Malaysian Journal of Pharmaceutical Sciences,
Vol. 2, No. 1, 9 – 20 (2004)

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APPROPRIATE USE OF ANTIBIOTICS AND PATIENT OUTCOMES IN MELIOIDOSIS

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Melioidosis is a common infectious disease in South East Asia and has high fatality rate. The objectives of this study were to determine appropriateness of antibiotic use in terms of drug choices and dosage regimens, and to compare mortality and hospital readmission between appropriate treatment and inappropriate treatment. Methods used is a retrospective medical chart review of patients admitted to Maharat Nakhonratchasima Hospital, a tertiary medical center in northeastern Thailand during 1997 – 2000. Patients whose diagnoses were confirmed with the positive culture of B. pseudomallei (N = 135) were included in the analysis. The overall mortality of patients with melioidosis was 50% and hospital readmission was 30%. For empirical treatment, 38% of patients received an appropriate choice of antibiotics. For documented treatment in an acute phase, 78% received appropriate antibiotic choice and 41% of the patients with the appropriate choice received the drugs in subtherapeutic doses. For the maintenance therapy, 50% of the patients who had positive culture reported during hospitalization received the appropriate antibiotics and 42% of those with the correct antibiotics received subtherapeutic doses. Based on multiple logistic regression analysis, appropriate use of antibiotics in terms of choices and dosage regimens in the acute phase was associated with a 69% decrease in risk of death (adjusted OR = 0.31, 95% CI: 0.12 – 0.82) and lowered risk of readmission by 78% (adjusted OR = 0.22, 95% CI: 0.05 – 0.95). The mortality rate of melioidosis was very high even though effective antibiotics were available. Appropriate use of antibiotics in the acute phase could increase patient survival and reduce hospital readmission.

Keywords: *Antibiotics, Melioidosis, Mortality, Readmission*

INTRODUCTION

Melioidosis is a common infectious disease in South East Asia. In Thailand, approximately two to three thousand cases with clinical melioidosis are reported each year. In highly endemic areas like northeastern Thailand, the incidence rate was as high as 3.6 – 5.5 per 100,000 population (Suputtamongkol *et al.* 1994). Melioidosis is caused by *Burkholderia pseudomallei*, a Gram-negative bacillus. The most common clinical manifestation of melioidosis includes fever, septicemia, pneumonia, and abscess of skin, muscle, lymph node, parotid gland, liver or spleen (Chaowagul and Lumpikanon 1997). Diagnosis of the disease is difficult

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and mostly based on clinical presentation. The definitive diagnosis is achieved by isolation of *B. pseudomallei* from various specimens such as blood, urine, sputum and skin lesion. Experience of laboratory staff is an important factor for successful isolation of the organism (Chaowagul 1998).

During the last decade, improvement in clinical outcomes as a result of new antibiotic treatment has been reported in several randomized controlled trials (Sookpranee *et al.* 1992; Rajchanuvong *et al.* 1995; Thamprajamchit *et al.* 1998; Chaowagul *et al.* 1999; Chetchotisakd *et al.* 2001; Samuel 2001). Initially, conventional treatment has included the use of chloramphenicol, doxycycline and cotrimoxazole. Case fatality rate for the conventional treatment was as high as 47–74% (Sookpranee *et al.* 1992; Suputtamongkol *et al.* 1994). Ceftazidime has been reported to reduce mortality to 37–47% (White *et al.* 1989; Suputtamongkol *et al.* 1994; Simpson *et al.* 1999; Samuel 2001) whereas the combined ceftazidime and cotrimoxazole could reduce the mortality to 18–21% (Thamprajamchit *et al.* 1998). Case fatality for other antibiotics varied: 16% for cefoperazone/sulbactam combined with cotrimoxazole 46% for amoxiclave, and 36.1% for imipenem (Suputtamongkol *et al.* 1994; Rajchanuvong *et al.* 1995; Thamprajamchit *et al.* 1998; Simpson *et al.* 1999). For an acute treatment, initiation of ceftazidime could lower the rate of relapse more than amoxiclave or the conventional treatment (Suputtamongkol *et al.* 1994). For a maintenance phase of 8 weeks, the conventional treatment was found a less frequent relapse than amoxiclave (Chaowagul *et al.* 1993).

In general, diagnosis of melioidosis is difficult and requires experienced medical specialists. Patients may receive an inappropriate medication due to limitation in diagnostic process that often requires laboratory results. Use of appropriate antibiotic regimens could reduce mortality and healthcare costs. However, no prior studies have been designed to identify variations in patterns of antibiotic use in patients with melioidosis. Effect of the appropriate use of antibiotics on patient outcomes based on the real world practice is not well understood. This study aimed to examine drug use patterns in patients with melioidosis and its association with patient outcomes. The appropriateness of antibiotic prescribing and mortality, as well as hospital readmission were determined. Results of this study would provide better understanding toward a quality treatment of melioidosis.

