RHEUMATOLOGICAL MANIFESTATIONS IN MELIOIDOSIS PATIENTS

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ABSTRACT

This study comprised a retrospective review of culture-proven melioidosis cases at Sappasithiprasong Hospital, Ubon Ratchathani, northeastern Thailand, for the period February 2002-May 2005. The prevalence of rheumatological patients among the melioidosis population was 14.4% (98/679). Rheumatological patients tended to occur among females and those aged 41-60 years. Melioidosis patients with diabetes mellitus (DM) and thalassemia had 2.5 and 10 times independent risks, respectively of rheumatological involvement than non-rheumatological involvement. DM also showed 9-fold risk of more than one-site involvement for rheumatological melioidosis patients. Compared with non-rheumatological cases, rheumatological cases tended to have less severe clinical course—less mortality and less severe complications, including shock and respiratory failure. They also tended to have more chronicity—with subacute or chronic duration of symptoms, and with the complication of anemia. They were prone to prolonged hospital stay, changes in antibiotic therapy, and recurrent infections. Rheumatological patients with more than one-site involvement had prolonged treatment duration with parenteral antibiotics.

Melioidosis arthritis cases comprised most of the rheumatological patients (82.7%). Involvements of joint, bone and muscle overlapped; 80% of bone infections also had joint involvement, and 50% of muscle infections also had joint involvement. Melioidosis arthritis cases, like septic arthritis, were prone to involvement of the lower extremities. 21% of patients with melioidosis arthritis had bone infections, especially those with joint symptoms or signs > 2 weeks. Therefore, patients with melioidosis arthritis should be meticulously evaluated by X-ray of the adjacent long bones, or bone scans, to detect any occult metastatic bone infection during the course of hospital stay. In endemic areas, with presentation of fever, arthralgia and swollen joints, blood or local pus/synovial fluid for culture should be obtained aggressively for early diagnosis and the institution of appropriate antibiotics, to prevent adjacent bone infection.

KEY WORDS: RHEUMATOLOGICAL MELIOIDOSIS/ARTHRITIS/PYOMYOSITIS /OSTEOMYELITIS/*BURKHOLDERIA PSEUDOMALLEI*

58 P.

CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Term
ALK-P	Alkaline phosphatase
AUG	Co-amoxiclav.
Bil(T)	Total bilirubin
Bil(D)	Direct bilirubin
B. pseudomallei	*Burkholderia pseudomallei*
BUN	Blood urea nitrogen
CAZ	Ceftazidime
COPD	Chronic obstructive pulmonary disease
CBC	Complete blood count
CI	Confidence interval
CLD	Chronic liver disease
CNS	Central nervous system
Cr	Creatinine
CRF	Chronic renal failure
CT	Computed tomography
DM	Diabetes mellitus
FCT	Fever clearance time
Hb	Hemoglobin
$HCO3^-$	Serum bicarbonate
HIV	Human Immunodeficiency Virus
IHA	Indirect hemagglutination
IMP	Imipenem
KUB	Kidney, Ureter and Bladder
K	Serum potassium
Na	Serum sodium

LIST OF ABBREVIATIONS (cont)

Abbreviation	Term
OR	Odds ratio
PLT	Platelet
RA	Rheumatoid arthritis
ROM	Range of motion
SGOT	Serum glutamate oxaloacetate transaminase
SGPT	Serum glutamate pyruvate transaminase
SLE	Systemic lupus erythematosus
SPSS	Statistical Package for the Social Sciences
TB	Tuberculosis
TMP-SMX	Trimethoprim-sulfamethoxazole
WBC	White blood cell

CHAPTER I
INTRODUCTION

Melioidosis is caused by the Gram-negative saprophyte called *Burkholderia pseudomallei*. Melioidosis has a diverse spectrum of clinical presentation and can affect any organ. In the latter half of the 20th century, melioidosis emerged as an infectious disease of major public health importance in Southeast Asia and Northern Australia. In Ubon Ratchathani, Thailand, *B. pseudomallei* accounts for up to 20% of community-acquired bacteremias (Chaowagul et al., 1989). At the Royal Darwin Hospital, Australia, it has been the most common cause of fatal community-acquired bacteremic pneumonia (Douglas et al., 2004). Despite improvements in antibiotic therapy, melioidosis is associated with a significant mortality and morbidity.

The choice of antibiotic regimen has not been shown to have an impact on mortality within the first 48 hours of admission (White et al., 1989), and mortality rate reaches approximately 50% in severe melioidosis patients (White, 2003). In Australia, the mortality rate is unacceptably high approaching 20% among all patients with melioidosis (Currie et al., 2003). Melioidosis has been called the 'remarkable imitator' due to its characteristic to mimic a broad range of clinical presentations. In particular, less common forms of localized melioidosis are underreported (Leelarasamee, 2000).

