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Original Article

Hepatic/splenic abscess and/or skin and soft tissue infection as predictors of melioidosis in children

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Abstract

Introduction: Melioidosis can have multiple organ involvement which can then mimic other infections. The aim of this study was to determine if there are any factors significantly associated with melioidosis which can inform diagnostic evaluations before receiving the results of confirming laboratory testing.

Methodology: The charts of patients aged < 16 years admitted to Songklanagarind Hospital during 2002-2014 with a clinical presentation suspicious of melioidosis were reviewed.

Results: Of the 145 suspected cases, 27 patients had a confirmed diagnosis of melioidosis by either serology and/or culture. The melioidosis group had a higher proportion of patients with liver or splenic abscess (44.4% *vs.* 11.9%, $p < 0.01$) and were less likely to have splenomegaly by physical examination (3.7% *vs.* 22.9%, $p = 0.02$) than patients without melioidosis. Logistic regression analysis found that patients suspected of melioidosis who had (a) hepatic abscess or (b) splenic abscess or (c) skin or soft tissue infection were more likely to have melioidosis with likelihood ratios of 5.6, 4.0, and 2.2 respectively, and specificities of 0.94, 0.89, and 0.68 respectively. Suspected patients who did not have hepatic abscess, splenic abscess, or soft tissue infection were unlikely to have melioidosis with negative predictive value of 0.90.

Conclusion: patients who have clinically suspected melioidosis without skin or soft tissue infection should have hepatic-splenic ultrasonography performed, and suspected patients who have one of these 3 findings should be treated initially as melioidosis while waiting for culture or serologic test results.

Key words: *Burkholderia pseudomallei*; melioidosis; liver abscess; splenic abscess; soft tissue infection.

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Introduction

Melioidosis is caused by *Burkholderia pseudomallei*. It is an important public health problem in areas in which it is endemic such as Southeast Asia and northern Australia [1, 2]. Clinical presentation ranges from a localized infection, such as parotitis or skin abscess, to severe septicemia [3-5]. In a study from northeastern Thailand, Limmathurotsakul *et al*. reported an estimated melioidosis mortality rate of 8.6 per 100,000 population (95% confidence interval (95% CI): 7.33-10.11), the third most common cause of death from infectious disease in northeastern Thailand, following human immunodeficiency virus/acquired immunodeficiency syndrome and tuberculosis [5]. Due to the high mortality rate, when a patient presents with clinical symptoms suspicious for melioidosis, the physician in an endemic area usually prescribes empirical antibiotics to cover melioidosis while waiting for confirmation from laboratory investigations.

Melioidosis can have multiple organ involvement which can then mimic other infections [6,7]. Currently there are no known pathognomonic features or specific criteria which can lead a physician to a confident diagnosis of melioidosis. When melioidosis is suspected, the gold standard diagnostic test for melioidosis is culture of blood, pus, or bodily secretions, but even that has a sensitivity of only 60% [8]. Besides cultures, there are other tests used to diagnose melioidosis, such as the indirect hemagglutination antibody (IHA) test or immunofluorescent assays for immunoglobulin M or G (IFA IgM, IgG), which have sensitivities of 76% and 73% and specificities of 91% and 99%, respectively [9,10]. Another method used to diagnose melioidosis is the polymerase chain reaction (PCR) to detect *Burkholderia pseudomallei*, but PCR testing is not available in many hospitals in Thailand.

The aim of this study was to determine if there are any factors significantly associated with melioidosis

which can inform diagnostic evaluations of children suspected of having this infection.

Methodology

We retrospectively reviewed the medical records of all children (aged < 16 years) with clinically suspected melioidosis who visited the outpatient clinic of or who were admitted to Songklanagarind Hospital, the major tertiary care and referral center in southern Thailand, during January 2002-December 2014.

Patients originally clinically suspected of having melioidosis due to (1) prolonged fever with unidentified cause for 1 week, or (2) to localized infection with unidentified cause and not responding to antibiotics (except for co-trimoxazole, amoxicillin/clavulanate, ceftazidime) for 1 week were divided into those confirmed to have and not to have melioidosis. Cases were confirmed by having a 1) positive culture or 2) positive serology (immunofluorescence assay Ig M ≥ 1:20 or indirect hemagglutination assay ≥ 1:160) for melioidosis with symptom improvement after specific treatment. Patients were confirmed as not having the disease when all the tests were negative for melioidosis without any symptom improvement after empirical treatment for melioidosis.

