Original Article

Epidemiology and Clinical Outcome of Melioidosis at Chonburi Hospital, Thailand

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ABSTRACT

A retrospective study was conducted to evaluate the epidemiological data, clinical features, and clinical outcome of culture-proven melioidosis at Chonburi Hospital, East Thailand, from January 2001 to December 2006. Case records were available for 83 of 127 cases, diagnosed with melioidosis. Most patients were male (70%), with the mean age of 52 years (range 21-77 years). Seventy percent of patients had at least one risk factor with the most common being diabetes (57.8%). There was no seasonal variation in the occurrence of the disease. Fever of unknown and severe community-acquired pneumonia were commonly diagnosed on admission. Clinical manifestations included disseminated septicemia (78.3%), non-disseminated septicemia (20.6%), and localized infections (1.2%). The onset of the disease was acute in 44.6 percent, subacute in 22.9 percent, and chronic in 32.5 percent of patients. Ninety-nine percent of patients had bacteremia. The lung was the most common site of infection (88%), followed by the liver (77.1%). Most patients had multiorgan infection, with most commonly involving three organs. Fifty percent of the patients received appropriate antibiotic therapy, with ceftazidime plus cotrimoxazole being the most common regimen. The overall mortality rate was 47 percent. Factors significantly correlated with higher mortality rate were male sex, bacteremia, lung infection, acute onset, and treatment with inappropriate antibiotics. In conclusion, melioidosis is not uncommon in East Thailand. The case fatality rate is high, particularly in acute severe lung infection with bacteremia managed with inappropriate antibiotic therapy. Awareness, suspicion, and prompt effective treatment of high-risk patients will reduce the mortality. (*J Infect Dis Antimicrob Agents 2008,25:1-11.*)

INTRODUCTION

Melioidosis is a tropical infectious disease caused by Gram-negative bacterium, *Burkholderia pseudomallei*. It is an environmental saprophyte found in the soil and surface water in endemic regions of Southeast Asia and North Australia.[1-3] It occurs sporadically in animals and humans in these areas. The first case of melioidosis in Rangoon was

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reported by Whitmore and Kristinawany in 1912.[4] During and after World War II, melioidosis was reported in soldiers who returned from Southeast Asia.[5-7] Sporadic cases were occasionally reported from other countries, particularly from East Asia and North Australia. In recent years, case reports of infections in humans have increased in number from South China, Taiwan, South India, and various parts of the world.[8-10] Most cases reported outside Southeast Asia were from travelers to endemic areas.[11-13] In the latter half of the 20th century, melioidosis emerged as an infectious disease of major public health importance in Southeast Asia and North Australia.[14,15]

Melioidosis is a disease of the rainy season in endemic areas.[12] It mainly affects people who have direct contact with wet soils and have an underlying predisposition to infection.[16] The majority of cases have at least one identifiable risk factor, and the most important of which are diabetes, alcoholism, and chronic renal disease, although 20 percent to 36 percent of cases have no evident predisposing risk factor.[17-19]

The spectrum of melioidosis in humans varies from subclinical to overwhelming protean manifestations, resembling other acute and chronic bacterial infections.[20,21] The majority of studies have found that pneumonia is the most common presentation of melioidosis in approximately half of all cases, but there is a great clinical diversity, from localized skin ulcers or abscess to fulminated sepsis with multiple abscesses in the lungs, liver, spleen, kidneys, skeletal muscles, bones, joints, skin and soft tissue.[22-25] In a third of pediatric cases, it presents as a parotid abscess.[26] Most patients have bacteremia with severe disseminated disease, and the mortality rates remain high despite recent significant advances in the antibiotic treatment regimens.[27-29]

In 1955, Jittivej and colleagues reported the first case of melioidosis in Thailand.[30] By 1985, over 800 cases had been documented during the following 20 years, mostly from Northeast Thailand, where melioidosis accounted for 20 percent of all community-acquired septicemia.[14,16] In 1997, a study by Vuddhakul and colleagues found *B. pseudomallei* in soil samples from various parts of Thailand, especially the Northeast which has the highest incidence of melioidosis in this area.[31] In 2005, 26 cases of melioidosis were reported from Maharaj Nakorn Chiang Mai Hospital, a referral center in North Thailand.[32] Melioidosis has also been diagnosed at Chonburi Hospital, Chonburi, East Thailand. The aim of this study was to determine the clinical manifestations, risk factors, and the clinical outcome of patients with melioidosis at Chonburi Hospital.