The disease can involve multiple systems, and most common organ involvement is the respiratory system. There have been reports of melioidosis from various parts of the tropical area. The infection may be disseminated or localized. Melioidosis can imitate other common infectious diseases and conditions, such as tuberculosis or secondary tumors of bones and joints (Kosuwon et al., 1993). It hence poses a diagnostic dilemma and lightens the importance of awareness of the disease. This applies to both endemic areas and non-endemic areas due to the globalization and case of traveling (Currie, 2003).

Nearly half of extra-pulmonary involvements have manifested in melioidosis patients (Cheng and Currie, 2005). Rheumatological involvement including bone, joint and muscle comprised 5—27% of melioidosis cases (Chetchotisakd et al., 2001; Punyagupta, 1989; Simpson et al., 1999). The rheumatological involvement may appear very early during course of the disease, and often being misdiagnosed. The disease has been extensively studied over the past twenty years but the knowledge on rheumatological aspect is very limited. It is important to clarify and understand the associated clinical features and risk factors; especially, when septic arthritis was delayed treated, subsequent long term morbidity or osteomyelitis might ensue. The poor penetration of antibiotics in osteomyelitis might prolong and complicate the treatment course. There was limited data to show whether such manifestation will cause antibiotics resistance or recurrence of disease.

We retrospectively reviewed the culture-proven melioidosis cases at Sappasithiprasong Hospital in Ubon Ratchathani, Northeast Thailand, from February 2002 to May 2005. This study aimed to determine the prevalence of rheumatological involvements in melioidosis patients, to describe the characteristics of rheumatological involvements, and to compare the non-rheumatological melioidosis cases with rheumatological melioidosis cases from the demographic and clinical profiles, laboratory results, treatment and outcomes.

CHAPTER II
OBJECTIVES

1. To compare the difference between the rheumatological cases and non-rheumatological cases from demographic profiles, clinical features, laboratory results, treatments and outcomes.
2. To determine the prevalence of rheumatological involvement among culture-proven melioidosis patients in Ubon Ratchathani.
3. To describe the classification and characteristics of rheumatological melioidosis cases.

CHAPTER III
LITERATURE REVIEW

Risk factors

Melioidosis is a seasonal disease in endemic areas. In Thailand, 90% of cases occur during rainy season months from late May to mid-October (Chaowagul et al., 1989). It mainly affects people who have direct contacted with wet soils and have an underlying predisposition to infection. These are patients with diabetes mellitus, renal disease, cirrhosis, thalassemia, alcoholism, or those who are immunosuppressed as the result of either disease or drug treatment. However, melioidosis does not seem to be associated with HIV infection (Kanai et al., 1992; Chierakul et al., 2004). The most common underlying disease in melioidosis patients is diabetes mellitus, in which nearly 50% of patients with melioidosis have diabetes mellitus (DM), usually maturity onset diabetics, often with evidence of poor control of blood glucose before infection. Melioidosis may present at any age; peak incidence is in the fourth and fifth decades of life, coinciding with development of underlying predisposing illness (White, 2003).

Epidemiology

Melioidosis is regarded as endemic to Southeast Asia and northern Australia. The endemic area includes Northeast Thailand, northern Australia, Singapore, Malaysia, Myanmar and Vietnam. In Thailand, *B. pseudomallei* is widely distributed in soil and, more particularly, in pooled surface water such as in rice paddies (Wuthiekanun et al., 1995). In Northeast Thailand, between 1987 and 1991, the average annual incidence was estimated to be 4.4 per 100,000, but this number is increasing steadily with the demographic transition, since improved health services and economic conditions allow people to live longer (White, 2003).

Mode of transmission

Melioidosis in man is usually acquired by inoculation or inhalation, but not by ingestion. Occasional nosocomial infections have ever been reported (Ashdown, 1979), and infection can be acquired in the laboratory (Green and Tuffnell, 1968). Vertical transmission at childbirth as well as sexual transmission has also been reported (Lumbiganon et al., 1988; Halder et al., 1993; Abbink et al., 2001; McCormick et al., 1975). Rice farmers incur many minor cuts and abrasions while immersed for much of the day in water containing *B pseudomallei*, but they do not develop active infection unless an underlying predisposing condition develops. Overall the risk of disease is roughly proportional to the concentration of organisms in the soil (Smith et al., 1995).