Demographic characteristics and potential risk factors for melioidosis recorded were patient's age and sex and history of underlying diseases, such as diabetes mellitus (DM), thalassemia or renal disease, which have been reported to be associated with melioidosis [1,4]. Other factors recorded included the clinical presentation, including lymphadenopathy defined as lymph nodes > 1 cm diameter or inguinal nodes > 1.5 cm diameter), hepatomegaly, splenomegaly, laboratory results (complete blood count (CBC), blood chemistry, and liver function tests); outcomes (respiratory failure requiring mechanical ventilation, acute kidney injury (AKI) defined by a creatinine level ≥ 0.3 mg/dL higher than the baseline value or a ≥ 1.5-fold increase from the baseline value or shock [11]. All data were collected from the Hospital Information System, which is the computerized hospital records database of Songklanagarind Hospital.

Ethical approval was obtained from the Research Ethics Committee of the Faculty of Medicine, Prince of Songkla University.

Data were evaluated using descriptive statistics (means, standard deviations, medians and interquartile ranges (IQR) where appropriate) for continuous data. Percentage frequencies were used for categorical data. For analytical statistics, the Chi-square test or Fisher's exact test was used to compare categorical data. The rank sum test and Student's t-test were used to analyze continuous variables. Logistic regression analysis was used to identify independent clinical predictors of melioidosis. A p-value < 0.05 was considered statistically significant. For the application of the model in actual practice, a score was allocated to each identified predictor to reflect the relative magnitude of the respective regression coefficient. The R program (version 3.3.3, R Core team, Vienna, Australia) and STATA release 14.1) were used for analysis.

Results

Clinical characteristics of confirmed and non-confirmed melioidosis patients

During the 13-year study period, there were 145 patients suspected of having melioidosis, of whom 27 were confirmed to have melioidosis (5 cases confirmed by both culture and serology, 11 cases confirmed by culture only and 11 cases confirmed by serology only).

Of the remaining 118 patients who had negative testing for melioidosis, 24 patients had another infectious disease, 8 had a malignancy, 13 had a connective tissue disease and 73 were never given a specific diagnosis. Of the 24 patients with another infectious disease, 6 were diagnosed as having tuberculosis, 3 each as having mycoplasma infection and atypical dengue viral infection, 2 each as having Epstein-Barr virus infection, scrub typhus, staphylococcal infection, and candidiasis, and 1 each as having *Acinetobacter baumannii* pneumonia, enteric fever, cryptococcal meningitis and nocardiosis. Of the 73 patients who had no specific diagnosis, the empirical antibiotic to cover melioidosis was discontinued without relapsing of melioidosis.

When the baseline characteristics of confirmed cases were compared with confirmed non-cases, the following were not significantly associated with melioidosis: median age, presence of underlying disease, presence of fever, lymphadenopathy, hepatomegaly, pneumonia, osteomyelitis, arthritis, or parotitis. The proportions of patients who had hepatic and/or splenic skin or soft tissue infection were significantly different between the two groups (Table 1). However, the number of patients who had splenomegaly was significantly lower in the confirmed group than in the non-melioidosis group (Table 1).

The medians (IQR) of the hemoglobin levels, white blood cell or platelet counts, or percentages of neutrophils and lymphocytes were not significantly different between the two groups (Table 1).

Clinical outcomes of melioidosis and non- melioidosis patients

The proportions of patients with respiratory failure, AKI, shock or death in the confirmed group were not significantly different from those in the non-melioidosis group (Table 1).

Clinical predictors for pediatric melioidosis

Logistic regression analysis showed subjects with liver abscess were more likely to have melioidosis with OR (95% CI) of 8.54 (2.45, 29.84) when compared to those without liver abscess. Subjects with splenic abscess were significantly more likely to have melioidosis with odds ratio (OR) and 95% confidence interval (CI) of 3.85 (1.05, 14.11) than those without splenic abscess. Subjects with skin and soft tissue infection were more likely to have melioidosis with OR (95% CI) of 3.14 (1.18, 8.35) compared to those without skin and soft tissue infection (Table 2). For the application of the model in current practice, a score was allocated to each identified predictor to reflect the relative magnitude of the respective regression coefficient (Table 2). The receiver operating characteristic (ROC) of the area under the curve (AUC) from the model was 0.73 which was equal to the ROC AUC from the score.

