 months	Shock and prolonged coagulation	Recovered and discharged. Remained well on follow-up after 1 year
EM: amoxicillin-clavulanate for 2 days DE: ceftazidime and imipenem for 10 days	None	Discharged well
EM: penicillin and erythromycin	Thrombocytopenia	Discharged well and remained well 40 months after discharge
EM: I&D, cloxacillin DE: ceftazidime and amoxicillin-clavulanate for 1 week	None	Discharged well to Jengka hospital (to complete antibiotic for 3 further weeks)
EM: I&D, cloxacillin, gentamicin for 5 days	None	Discharged well and remained well 40 months after discharge
EM: I&D, cloxacillin, cefotaxime, metronidazole DE: ceftazidime, imipenem, cloxacillin for 2 weeks	Thrombocytopenia	Discharged well and remained well 42 months after discharge
EM: I&D, amoxicillin-clavulanate for 8 days	None	Discharged well
EM: I&D, cloxacillin for 5 days	None	Discharged well
EM: I&D, cloxacillin DE: cefuroxime for 2 days then cefoperazone for 10 days	None	Discharged well and remained well 1 month after discharge

population per year. This study may have underestimated the incidence because some patients with localized infection might not seek treatment from a hospital. Edmond et al [3] reported a higher incidence of pediatric melioidosis (5.84/100,000 population) in the Northern Territory of Australia, but their study included patients with positive serology and/or positive polymerase chain reaction. In contrast, our results were based entirely on body fluid cultures.

The main agricultural activities in Pahang state involve oil palm and rubber cultivation and the Malays are the main ethnic group involved in these plantation activities. This may explain the high incidence of pediatric melioidosis among Malays in our study. Most patients were treated during the months of April to June (the rainy season in Pahang is from November to January) in contrast to previous studies in which most cases were treated during the rainy season [3,4,6].

Diabetes mellitus, renal failure and chronic lung disease are strongly associated with melioidosis in adults [1]. Lumbiganon and Viengnondha [4] found only 20% of their pediatric patients had predisposing factors and none of the patients with localized melioidosis had any predisposing factor. In their study, diabetes mellitus, hematologic malignancy, aplastic anaemia, chronic renal failure and nephrotic syndrome were common predisposing factors. Interestingly, 2 of their patients developed rapidly progressive pneumonia after near drowning. In the 2 case series reported by Edmond et al [2,3], 3 out of 15 cases had predisposing factors (cystic fibrosis, diabetes mellitus and rheumatic heart disease). In contrast, none of our pediatric patients had any history of medical illnesses.

Pneumonia is the most common focus of infection in septicemic melioidosis, but abscesses involving other organs are not uncommon [3,4]. In our study, 38.4% of cases presented with septic shock, which had an associated mortality rate of 80%, consistent with results in the previous study [4].

Localized melioidosis is a more common presentation in the pediatric age group. In our study, 46.2% of the patients had localized disease, compared to approximately 65% in a study from Thailand [4]. Among patients with localized melioidosis in Thailand,

head and neck involvement was the most common presentation. Dance et al reported that 38% of patients with localized melioidosis had involvement of the parotid gland [7]. They also found an association of acute suppurative parotitis with mumps. In contrast, none of the cases reported in studies from Australia had parotitis [2,3]. In our study, 2 patients (33.3% among patients with localized melioidosis) had acute suppurative parotitis. The difference in the incidence of acute parotitis is probably due to poor recognition or different strains of *B. pseudomallei.*

All patients with localized melioidosis in our series underwent incision and drainage of pus. The diagnosis of melioidosis was made after a positive culture for *B. pseudomallei* from pus. Four out of 6 cases did not receive recommended antibiotics and none of them was prescribed maintenance therapy. Surprisingly, all of these patients responded well to incision and drainage, and were discharged after a short hospital stay. Only 1 patient made a scheduled visit 1 month after discharge and he was well. Two of the patients who were lost to follow-up were contacted by phone more than 3 years after diagnosis, and both were well without relapse. One patient was only given cloxacillin and gentamicin, to which *B. pseudomallei* is usually resistant. It is possible that localized melioidosis may not need to be treated as aggressively as septicemic melioidosis. Lumbiganon et al [8] had similar findings. Our literature search found a lack of consensus guidelines for the management of localized melioidosis. To address this issue, a randomized controlled trial is needed to study the treatment of localized melioidosis in the pediatric age group, especially in endemic countries.

Two studies have reported pharyngocervical melioidosis in Thailand [4,9]. In our study, 2 patients presented with symptoms of upper respiratory tract infection but without lymphadenopathy, and acute pharyngitis was diagnosed. Both of these patients had positive blood culture but normal chest X-ray. It is very difficult to distinguish this form of melioidosis from acute pharyngitis caused by viral or other bacterial infection as there is no specific differentiating feature. Kanaphun et al [10] demonstrated the association of throat swab and active melioidosis in Thailand but unfortunately our patients had no throat swabs taken. Clinicians should suspect this form of melioidosis in any pediatric patient with acute pharyngitis with or without neck abscess, especially if the child is from an endemic area or has visited an endemic area in the recent past.

B. pseudomallei is intrinsically resistant to aminoglycosides [11]. All isolates in this study were sensitive to ceftazidime, imipenem, ciprofloxacin and amoxicillin-clavulanate. Unfortunately, some of these drugs are not easily available in the district hospitals in Pahang. This may have caused difficulties in providing optimal treatment in suspected or confirmed cases. Resistance to co-trimoxazole was found in 46.2% of isolates in our study and this was higher than expected, probably due to an unclear endpoint as zone edges for co-trimoxazole in disk diffusion test were seen to be very indistinct [1]. This has also resulted in over-reporting of resistance to co-trimoxazole in previous studies [12,13]. Piliouras et al suggested E-test should be used in assessing sensitivity of co-trimoxazole against B. *pseudomallei* [13].

In conclusion, melioidosis is less common in children than in adults and is often not associated with underlying illnesses. Localized melioidosis involving the head and neck is a common pediatric presentation and the prognosis is excellent. It remains unclear whether localized melioidosis requires the same aggressive treatment as septicemic melioidosis, which is associated with extremely high mortality, especially in patients with septic shock.

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