Clinical features

Pneumonia is the most common presentation of melioidosis and is involved in approximately half of all cases (45-58%) from all reports. Other clinical manifestations include bacteremia (43-58%), skin or soft tissue infection (13-24%), septic shock (16-30%), genitourinary infection (7-19%), organ abscess (7-18%) (liver, spleen, intra-abdomen, prostate, parotid gland), bone or joint infection (4-12%), neurological involvement or brain abscess (3-6%) and pericardial effusion (1-3%) (Cheng and Currie, 2005).

Bone and joint infections are not rare and may be difficult to differentiate from other causes of infection, except that the systemic features of the illness may be more prominent. Surgical drainage is often required, together with long courses of intravenous antibiotics (Popoff et al., 1997). Skin and soft tissue infections are common and may be due to the source of systemic infection or result from hematogenous spread. Skin and soft tissue lesions may progress rapidly and resemble necrotizing fasciitis from other organisms (Wang et al., 2003).

Markers of organ dysfunction, including leukopenia, (particularly lymphopenia), hepatic dysfunction, renal dysfunction, and metabolic derangements (hypoglycemia and acidosis), on admission appear to predict mortality (Chaowagul et al., 1989; Cheng et al., 2003; Currie et al., 1993).

Diagnosis

Isolation of *B. pseudomallei* from bodily fluids of patients remains the "gold standard" for diagnosis. Culture should be performed on routine blood agar and Ashdown's selective medium (Walsh and Wuthiekanun, 1996). Swabs from contaminated sites should be incubated in a selective broth to increase the yield of detection (Walsh et al., 1995).

Gram stain of *B. pseudomallei* shows bipolar staining, so called 'safety-pin appearance', but this is not specific. A number of techniques have been employed to reduce the time required to achieve a diagnosis, including antigen detection on specimens or on culture supernatant, antibody detection, molecular techniques, and rapid culture techniques. Although many of these rapid tests have been developed, few have been extensively tested in the field, and only IHA and immunofluorescent test are currently used clinically (Cheng and Currie, 2005).

Management

The response to therapy is often poor, with a median duration of fever of nine days. Treatment failure has been defined in study as fever for longer than 14 days or bacteremia for longer than seven days (Simpson et al., 1999). Persistent positive cultures from other sites and radiological abnormalities are not uncommon and do not necessarily portend a poorer prognosis (Currie et al., 2000 [i]; Suputtamongkol et al., 1994).

Melioidosis is difficult to treat, and response to treatment is often disappointingly slow, despite administration of high dose parenteral antibiotics. There are two phase treatments, induction therapy for acute phase and oral eradication therapy for maintenance phase. The antibiotic of choice for acute phase is ceftazidime (White et al., 1989). Other third generation cephalosporins are less effective. Carbapenems kill *B. pseudomallei* more rapidly than ceftazidime does (Simpson et al., 1999). Parenteral amoxicillin-clavulanate has been associated with similar mortality but a higher rate of treatment failure compared with ceftazidime (Suputtamongkol et al., 1994). Cefoperazone-sulbactam has also proved effective (Chetchotisakd et al., 2001).

Systemic infections respond very slowly to specific treatment. Patients with large abscesses or empyema often have fluctuating fevers for more than one month. Physicians who are not experienced in the management of melioidosis often switch antibiotic treatment prematurely, fearing the emergence of drug resistance (White, 2003).

High dose parenteral treatment should be given for at least 10 days for systemic infections and the oral switch treatment should only be made when there is a clear evidence of clinical improvement. Enlargement of an abscess or appearance of new abscesses, especially in skeletal muscle, or seeding to a joint, is not uncommon in the first week of treatment, and is not necessarily a sign of treatment failure. Blood cultures should be negative by the end of the first week of oral treatment, whereas infected sputum or draining abscesses can remain culture-positive for one month in infections that are responding to treatment (White, 2003).

Oral eradication treatment was a conventional four-drug combination; chloramphenicol, doxycycline, trimethoprim, and sulfamethoxazole (TMP-SMX). Chloramphenicol is usually given for the first four weeks whereas doxycycline and TMP-SMX are continued to complete a full 20 weeks of treatment (Rajchanuvong et al., 1995). Current study showed that a combination of TMP-SMX and doxycycline is as effective as and better tolerated than the conventional four-drug regimens (Chaowagul et al., 2005). In pregnant women or children, high dose of amoxicillin-clavulanate can be given as an alternative (Suputtamongkol et al., 1991).