Suspected patients who had hepatic abscess, splenic abscess, or skin or soft tissue infection had likelihood ratios (LR) of having melioidosis of 5.6, 4.0, and 2.2 respectively, with specificities of 0.94, 0.89, and 0.68 respectively. Suspected patients who did not have hepatic abscess, splenic abscess, or soft tissue infection (total score < 10) were unlikely to have melioidosis with negative predictive value of 0.90 (Table 3).

Discussion

This is the first study to make a comparison of various diagnostic factors between confirmed and non-confirmed cases in children with clinically suspected melioidosis. The study found that hepatic or splenic abscess and/or skin and soft tissue infection were the most common clinical profiles and the most important clinical predictors of pediatric melioidosis. A previous study on melioidosis in our hospital from 2002 to 2011

Table 1. Demographic and clinical data of confirmed and non-confirmed cases.

Characteristics	Confirmed cases (N = 27)	Non-confirmed cases (N = 118)	p-value
Age in years, median (IQR)	8.4 (3.7-12.4)	8.0 (3.9-11.4)	0.90
Male, n (%)	15 (55.5)	78 (66.1)	0.30
Underlying disease, n (%)			
DM, thalassemia, or renal disease	6 (22.2)	12 (10.2)	0.09
Clinical presentation, n (%)			
Fever	24 (88.9)	96 (81.4)	0.35
Lymphadenopathy	7 (25.9)	38 (32.2)	0.68
Hepatomegaly	11 (40.7)	53 (44.9)	0.69
Splenomegaly	1 (3.7)	27 (22.9)	0.02
Clinical diagnosis, n (%)			
Hepatic abscess	8 (29.6)	6 (5.1)	< 0.01
Splenic abscess	6 (22.2)	9 (7.6)	0.02
Hepatic and/or splenic abscess	12 (44.4)	14 (11.9)	< 0.01
Skin and soft tissue infection	9 (33.3)	4 (3.4)	< 0.01
Pneumonia	7 (25.9)	20 (16.9)	0.28
Osteomyelitis and/or arthritis	4 (14.8)	6 (5.1)	0.07
Parotitis	4 (14.8)	15 (12.7)	0.77
Un-identified source	1 (3.7)	23 (19.5)	0.05
CBC[a], median (IQR)			
Hemoglobin (g/dL)	9.9 (9.0-10.5)	10.1 (8.8-11.7)	0.81
WBC ($\times 10^3$ cell/mm^3)	12.7 (9.2-18.6)	10.2 (6.0-15.6)	0.10
Neutrophils (%)	63 (49-73)	58 (40-77)	0.81
Lymphocytes (%)	24 (16-43)	22.5 (12-40)	0.32
Platelets ($\times 10^3$ cell/mm^3)	365 (288-504)	323 (157-480)	0.16
Serious Outcome, n (%)			
Respiratory failure	2 (7.4)	19 (16.1)	0.24
Acute kidney injury	1 (3.7)	8 (6.8)	0.55
Shock	1 (3.7)	12 (10.2)	0.29
Death	1 (3.7)	10 (8.5)	0.40

[a]Data from 25 confirmed cases and 112 non-confirmed cases; DM, diabetes mellitus; CBC, complete blood counts; WBC, white blood cell counts

Table 2. Logistic regression predictions for pediatric melioidosis.