METHODS

This study is a retrospective medical chart review of patients admitted to a tertiary medical center in northeastern Thailand during 1997–2000. Of 160 patients diagnosed with melioidosis, 130 patients with 135 episodes of the infection were reported the positive culture of *B. pseudomallei* in the medical charts, hence, included in the analysis. Children aged under 14 years were excluded. Antibiotics given were reviewed for the appropriate choice. Dosage regimens were evaluated whether they were therapeutic or subtherapeutic. A list of drugs of choice and appropriate dosage regimens (Table 1) was developed using results from several randomized controlled trials (White *et al.* 1989; Suputtamongkol *et al.* 1991; Sookpranee *et al.* 1992; Chaowagul *et al.* 1993; Suputtamongkol *et al.* 1994; Rajchanuvong *et al.* 1995; Chaowagul *et al.* 1997; Thamprajamchit *et al.* 1998; Chaowagul *et al.* 1999; Simpson *et al.* 1999; Chetchotisakd *et al.* 2001) and was approved by medical experts in infectious disease area. Decision on appropriateness of the antibiotics given was made through consensus of two hospital pharmacists. When there was a disagreement, the third opinion was sought from an infectious disease clinician. The appropriateness of antibiotic use was determined for empirical treatment in all cases, and for documented and maintenance treatments in cases with known culture and sensitivity during hospitalization period. Patient outcomes examined in this study were mortality and hospital readmission within 28 days after the discharge. The mortality was defined according to the following conditions: death during hospitalization and hospital discharge with unimproved conditions or against advice. The latter condition was verified for death of the patients through National Death Registry.

Statistical Analysis

Mortality and readmission rates were compared across patterns of antibiotic prescribed using appropriate inferential statistics, and analyzed by STATA software version 6.0 (College Station, Texas). Association between appropriateness of antibiotic use and patient outcomes was measured by odds ratio (OR) that was adjusted for underlying diseases, organ involvement, and culture-proven results from various specimens, using multiple logistic regression analysis.

RESULTS AND DISCUSSION

Patients

Of 135 total episodes of melioidosis, 130 were new cases with definite diagnosis and 5 were relapse cases. Most patients were admitted to medical wards (70%), surgical wards (21%), and orthopedic and other wards (6%), whereas only 3% were treated in the hospital's outpatient departments. Septicemic form of melioidosis was found in 51% of the patients: 41 cases with proven positive blood culture and 28 cases with sepsis manifestation. Non-septicemic form occurred in 17 cases of multifocal localized melioidosis and 49 cases of localized melioidosis.

Majority of the study patients aged from 46–60 years and had poor socio-economic status (Table 2). Most of them were farmers who lived in the rural area and were likely to be exposed to soil and water. In terms of the patient's payment status, 87% were eligible to Public Welfare Scheme. Eighty four percent had at least one underlying disease such as diabetes (45%), hepatic disease (16%), renal disorders (13%) and blood disorders (13%). Clinical spectrum of the disease varied from an acute sepsis to a chronic localized infection. Fifty two percent had ulcer or abscess of bone, joint, skin or muscle. Based on hospital admission, 11% were presented with septic shock and 22% had dypsnea. Duration of clinical manifestation before the admission varied with the median onset of 7 days. Indirect hemagglutination (IHA) titer test was performed in only 45 cases or 33%. Thirty three of the patients (73%) had the positive result with titers higher than 1:160. Overall, 54% of the patients had definite melioidosis diagnosed during hospitalization period. Thirty percent had culture results after they died or discharged against advice, whereas 15% were reported of the culture results after they were discharged or referred from the hospital.