Despite this long antibiotic course, the rate of relapse is about 10%, which rises to nearly 30% if antibiotic treatment lasts for 8 weeks or less (Rajchanuvong et al., 1995; Chaowagul et al., 1999; Currie et al., 2000 [ii]; Suputtamongkol et al., 1991; Chaowagul et al., 1993). In Thailand, the median time to relapse is 21 weeks. Risk of relapse is related to adherence to treatment and the initial extent of disease, but not to the underlying condition (Chaowagul et al., 1993). The prognosis of melioidosis is much better in children than in adults, and relapse is rare. Adult patients require follow-up throughout their lives (White, 2003).

Rheumatological melioidosis

Regarding our interest in rheumatological melioidosis, there have been limited complete case analyses over the last ten years; only three important studies have been published (Kosuwon et al., 2003; Kosuwon et al., 1993; Popoff et al., 1997). Two of them (Kosuwon et al., 2003; Kosuwon et al., 1993) came from the same group of investigators and patients but different period of time in Khon Kaen where high prevalence (27%, 27/100) of musculoskeletal melioidosis was ever reported (Chetchotisakd et al., 2001). One took place from 1988 to 1991 (Kosuwon et al., 1993), and the other from 1997 to 2000 (Kosuwon et al., 2003). These two papers compared melioidosis patients with non-melioidosis patients resulting from other bacterial infection. Kosuwon (1993) reviewed the patients with bone, joint and muscle infections, and Kosuwon (2003) enrolled those of joint infection only.

In the report of Kosuwon (1993), they compared 21 cases of musculoskeletal melioidosis with 39 control patients of musculoskeletal infections from other bacteria. The most common underlying diseases found in those melioidosis patients were DM (33%) and thalassemia (5%). 52% of musculoskeletal melioidosis cases presented with sub-acute duration (2—4 weeks) of symptoms, 29% of chronic duration (more than 4 weeks), and 19% of acute duration (less than 2 weeks). The most frequently involved location was knee (33%).There were five cases with melioidosis osteomyelitis and four cases with melioidosis pyomyositis. All melioidosis patients were managed with operative debridement and a combination of drugs -- usually TMP-SMX, doxycycline, and kanamycin or chloramphenicol -- for six months. The mean duration of follow-up was one and a half years. Of the twenty-one patients, eighteen had an excellent or good outcome in terms of motion of the joint and absence of relapse.

Kosuwon (2003) conducted a similar retrospective study of 77 patients with septic arthritis, of which 25 of the patients had melioidosis septic arthritis, and 52 had non-melioidosis septic arthritis. The most common underlying diseases found in those melioidosis patients was DM (72%). 44% of musculoskeletal melioidosis cases presented with sub-acute duration of symptoms, 16% of chronic duration, and 40% of acute duration. The most frequently involved location was shoulder (32%). Patients with melioidosis septic arthritis differed significantly from those with non-melioidosis septic arthritis with regard to the frequency of diabetes mellitus (OR 15.7, CI 4.5 to

55.6) and to the involvement of upper-extremity joints (OR 4.51, CI 1.04 to 19.65). 88% (22/25) of patients with melioidosis septic arthritis responded to treatment, which were six months of antibiotic therapy combined with needle aspiration (36%), as well as surgical drainage of the affected joints when clinically indicated (64%).

Popoff (1997) published the result of prospective study of 115 patients presenting with melioidosis between 1989 and 1995. Only four patients were found to have osteomyelitis. Infection often but not always occurred in well-recognized risk groups, especially diabetic and alcoholic. Subacute presentations usually mimicked other disease processes and patients were not always clinically sepsis. Patients underwent surgical drainage and received combined antibiotics treatment which always included at least two weeks of intravenous ceftazidime and three to six months of oral eradication therapy. Relapse usually occurred in non-compliant patients. The author concluded that due to the potential long latency of the disease and the possibility of reactivation, follow-up should probably be life-long.

Other sporadic case reports highlighted the importance of the disease mimicking TB spondylitis (Wilairatana P and Wilairatana V, 1994) and involvement of unusual sites. Large joints and axial bones (vertebral bodies and iliac bone) were commonly involved. The involvement of odd joints such as the sternomanubrial or sacroiliac joint was occasionally reported (Borgmeier and Kalovidouris, 1980; Diamond and Pastore, 1967).

From the reports of Kosuwon (1993), Popoff (1997) and Wilairatana (1994), twenty-three melioidosis osteomyelitis cases with involvements of long bone and spine included 22%(5/23) of humerus involvement, 22%(5/23) femur, 22%(5/23) tibia, 30.4%(7/23) lumbar spine, and 4.3%(1/23) iliac bone. There were five melioidosis pyomyositis cases from the reports of Kosuwon (1993) and Yee (1994), including two patients with Psoas muscle abscess, two with calf muscle abscess, one with paravertebral muscle abscess, and one with suprapinatus muscle abscess.