Variable	Crude OR	Adjusted		*p*-value	*Score*
		OR	coefficient		
Hepatic abscess	7.86	8.54 (2.45, 29.84)	2.14	< 0.001	19
Splenic abscess	3.93	3.85 (1.05, 14.11)	1.35	0.049	12
Skin or soft tissue infection	2.43	3.14 (1.18, 8.35)	1.14	0.023	10

which recruited all patients aged more than 1 year found that the median (IQR) age of infection was 49 (34-58) years and the proportion of patients with hepatic abscess was 19.4% and with splenic abscess was 20.9% [3]. In the current study which enrolled only children in contrast to the all-ages study, we found similar proportions of children with hepatic abscess 29.6% (8/27) and splenic abscess 22.2% (6/27). Another earlier study including the overall data of 686 cases of melioidosis reported from six hospitals in Thailand (Khon Kaen Hospital (1982-1985), Ubon Ratchathani (1982-1985), Srinagarind Hospital (1978-1985), Nakorn Ratchasima (1983-1985), Chulalongkorn Hospital Bangkok (1980-1985) and Nontaburi (1983-1985)) found that 7% and 2%, respectively, of patients had co-hepatic or -splenic abscess [12]. Also, a study of 252 cases of melioidosis in Royal Darwin Hospital, Australia between 1989 and 1999 found hepatic abscess in 2% (5/252) and splenic abscess in 4% (11/252) [4]. In 2004, Silapapojakul [13] reported that the lungs were the most commonly affected organ (73%) in patients who had the septicemic form of melioidosis in southern Thailand but our study found pneumonia in only 25.9% of the confirmed cases.

It is probable that the high incidence of hepatic and/or splenic abscess (44.4%) in our study was because our hospital is the main referral center for all of southern Thailand, and severe cases of melioidosis from all of this area are referred here. Also, 59% of our patients had ultrasonography or computerized tomography (CT) so we were able to identify patients with silent hepatic and/or splenic abscess. Maude *et al*. [14] performed a prospective, observational study of 230 Thai adult patients with culture-confirmed melioidosis in which all patients had abdominal ultrasound. One or more abscesses were detected in the liver and/or spleen in 77 (33%) cases, which was similar to our study. They also found that 27%, 31% and 9% of their patients with liver and/or spleen abscesses presented with abdominal pain, hepatomegaly, and splenomegaly, respectively.

A previous study in children found splenomegaly by physical examination in disseminated melioidosis in 9/23 subjects (39%) and no splenomegaly in those with local infection (0/19 subjects) [15]. In our study, however, we found that no splenomegaly was a good clinical predictor of melioidosis among those suspected of melioidosis; only 1 patient with thalassemia major had splenomegaly. The difference between our study and the previous study could be explained by noting that overall their subjects had more severe disease, with 10 children (24%) dying [15]. The fatality rate in our study was 3.4% (1/27 subjects had aplastic anemia and died from disseminated melioidosis). These findings indicate that splenomegaly in a melioidosis patient without an underlying disease associated with splenomegaly is uncommon except in patients with disseminated melioidosis.

In our study, 41.6% (5/12) of the patients with hepatic and/or splenic abscess had abdominal tenderness, 75% (6/8) with hepatic abscess had hepatomegaly, and 33.3% (2/6) with splenic abscess had splenomegaly by ultrasonography. These findings indicate that high quality diagnostic imaging should be used for early detection of hepatic or splenic abscess.

This study has some limitations. First, it was a retrospective study, thus there was some missing information. Second, 11/27 cases confirmed by serology might not have had melioidosis, since melioidosis is endemic in Thailand and it is possible that the positive serology might have been from a remote infection. However, most of these 11 patients were younger than 6 years, and unlike adults, in younger children a positive serology is more likely to

Table 3. Likelihood ratio (LR), sensitivity, and specificity of predictive scores.

Variable	Score	LR	Sensitivity	Specificity
Skin or soft tissue infection	≥ 10	2.2	0.70 (0.50, 0.86)	0.68 (0.59, 0.76)
	< 10	0.4		
Splenic abscess	≥ 12	4.0	0.44 (0.25, 0.65)	0.89 (0.82, 0.94)
	< 12	0.6		
Hepatic abscess	≥ 19	5.6	0.33 (0.17, 0.54)	0.94 (0.88, 0.98)
	< 19	0.7		

be from an acute infection. Furthermore, we included only those subjects who had shown a good response when treated as melioidosis. Third, splenomegaly was defined by a palpable spleen from the physical examination, which does not have the sensitivity of ultrasonography or CT.

Conclusion

We conclude that patients who have clinically suspected melioidosis should have hepatic-splenic ultrasonography performed even though they have no abdominal tenderness or hepatosplenomegaly, and those with hepatic and/or splenic abscess should be treated initially as melioidosis while waiting for culture or serologic test results.

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