Table 1: Drug of Choice and Appropriate Dosage Regimen for Melioidosis Treatment

	Drug of choice and daily dose	Regimen defined in this study
1.	**Acute phase** (for at least 10 – 14 days)	
1.1	Conventional treatment:	
	- Co-trimoxazole 8 mg + 40 mg/kg/day	3 Amp q 12 hr or 2 Amp q 8 hr
	- Doxycycline 4 mg/kg/day	100 mg q 12 hr or 200 mg q 24 hr
	- Chloramphenicol 100 mg/kg/day	1 g q 6 hr
1.2	Ceftazidime 120 mg/kg/day	2 g q 8 hr
1.3	Ceftazidime 100 mg/kg/day	2 g q 8 hr
	+ Co-trimoxazole 8 mg + 40 mg/kg/day	3 Amp q 12 hr or 2 Amp q 8 hr
1.4	Amoxicillin/clavulanic acid 160 mg/kg/day (as Amoxicillin 120 mg/kg/day)	2.4 g q 8 hr or 1.2 g q 4 hr
1.5	Imipenem/cilastatin 50 – 60 mg/kg/day (for 7-14 days)	1 g q 8 hr
1.6	Cefoperazone/sulbactam (as Cefoperazone 25 mg/kg/day)	1 g q 12 hr
	+ Co-trimoxazole 8 mg + 40 mg/kg/day	3 Amp q 12 hr or 2 Amp q 8 hr
1.7	Piperacillin 12 – 18 g/day	2 g q 4 hr
	± Cefotaxime 6 g/day	2 g q 8 hr
	± Chloramphenicol 100 mg/kg/day	1 g q 6 hr
	± Co-trimoxazole 8 mg + 40 mg/kg/day	3 Amp q 12 hr or 2 Amp q 8 hr
2.	**Maintenance phase** (for at least 12 – 20 weeks)	
2.1	Co-trimoxazole 10 mg + 50 mg or 8 – 12 mg + 50 mg/kg/day	3 x 2 pc or 2 x 3 pc or 3 x 3 pc
	and/or Doxycycline 4 – 6 mg/kg/day	1 x 2 pc or 2 x 1 pc (with 100 mg)
	(± Chloramphenicol 40 – 50 mg/kg/day for 4 weeks), then Co-trimoxazole + Doxycyline for total course of 20 weeks	2 x 4 pc (with 250 mg)
2.2	Amoxicillin/clavulanic acid 30 mg + 15 mg/kg/day (for 8 – 20 weeks) or	2 x 3 pc (with 375 mg) or 1 x 3 pc (with 750 mg)
	(+ Amoxicillin 30 mg/kg/day)	1 x 3 pc (250 mg) or 1 × 2 pc (500 mg)
2.3	Ciprofloxacin 20 – 25 mg/kg/day or	1 x 2 pc (with 500 mg)
	Ofloxacin 12 mg/kg/day (for 12 – 40 weeks)	1 x 2 pc (with 200 mg)

Note: For septicemia or severe localized melioidosis: Co-trimoxazole (sulfamethoxazole 400 mg plus trimethoprim 80 mg) one 5 ml-Amp.

2. Oral maintenance treatment (after successful intravenous therapy) for severe, or mild or chronic localized melioidosis: Co-trimoxazole (sulfamethoxazole 400 mg plus trimethoprim 80 mg) 1 Tab.

Source: White *et al.* (1989); Suputtamongkol *et al.* (1991); Sookpranee *et al.* (1992); Chaowagul *et al.* (1993); Suputtamongkol *et al.* (1994); Rajchanuvong *et al.* (1995); Chaowagul *et al.* (1997); Thamprajamchit *et al.* (1998); Chaowagul *et al.* (1999); Simpson *et al.* (1999); Chetchotisakd *et al.* (2001).

Table 2: Demographic, Socio-Economic and Clinical Characteristics of the Patients (N = 130)

Characteristics	Frequency	%
Age		
15 – 30 years	9	6.9
31 – 45 years	37	28.5
46 – 60 years	55	42.3
≥ 61 years	29	22.3
Gender		
Male	74	56.9
Female	56	43.1
Occupation		
Farmer	76	58.5
Labour	17	13.1
Housekeeper	27	20.8
Others	10	7.7
Residential area		
Urban Nakhonratchasima	11	8.5
Rural Nakhonratchasima	100	76.9
Other provinces	19	14.6
Payment status		
Out-of-pocket payment	5	3.9
Civil Servant Medical Benefit Scheme	4	3.1
Social Security Scheme	2	1.5
Public Welfare Scheme	113	86.9
Others or not indicated	6	4.6
Underlying diseases		
Diabetes mellitus	61	45.2
Hepatic disease	22	16.3
Renal disorders	17	12.6
Blood disorders	17	12.6
Organ involvement		
Lung	44	32.6
Bone and joint	37	27.4
Skin and muscle	33	24.4
Liver	25	18.5
Urinary tract	19	14.1
Spleen	10	7.4

Appropriate Use of Antibiotics and Patient Outcomes

Table 3 shows rates of failure to receive the appropriate antibiotics choice in three treatment stages. For empirical treatment, the failure rates were 58% in septicemia group and 67% in non-septicemia group. Among those who received appropriate antibiotics (N = 51), 45% received the drugs in

subtherapeutic doses. Table 4 presents drugs that were prescribed for the empirical treatment.