The clinical appearance of musculoskeletal melioidosis can mimic acute or chronic forms of other infections or rheumatoid disorders (Kosuwon et al., 1993). Latent melioidosis is well recognized, with intervals up to 26 years prior to the development of clinically recognizable disease having been reported (Mays and Ricketts, 1975).

A diagnosis of melioidosis septic arthritis or osteomyelitis should be considered when septic arthritis or osteomyelitis is seen in an individual who is indigenous to or has ever visited certain area of Southeast Asia. Diagnosis requires a high index of clinical suspicion and depends on aggressive microbiological confirmation. It is important for physicians to keep alert for this condition so that early and appropriate treatment can be instituted to reduce mortality and prevent long-term morbidity.

CHAPTER IV
MATERIALS AND METHODS

Study design:

This study is a retrospective study.

Study site

The study will be carried out at Sappasithiprasong Hospital in Ubon Ratchathani. Ubon Ratchathani is located in the Northeast Thailand. The hospital is the 1000-bed, regional referral center of the lower part of Northeast Thailand.

Study population

Records of culture-proven melioidosis patients who were admitted to Sappasithiprasong hospital during 2002 to 2005 were eligible for this study.

Inclusion criteria:

We enrolled culture-proven melioidosis patients admitted to the hospital during the above period.

Culture-proven melioidosis patients are defined as patients who had *B. pseudomallei* isolated from at least one of their clinical specimens, including blood, sputum, throat swab, synovial fluid, pleural effusion, urine or pus.

Exclusion criteria:

The patients who were eligible for study but most of their clinical details essential for this study were missing would be excluded.

Sample size

We use the following formula to estimate the sample size.

$$n = ([Z_{\alpha/2}]^2 pq)/\delta^2$$

n: number of sample

p: prevalence; q = 1-p

δ: error allowance, if power is 95%, then δ equals to 5% divided by 2

$Z_{\alpha/2} = 1.96$, if α (type I error) = 0.05

The prevalence of rheumatological involvements in melioidosis derived from previous three reports which were 27% of melioidosis patients with musculoskeletal involvements in Khon Kaen (Chetchotisakd et al., 2001), 9.8% of those with bone and joint involvements in Ubon Ratchathani (Simpson et al., 1999) and 5% of those with bone and joint involvements from Thailand Infectious Diseases Association series reported from four hospitals in Northeast Thailand and two hospitals from Central Thailand (Punyagupta, 1989). According to this information, we chose the prevalence conforming to our study site - Ubon Ratchathani. We set the prevalence at 10%, a power of 95% and an error allowance of 0.025.

$$n = \frac{(1.96)^2(0.1)(0.9)}{(0.025)^2} = 553$$

Therefore, the sample size should be at least 553. The estimated sample size is 600. Taking into account an annual incidence of melioidosis in Ubon Ratchathani (around 200 cases per year), we decided to conduct retrospective study over three years period starting from 2002 to 2005.

Operational definition:

Patients with rheumatologic involvements are defined as patients whose either joints, bones or muscles were affected.

The definitions of clinical spectrum include the following:

1. Arthritis: arthralgia with swelling and limited range of joint motion.
2. Osteomyelitis: diagnosed either by surgical/aspirated pus or by imaging study (x-ray or CT)
3. Pyomyositis: diagnosed from either one of the following -- Ultrasonography, CT or pus aspiration

4. Recurrent infection is defined as a new presentation with acute culture-confirmed melioidosis after resolution of symptoms and completion of at least the effective parental antibiotics treatment for 10-14 days and oral effective antibiotics at least 12 weeks or up to 20 weeks (Currie et al., 2000 [ii]).

Clinical assessment:

1. Demographic profiles: sex, age, and occupation.
2. Risk factors: diabetes mellitus, thalassemia, renal calculi, chronic liver or renal diseases, drug/alcohol abuse, major trauma and near drowning.
3. Clinical details: previous medications (antibiotics, steroids, oral hypoglycemic agent and insulin); presenting symptoms and duration from onset until hospitalization; duration of rheumatologic symptoms; other associated organ involvements; location, pattern and number of involved joints, bones and muscles.
4. Microbiological data: culture from any sites and antibiotics sensitivity pattern
5. Management: other combined infections; fever clearance time (FCT); surgical intervention; duration of hospitalization; morbidity and systemic complications and local complications, which include sinus tract, deformity, and limited range of motion (R.O.M.).
   FCT is defined as the period from effective antibiotics treatment to defervescence starting at the point at which temperature remains less than 37.5^{o}C for 48 hours.
6. Antibiotics: parenteral and oral antibiotics regimens and duration.
7. Laboratory: on admission and follow-up tests – complete blood count and WBC differentiation〔WBC, Hb, PLT, neutrophils (%), lymphocytes (%)〕, renal function (BUN, Cr), liver function (SGOT, SGPT, ALK-P, Bil [T, D]), blood sugar, acidosis (HCO_3^-).
8. Outcome: died within 48 hours after treatment (early death), died after 48 hours of treatment (late death), mortality, switching of antibiotics and recurrent infection.