PATIENTS AND METHODS

We conducted a retrospective study at Chonburi Hospital. Inclusion criteria were patients diagnosed with melioidosis and hospitalized at Chonburi Hospital from 1 January 2001 to 31 December 2006.

Definitions

Melioidosis was diagnosed when patients had compatible clinical manifestations and positive cultures for *B. pseudomallei* from either blood, sputum, pus from infected organs (e.g. liver or spleen), joint fluid, or other clinical specimens. Abscesses in internal organs were detected using abdominal ultrasonography or abdominal computed tomogram. Patients were classified by the onset and severity of the disease. The onset of the disease was classified as acute if the patient presented within seven days of the first symptom, subacute if the patient presented within 7-30 days of the first symptom, and chronic presentation was defined as a presentation more than one month after the first symptom.[33] Severity of the disease was classified as disseminated septicemia, non-

disseminated septicemia, or localized melioidosis.[34]

B. pseudomallei were identified by standard microbiological laboratory methods. Antimicrobial susceptibility testing of antibiotics was determined by the standard disk diffusion method. The antimicrobial agents used in susceptibility testing were ceftazidime, cefoperazone-sulbactam, amoxicillin-clavulanate, piperacillin-tazobactam, imipenem, levofloxacin, ciprofloxacin, gentamicin, amikacin, tetracycline, and cotrimoxazole.

Appropriate antibiotic therapy was defined when patients received effective antibiotics against *B. pseudomallei* within 48 hours. Inappropriate antibiotic therapy was defined as delayed appropriate antibiotic therapy when patients received effective antibiotics after more than 48 hours, or no appropriate antibiotic therapy when patients did not receive any effective antibiotics against *B. pseudomallei*.

Data were collected from the medical records including demographic data (age, sex, occupation, and underlying diseases), laboratory findings, treatment regimen, length of hospital stay, fever clearance time, and outcome.

Statistical analysis

Data were analyzed with the SPSS program version 15.0 (SPSS for Window). Demographic data, clinical manifestations, treatment, and patient outcome were shown as percentages, mean including range, and standard deviation, as appropriate. The comparison between patients who survived and those who died was done using the Student's t-test, Chi-square test, or Fisher's exact test, as appropriate.

A two-tailed P-value of less than 0.05 was considered significant.

RESULT

Demographic data and risk factors

During the six-year period from 2001 to 2006, 127 cases were hospitalized at Chonburi Hospital with culture-proven melioidosis, however medical records were available for only 83 patients. The demographic characteristics and associated conditions of all patients are shown in Table 1. The median age of affected patients was 51 years (range 21-77 years), with the male sex being predominated (62 patients, 74.4%). Hired labor was the most common occupation (57.8%), followed by farmer (21.7%), housewife (16.8%), and merchant (3.6%). Sixty-three (75.6%) patients were referred, and most patients were from community or general hospital within Chonburi Province (54 patients), Prachin Buri (3 patients), Rayong (3 patients), Chanthaburi (2 patients), and Chachengsao (1 patient). There was no seasonal variation in the occurrence of the disease.

Two-thirds of patients had at least one underlying disease, and 50 percent had more than 1 underlying disease. Diabetes mellitus (48 patients, 57.8%) was the most common, followed by renal disease (10 patients, 12.0%), hemoglobinopathy (3 patients, 3.6%), and HIV infection (2 patients, 2.4%).