Table 3: Failure Rates in Receiving Appropriate Choice of Antibiotics

Treatment	Septicemic group	Non-septicemic group
Empirical treatment (N = 135)	N = 69	N = 66
Not receiving appropriate antibiotics	40 (58.0%)	44 (66.7%)
Documented treatment in an acute phase (N = 69)[a]	N = 30	N = 39
Not receiving appropriate antibiotics	4 (13.3%)	11 (28.2%)
Maintenance treatment (N = 52)[a]	N = 16	N = 36
Not receiving appropriate antibiotics	9 (56.3%)	17 (47.2%)

[a] Patients who had positive culture results known during hospitalization period

Table 4: Antibiotics Used in an Empirical Treatment of Melioidosis

Drugs	N
Appropriate choice	51 (37.8%)
Ceftazidime alone	7
Ceftazidime + Co-trimoxazole	9
Ceftazidime + Co-trimoxazole + other antibiotics	2
Ceftazidime + other antibiotics	17
Amoxicillin /clavulanic acid alone	6
Amoxicillin/clavulanic acid + other antibiotics	7
Imipenem/cilastatin + other antibiotics	2
Cefoperazone/sulbactam+ Co-trimoxazole	1
Inappropriate choice	84 (62.2%)
Penicillins $\pm$ Aminoglycosides	40
Cephalosporins $\pm$ other antibiotics	36
Other antibiotics	3
No antibiotics	5

In 62 patients who did not have evidence of definite melioidosis during the hospitalization, 73% did not receive the appropriate antibiotics in the acute phase and 69% died thereafter.

Seventy three patients had definite melioidosis diagnosed during the hospitalization. Sixty nine received intravenous therapy in the acute phase and their treatments were analyzed for documented treatment and maintenance treatment. For the documented treatment, the rates of failure in receiving appropriate choice of antibiotics were 13% and 28% in septicemia and non-septicemia groups, respectively. Twenty nine percent of the patients who were prescribed the appropriate antibiotics received subtherapeutic doses. Duration of the antibiotic use in the patient group that survived was 15 days, on average, and 69% of these patients received

the medication for at least 10 days. Amoxicillin/clavulanic acid and imipenem/cilastatin were prescribed in the subtherapeutic doses for all patients.

Fifty-two of the 73 cases with definite diagnosis during hospitalization were treated during maintenance phase. For the maintenance treatment, the rates of failure to receive the drug of choice were 56% of septicemic patients and 47% of non-septicemic patients. Twenty seven percent of these patients received antibiotics for at least 12 weeks (an average of 9 weeks). Overall, 42% of the patients who were prescribed the appropriate antibiotics received subtherapeutic doses. Out of 123 cases receiving intravenous therapy in the acute phase, 75 patients (61%) received appropriate antibiotics. The most common antibiotics were concomitant ceftazidime and co-trimoxazole (55%), ceftazidime with others (27%), amoxicillin/clavulanic acid monotherapy or with other antibiotics (12%). Coadministration of imipenem and ceftazidime were found in 4%, and conventional antibiotics were used in one patient.

For patients with severe melioidosis, majority (79% of disseminated melioidosis; 58% of non-disseminated melioidosis and 71% of multi-localized melioidosis, respectively) received appropriate choice of antibiotics. However, only half of the patients with localized melioidosis received appropriate antibiotics.

Twenty eight percent of the patients with an appropriate antibiotic choice were given subtherapeutic doses. Thirteen out of 17 patients who took amoxicillin/clavulanic acid received the drug in subtherapeutic dose.

In the septicemic group, mortality and readmission rates in patients who received the appropriate antibiotics for the acute treatment were lower than those who received the inappropriate antibiotics (Table 5). In the non-septicemic group, the mortality rates were similar between those who received the appropriate antibiotics and those who did not. A similar result was found in the maintenance therapy where the mortality and readmission rates were relatively higher in patients receiving the inappropriate antibiotics. The differences in patient outcomes with respect to the appropriateness of antibiotics choices did not reach statistical significance based on univariate analysis.