Data collection:

Individual clinical assessments associated with the interest of this research will be set up through a case record form (Appendix). Data will be entered and stored in computer using Microsoft Excel Program, before transferring into SPSS for analysis.

Data analysis:

Data were analyzed using SPSS version 11.0.0 (SPSS, Inc., Chicago, IL) software. Data from the Microsoft Excel files will be retrieved to the SPSS database for further analysis. Continuous data will be presented as means and standard deviations (for normally distributed data) or medians and range (for non-normally distributed data). Categorical data will be presented as numbers and percentages, respectively. We used non-parametric tests for non-normally distributed data with Mann-Whitney *U* test for two unpaired groups and Kruskal-Wallis test for three or more unmatched groups. Categorical data was compared with the $\chi 2$ test or Fisher exact test, as appropriate. Multiple logistic regression (backward selection) was performed for the prediction of the independent contributing factors which were expressed by odds ratio and 95% confidence interval. Survival analysis was performed using Kaplan-Meier method, with groups compared using log-rank test or Wilcoxon test, as appropriate. The P-value of ≤ 0.05 is accepted as statistical significance.

CHAPTER V
RESULTS

Demographic profile

From February 2002 to May 2005, we reviewed 679 culture confirmed melioidosis patients. Of these there were 98 (14.4%) patients had rheumatological involvement. We divided all melioidosis cases into two groups, rheumatological and non-rheumatological groups and compared both groups from different aspects.

The demographic profile was shown in Table 1. Gender and age distribution were significantly different between two groups. Female patients constituted 49.0% (48/98) in rheumatological group compared with 38.0% (221/581) in non-rheumatological group (P=0.04). Age range from 41 to 60 yr comprised 62.2% (61/98) and 45.8% (266/581) of cases in rheumatological and non-rheumatological groups (P=0.003). If we categorized age group as children and adult, there was no difference between two group (P=0.13). Or if we categorized age group as aged over 45 years and under 45 years, there was also no difference between two groups (P=0.86). 75.0% (494/656) of melioidosis patients were rice farmers with 83.0% (79/90) in rheumatological group and 74.0 %(415/566) in non-rheumatological group (P=0.05).

Risk factors

Risk factors were listed in Table 2. There were 23.0% of melioidosis cases of no known risk factor. Non-rheumatological group had significantly patients of no known risk factor than that of rheumatological group ($p<0.001$). From univariate analysis with individual known risk factors, there were significantly different in DM and thalassemia between two groups. Sex and age were not the risk factors for rheumatological involvement in multiple logistic regression analysis adjusted for age, sex, DM, thalassemia, CRF, renal calculi and steroid use. In the final model, DM (OR, 2.49; 95%CI, 1.41-4.39, $P = 0.002$), and thalassemia (OR, 9.56; 95%CI, 2.47-37.07, P

= 0.001) were independent risk factors for rheumatological involvement of melioidosis.

Presenting symptoms/signs and physical examination

Regarding the duration of symptoms or signs (S/S) before admission, rheumatological group had significantly longer duration (median 14 days, range 0-150 days) than non-rheumatological cases (median 7 days, range 1-365 days) (*P*=0.002) (Table 3). We classified the duration of S/S into three categories -- acute duration which was defined as S/S presented in less than two weeks, subacute duration as those within two to four weeks, and chronic duration as those over four weeks. Using Chi-square test for acute, subacute and chronic duration, we found there was significant difference between two groups (*P*=0.006). Therefore we analyzed each duration and found non-rheumatological group had 58.8% (340/578) of acute duration significantly more than 42.7% (41/96) in rheumatological group (*P*=0.003). There was no difference for subacute or chronic duration between both groups (*P* >0.01) (Table 4). The most frequent presenting symptoms and signs were fever (85.4%), cough (37.4%), dyspnea (35.5%), sputum (23.3%) and chill (20.0%). Rheumatological cases presented with abscess significantly higher than non-rheumatological cases (*P*=0.001). Non-rheumatological cases presented with dyspnea, cough, sputum, loin pain, anorexia and abdominal pain significantly higher than non-rheumatological cases. Physical examinations revealed the highest body temperature during the hospital stay in rheumatological cases was significantly higher than that in non-rheumatological cases (*P*=0.01) (Table 3).