Clinical presentations

Most cases had disseminated septicemia (78.3%), 20.5 percent of the patients had non-disseminated septicemia, and 1.2 percent had localized melioidosis, particularly arthritis. Thirty-seven patients (44.6%), 19 patients (22.9%), and 27 patients (32.5%) had acute, subacute and chronic onset, respectively. The most common diagnosis on admission was fever of unknown origin (38.5%), followed by severe community-acquired pneumonia (32.4%). Ninety-eight point eight percent of the patients had bacteremia. The lung was the most common site of infection (88%), followed by the liver (77.1%), spleen (44.6%), joints (13.3%), prostate gland (8.4%), and skin and soft tissue (8.4%). Seventy-eight point three percent of the patients had more

Table 1. Demographic data and underlying disease of patients with melioidosis.

Variable	Number of patients (%)
Age (mean SD, range) (year)	51.14 12.349, 21-77
Male: female	62:21
Occupation	
Hired labor	48 (57.8%)
Agriculture	18 (21.7%)
Housewife/home duties	14 (16.8%)
Merchant	3 (3.6%)
Alcohol consumption	23 (27.7%)
Underlying disease	
None	26 (31.3%)
Diabetes mellitus	48 (57.8%)
Kidney disease	10 (12.0%)
Hemoglobinopathy	3 (3.6%)
HIV infection	2 (2.4%)
Diabetes mellitus and kidney disease	4 (4.8%)
Referred cases	62 (74.7%)
Chonburi province	51 (86.7%)
Other provinces	11 (13.3%)

than one site of infection, most frequently with three organs involved (37.9%) as shown in Table 2.

Microbiologic method used for identifying of *B. pseudomallei*

A total of 131 cultures of *B. pseudomallei* were isolated from 64 patients. Most of which were susceptible to meropenem (100%), imipenem (100%), ceftazidime (100%), cefoperazone-sulbactam (100%), ceftriaxone (90%), levofloxacin (90%), ciprofloxacin (57%), tetracycline (95%), and cotrimoxazole (80%), but were resistant to amiglycosides (100%)

Indirect hemagglutination (IHA) antibody against *B. pseudomallei* test was performed in 43 patients (51.8%). The results were positive in 31 of 43 patients tested (72%). IHA was positive in 17 of 29 bacteremic patients (58.60%). Titers ranged from 1:640 to 1:10,240.

Treatment and outcome

Appropriate antibiotics were prescribed to 64 of 83 patients (77.71%). These agents included ceftazidime with cotrimoxazone (25 patients), ceftazidime (14 patients), cefoperazone-sulbactam (5 patients), and cabarpenem (3 patients). Fifty percent of the patients received an appropriate regimen, and 26.50 percent (22 of 83 patients) received a delayed but appropriate regimen. Twenty-three percent (19 patients, 22.90%) never received appropriate antibiotic

Table 2. Clinical manifestations of all 83 cases with melioidosis.

Variable	Number of patients (%)
Onset	
Acute	37 (44.6%)
Subacute	19 (22.9%)
Chronic	27 (32.5%)
Severity	
Disseminated	65 (78.3%)
Non-disseminated	17 (20.5%)
Localized (arthritis)	1 (1.2%)
Diagnosis on admission	
Fever of unknown origin	33 (39.76%)
Severe community-acquired pneumonia	32 (38.55%)
Septic arthritis	6 (7.23%)
Lung abscess	4 (4.82%)
Liver abscess	3 (3.62%)
Skin and soft infection	3 (3.62%)
Recurrent urinary tract infection	2 (2.40%)
Site of the infection	
Blood	82 (98.8%)
Lung	73 (88%)
Liver	64 (77.1%)
Spleen	37 (44.6%)
Joint	11 (13.3%)
Genitourinary (prostatitis)	7 (8.4%)
Skin and soft tissue	7 (8.4%)
Number of sites of infection	
1 organ	18 (21.7%)
2 organs	25 (30.1%)
3 organs	31 (37.9%)
4 organs	9 (10.28%)

therapy for melioidosis; almost all were receiving ceftriaxone, and the diagnosis was made at postmortem.