Table 5: Mortality and Readmission in Patients Receiving Appropriate and Inappropriate Antibiotics

		Mortality (%)	Readmission (%)
1.	**Acute treatment** [N = 123]		
1.1	Septicemic group	N = 63	N = 15
	– Receiving appropriate antibiotics	26/39 (66.7%)	2/12 (16.7%)
	– Not receiving appropriate antibiotics	23/24 (95.8%)	2/3 (66.7%)
1.2	Non-septicemic group	N = 60	N = 49
	– Receiving appropriate antibiotics	10/36 (27.8%)	8/29 (27.6%)
	– Not receiving appropriate antibiotics	6/24 (25.0%)	3/20 (15.0%)
2.	**Maintenance treatment** [N = 71]		
2.1	Septicemic group	N = 16	N = 16
	– Receiving appropriate antibiotics	0/7 (0%)	1/7 (14.3%)
	– Not receiving appropriate antibiotics	4/9 (44.4%)	3/9 (33.3%)
2.2	Non-septicemic group	N = 55	N = 55
	– Receiving appropriate antibiotics	3/30 (10.0%)	6/30 (20.0%)
	– Not receiving appropriate antibiotics	2/25 (8.0%)	6/25 (24.0%)

In the acute phase, patients who had appropriate use of antibiotics by both choices and dosage regimens had a significantly decreased risk of death by 69% (adjusted OR = 0.31, 95% CI: 0.12–0.82) as compared with patients with inappropriate use (Table 6). Patients with sepsis manifestation had a significantly increased risk of death by 3 times (adjusted OR = 3.07, 95% CI: 1.09–8.59) as compared with patients without sepsis. The positive culture specimens that were found associated with an increased risk of death were collected from blood and urine. Patients with the positive blood culture had a higher risk of death about 3.7 times (adjusted OR = 3.69, 95% CI: 1.43–9.51) as compared with those with the negative culture. Patients with the positive urine culture had a higher risk of death about 17.6 times (adjusted OR = 17.59, 95% CI: 1.98–156.42) as compared with those with the negative results. In the present study, there were 12 patients who had positive cultures in the urine but did not have positive blood specimens, and all patients in this subgroup died. In addition, the appropriate antibiotics by both choices and dosage regimens in the acute phase decreased risk of hospital readmission by 78% (adjusted OR = 0.22, 95% CI: 0.05–0.95). A presence of diabetes as the underlying disease was not found associated with death or readmission of the study patients.

Table 6: Factors Associated with Death from Melioidosis (N=123)

Factors	Odds Ratio (OR)[a]	p-value	95% CI of OR
Appropriate use of antibiotics in an acute phase[b]	0.31	0.02	0.12–0.82
Sepsis manifestation	3.07	0.03	1.09–8.59
Positive culture for blood[c]	3.69	0.01	1.43–9.51
Positive culture for sputum/pus/effusion from lung[c]	1.92	0.16	0.78–4.74
Positive culture for urine[c]	17.59	0.01	1.98–156.43

[a] Based on multiple logistic regression analysis adjusted for underlying diseases and organ involvement

[b] Appropriateness in both antibiotic choices and dosage regimens

[c] Positive cultures of *B. pseudomallei*

In general, blood cultures are incubated until the culture media becomes turbid, which usually takes 1–4 days. Then bacteria are identified by biochemical characterization, which requires additional 1–2 days in the cases of *B. pseudomallei*. The laboratories usually require 2–6 days to report the positive identification of this organism (Tiangpitayakorn *et al.* 1997). Isolation and identification of *B. pseudomallei* process was too long to be of clinical use in many cases. Forty six percent of the patients studied did not have definite melioidosis diagnosed during the hospitalization period. As a consequence, 73% of these patients did not receive appropriate choice of antibiotics before they were discharged, referred or died.

Mortality rate due to septicemic melioidosis found in this study was relatively high and consistent with previous studies conducted in other Thai hospitals (Chaowagul *et al.* 1986; Werapattana 1992; Sirichot 1998). The mortality rate in the septicemic group was 78%, whereas in the non-septicemic group was 20%. In summary, for the empirical treatment, only 16 of 135 cases received the appropriate antibiotic treatment in terms of correct drugs and proper dosage regimens. Most patients would receive the appropriate treatment after the culture and sensitivity results were available. This may explain the high mortality rate found in the present study, even though treatment of choice generated from evidence-based studies was well established and publicised.

CONCLUSION

This study described information on epidemiology of hospital admission of melioidosis, selection of antibiotics for the treatment, and determination of the association between antibiotic use and patient outcomes. The most common problems in the treatment of septicemic melioidosis included relatively late hemoculture report, resulting in delayed diagnosis and treatment, and poor prognosis. Clinical manifestation of melioidosis is similar to several other infectious diseases. In the present study, appropriate use of antibiotics in the acute phase could decrease both risk of death and risk of hospital readmission. However, inappropriate acute treatment and subtherapeutic doses were commonly found. For the fatal infectious disease like melioidosis, there was still a room for an improvement in antibiotic prescribing to ensure the quality of medical practice.

Future research should involve a comprehensive study in other hospital settings. This would make the study results more generalizable to the public health community.

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