Laboratory parameters

Laboratory parameters were in Table 5. Rheumatological cases had higher WBC, platelet counts and HCO3 level than non-rheumatological cases significantly (*P*=0.046 for WBC, *P*=0.003 for platelet, *P*=0.007 for HCO3). Non-rheumatological cases had more elevated serum creatinine than rheumatological cases significantly (*P*=0.038). Local pus cultures were performed from 73 rheumatological cases, and 91.8% (67/73) were positive. There were 56.4% (380/674) for positive blood culture in all melioidosis cases with no difference in both groups.

The longest duration of positive local pus culture in rheumatological cases was 56 days after admission (n=67, median 6, range 0-56). There were limited resistance strains of *B. pseudomallei* in melioidosis cases. In rheumatological group, susceptibility profile showed only three cases whose bacterial isolates were resistant, with one strain of ceftazidime (CAZ) resistance and two strains of intermediate resistance of doxycycline and chloramphenicol. In non-rheumatological group, there were six cases whose bacterial isolates were resistant, with three strains of chloramphenicol resistance, two strains of doxycycline intermediate resistance, one strain of CAZ and co-amoxiclav intermediate resistance.

Overall tissue/organ involvements

For overall tissue or organ involvements, melioidosis cases had 35.5% (231/650) of lung, 17.4% (113/650) of soft tissue, 10.6% (69/650) of spleen, 10.0% (65/650) of liver, 5.5% (36/650) of parotid, 1.4% (9/650) of kidney, and CNS 0.8% (5/650). There was no significant difference between two groups except involvements of soft tissue and lung. Soft tissue involvement was significantly higher in rheumatological cases with 37.9% (77/95) when compared with non-rheumatological cases 13.9% (36/555) (P<0.001). Non-rheumatological cases had more lung involvement with 38.2% (212/231) in comparison with rheumatological cases 20% (19/95) (P<0.001). There were no differences in the involvements of liver and spleen, 9.5% (9/95) and 11.6% (11/95) in rheumatological cases; 10.1% (56/555) and 10.5% (58/555) in non-rheumatological cases, respectively. Overall, there was 56.4% (380/674) of patients with septicemia which was not different between two groups.

Complications

Complications were listed in Table 6. There were 83.5% (560/671) melioidosis patients with complications and of no difference between two groups for overall complications. The frequent complications in melioidosis were anemia 51.3% (256/499), hypotension 35.5% (229/648), respiratory failure 30.9% (207/670), acute renal failure 27.9% (187/671), and jaundice 16.4% (110/671). When we inspected individual complication between two groups, we found anemia, hypotension, respiratory failure, and mechanical ventilation were significantly different.

Complication of anemia was 63.9% (46/72) of rheumatological group higher than 49.2% (210/427) of non-rheumatological group (*P*=0.02). Hypotension, respiratory failure, and mechanical ventilation were found more frequently in non-rheumatological group than those in rheumatological group (*P*=0.02 for hypotension, *P*=0.02 for respiratory failure, *P*=0.004 for mechanical ventilation).

Treatment

Initial parenteral antibiotics regimens were shown in Table 7. There were 82.0% (432/526) of melioidosis cases received CAZ-based parenteral antibiotics, 16.0% (84/526) of co-amoxiclav (AUG)-based parenteral antibiotics and 2.0% (10/526) imipenem (IMP)-based. There was no difference regarding initial parenteral treatment for both groups.

For all melioidosis patients, initial parenteral treatment did not affect survival outcome (*P*=0.922). Among 366 survivors, we excluded the switching of antibiotics resulting from drug toxicity; therefore, the reasons for switching of antibiotics in our group might be associated with switching after any laboratory evidence suggestive of melioidosis, poor response, or treatment failure. Antibiotics switch were found 71.9% (44/64) in the group of initial parenteral treatment with co-amoxiclav or others antibiotics which were more significant than 28.1% (18/64) of antibiotics switch in the group of CAZ or IMP (*P*<0.001) (Table 8). It was also applied to either rheumatological or non-rheumatological group (each group, *P*<0.001). From analysis of survived cases, rheumatological cases underwent significantly more switching of antibiotics than non-rheumatological cases (*P*=0.002). There was no difference in the median time of total duration of parenteral treatment between two groups (Table 8).