Over all, the mortality rate was 47 percent (39 of 83 patients). Of patients who received appropriate antibiotic therapy, the mortality was 30.95 percent (13 of 42 patients), however, the mortality was 63.41 percent (26 of 41 patients) in those who received inappropriate therapy (Table 3). The mortality was 31.8 percent (7 of 22 patients) in those receiving delayed appropriate therapy, and 100 percent (19 of 19 patients) in those who never received appropriate therapy. Of all patients who died, the median length of hospital stay was 3.16 days (range 0 to 11 days). For the survivors, the median defervencence time was 9.49 days (range 5 to 15 days), and the median length of stay was 21.08 days (range 5 to 43 days).

Associated risk factors for mortality using a univariate analysis included male sex (87% versus 61%, p = 0.005), bacteremia (97% versus 72%, p = 0.043), lung infection (100% versus 77%, p = 0.002), acute onset (59% versus 30%, p = 0.007), receipt of inappropriate antibiotics (66% versus 34%, p = 0.003), as shown in Table 4.

DISCUSSION

Melioidosis is an endemic disease in Southeast Asia and North Australia, and may be much more common in other tropical areas.[12] In Thailand, most reports of melioidosis have been from endemic areas (Northeast Thailand), however there have also been reports from non-endemic areas.[31,32] In 1994, there was a report of several cases with pulmonary infection caused by *B. peudomallei* in near drowning with adult respiratory distress syndrome from Chonburi Hospital.[35] After that, increasing more patients have been diagnosed at Chonburi Hospital, East Thailand, which is not an endemic area. In addition, there have been no reported cases in the study of the Thai Research Fund, in 1997.[31]

Table 3. Treatment and outcome of all 83 patients with melioidosis.

	Survived (N = 44)	Died (N = 39)
Appropriate antibiotic therapy	29 (69.1%)	13 (30.9%)
Ceftazidime	5	6
Ceftazidime plus cotrimoxazole	21	3
Imipenem	1	1
Cefoperazone-sulbactam	2	3
Inappropriate antibiotic therapy	15 (26.6%)	26 (63.4%)
No appropriate antibiotic	0	19
Delayed appropriate antibiotic	15	7
Ceftazidime	2	1
Ceftazidimes plus cotrimoxazole	13	5
Imipenem	0	1

*All data are denoted as number of patients, otherwise indicated.

Table 4. Comparison of epidemiological and clinical data of all 83 patients with melioidosis who survived and those who died.

Characteristics	Survived *(N = 44)	Died *(N= 39)	P-value
Age (mean ± SD) (year)	50.75 ± 11.80	51.59 ± 13.07	0.215
Male	27	34	0.005*
Underlying disease	29	28	0.366
Bacteremia	43	39	0.053
Lung infection	34	38	0.002*
Liver infection	39	24	0.080
Spleen infection	24	13	0.081
Acute onset	13	23	0.007*
Disseminated infection	36	29	0.685
Inappropriate antibiotic therapy	15	26	0.003*

*All data are denoted as number of patients, otherwise indicated.

In this study, all patients were from provinces in the hospital catchment area. Most cases were male. The mean age was 51.14 years. The majority of cases were hired labors, not farmers who have more exposure to soils. Unlike other reports,[14] we diagnosed melioidosis throughout the year rather than near the end of the rainy season. This could be because labourer's occupation might lead to exposure to soils throughout the year. The majority of our patients (70%) had underlying diseases, with diabetes mellitus being the most frequent. One third of the patients had no risk factors, in consistent with previous studies.[17-19]

The majority of clinical cases presented with acute onset and disseminated septicemia. Fever of unknown origin easily and severe community-acquired pneumonia were the most common diagnoses on admission. Of cases with fever of unknown origin, an infection site was not demonstrable until ultrasound or computed tomogram examination of the abdomen showed abscesses in the liver or spleen, in combination with positive IHA antibody titers against *B. pseudomallei*. Of cases with severe pneumonia, most commonly had rapid deterioration needing ventilator support, and expired within 48 hours before obtaining bacteriogical results.

The clinical nanifestations from this study were generally similar to previous studies; most cases had bacteremia with abscess formation in multiple organs including the lungs, liver, spleen, skin or soft tissue, and joints,[22-25] but with clinical differences. First, genitourinary infection (commonly prostatitis or prostatic abscess) comprises 8.4 percent of cases, compared with fewer than 1 percent in a previous study.[34] Indeed, the occurence of prostatitis might be higher, and especially in elderly male patients. Second, the high frequency of pulmonary infection (82%), and 20 percent of the patients presented with severe community-acquired pneumonia. Inhalation might be the primary mode of acquisition, like the study of American soldiers in Vietnam.[24]

In this study, the IHA titers against *B. pseudomallei* were not sensitive, because the test was

positive only in 41.4 percent of patients with culture-proven melioidosis. Thus, in patients with abscesses of many organs, and negative blood cultures and IHA, melioidosis should not be excluded. This is in consistent with the study from Maharaj Nakorn Chiang Mai Hospital.[32]

We defined appropriate antibiotic therapy as a receipt of effective antibiotics against *B. pseudomallei* within 48 hours, because previous studies have shown that patients with melioidosis receiving appropriate antibiotics after more than 48 hours had a high mortality, suggesting irreversible severe disease.[27]

In this study, the initial antibiotics were third-generation cephalosporins, mostly ceftriaxone. Only eight patients received antimicrobials active against *B. pseudomallei* including ceftazidime (6 patients) and cefoperazone-sulbactam (2 patients). Although almost all isolates were susceptible to ceftriaxone (90%), all patients received this antibiotic had 100-percent mortality rate, in consistent with the previous study.[36]

In this study, the mortality rate of the patients who received inappropriate antibiotic therapy was twice to that of the patients who received appropriate antibiotic therapy. Thus, an awareness of infections caused by this organism and a prompt prescription of appropriate antibiotics should reduce mortality. Thirty percent of patients who received appropriate antibiotic therapy still died because these patients had severe sepsis and multi-organ failure. Most cases with severe pneumonia had rapid deterioration and death within 48 hours.

The mortality rate in this study was 47 percent. The case fatality rate of disseminated septicemic melioidosis was 55.4 percent, similar to the previous study.[37] Most of the deaths occurred in patients with acute onset, bacteremia, and in those who were referred from community or general hospitals which could not perform bacterial culture. The commonly used empirical antibiotic was ceftriaxone which is unfortunately ineffective against this organism, and this was probably a contributing factor in the deaths. Ceftazidime has been demonstrated to melioidosis contribute to a 50 percent reduction in mortality, from 74 percent to 37 percent.[27] The effectiveness of therapy with amoxicillin-clavulanate, cefoperazone-sulbactam, and imipenem were compared with ceftazidime in clinical trials. There was no difference among these drugs in overall mortality. Thus, ceftazidime-based regimens might be more cost-effective than using other anti-melioidosis antibiotics.[29,38-41]

In this study, the most common regimen was ceftazidime in combination with cotrimoxazole, although currently a trial of ceftazidime alone compared with ceftazidime with cotrimoxazole, showed no significant differences in mortality.[42] In this study, *B. pseudomallei* was only 80 percent susceptible to cotrimoxazole, however testing for cotrimoxazole resistance is problematic with the disk diffusion method, probably overestimating the extent of resistance.[43-44] The use of combination of ceftazidime and cotrimoxazole has the rationale for preventing of the emergence of resistance strain during the therapy. In addition, the tissue penetration of cotrimoxazole is better than beta-lactam antibiotics. However, in vitro studies suggest antagonism,[45] although clinical evidence for this is lacking.

The limitations of this study include the retrospective study and incomplete clinical data due to the unavailability of some medical records. We studied only clinical outcome of patients during hospitalization, thus long-term outcomes were not available. We excluded many patients which had clinical features similar to melioidosis because cultures and IHA test were negative (mostly in patients with risk factors and multiple abscess). Thus, reported cases of melioidosis are probably much

lower than actual numbers in this area. Despite these limitations, this study shows the presence of melioidosis in this area. Given the substantial influence of melioidosis on morbidity and mortality and the difficulty in diagnosis, awareness, suspicion and prompt appropriate treatment of high-risk patients will become much more important to improve clinical outcome.

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