Oral antibiotics regimens among survived cases were in Table 9. There were 14.3% (40/280) of non-rheumatological cases who did not receive oral antibiotics; which was significantly more than rheumatological cases (3.2%) (*P*=0.02). For patients receiving different kinds of oral antibiotics regimens, there was no difference between two groups. Up to 50.8% (32/63) of rheumatological cases received dual therapy (cotrimoxazole and doxycycline), 25.4% (16/63) co-amoxiclav, 14.3% conventional therapy (chloramphenicol, cotrimoxazole and doxycycline), 6.4%

cotrimoxazole or doxycycline. There were several reasons for patients with no oral antibiotics, such as they were discharged against advice or were transferred to other local hospital for further parenteral treatment.

Outcome

Mortality, fever patterns and FCT (fever clearance time) were listed in Table 10 and Figure 1. Non-rheumatological group had significantly higher mortality (P=0.001) and higher proportion of patients who had never cleared fever before discharging (P=0.02) than those in rheumatological group. From Mann-Whitney test for analysis of median time for FCT among survived cases, rheumatological cases had significant longer FCT (median 12.8 days, range 0-81.3 days) than non-rheumatological cases (median 7.2 days, range 0-56.0 days). But from Kaplan-Meier survival analysis of FCT (in days), excluding patients who had no fever before treatment was started and censoring patients at discharge without clearing of fever, there was no difference of time to 50% of patients who were defervescent between two groups (P=0.058, log-rank test).

Among patients who survived, rheumatological group had significantly longer hospital stay〔median (95%CI) for rheumatological group, 22(19.4-24.6); for non-rheumatological group, 14(13.0-15.0); P<0.001, log-rank test〕and more recurrent infections (P=0.005) than non rheumatological group (Table 11 and Figure 2). Co-infections of other pathogens cultured from any sites during hospital stay were listed in Table 12. Gram negative bacilli co-infections predominated (74.3%) in all melioidosis patients. There was no difference between two groups. The most frequent co-infected pathogens were *Acinetobacter spp.* (26.9%), *Klebsiella spp.* (23.7%) and *Pseudomonas spp.* (19.4%) for all melioidosis cases. Nearly one third (31.2%) of co-infections were composed of *Pseudomonas aeruginosa* (14.0%, 13/93) and *Klebsiella pneumoniae* (17.2%, 16/93).

Classification and characteristics of rheumatological melioidosis

Rheumatological cases were classified into three categories based on the involvements of joint, bone or muscle. The prevalence of rheumatological patients among all melioidosis population was 14.4% (98/679) with that of joint involvement (arthritis) 11.9% (81/679), bone (osteomyelitis) 3.6% (25/679), and muscle (pyomyositis) 3.50% (24/679). In rheumatologic group, patients with melioidosis arthritis comprised 82.7% (81/98), osteomyelitis 25.6% (25/98) and pyomyositis 24.5% (24/98). 29.7% (29/98) of rheumatological cases had overlapping involvements (Table 14). There were 20.5% (20/98) of cases involving joint and bone, and 12.3% (15/98) involving joint and muscle. Up to 20.5% (20/98) of melioidosis arthritis patients simultaneously had bone infection. There were 50.6% (41/81) of melioidosis arthritis cases presented with arthralgia (33.3%) or swollen joint (24.7%) before admission. When we only analyzed the arthritis group to find the relationship between duration of joint symptoms and signs and bone involvement, we found that 66.7% (8/12) of patients who had joint signs and symptoms for more than two weeks also had bone infection, which was significantly higher than 24.1%(7/29) of those who had no bone involvement (P=0.02) (Table 14).

Location of the involved areas was listed in Table 15. Lower extremity was the main target lesion site in each category with more than 70% involvements. Knee, ankle, and hip were the first three frequently involved areas in melioidosis arthritis patients; shoulder was the most frequently involved site in upper extremities. Femur and tibia were the most frequently involved sites for melioidosis osteomyelitis. Leg and thigh were the most frequently involved sites for melioidosis pyomyositis. Diabetes and rice farmer were not associated with lower extremity involvement (P > 0.05). 75.3% (61/81) of patients had mono-arthritis; the rest [24.7% (20/81)] of them had oligo-arthritis which included 17.3% (14/81) of two-joint involvement, 6.2% (5/81) three-joint, and 1.2% (1/81) four-joint. Twenty two percent (14/65) of patients with arthritis involving the lower extremities had more than one site involvement, in contrast to 5.6% (1/18) of those in the upper extremities. Involvement of only one location was 72.0% (18/25) in bone category and 83.3% (20/24) in muscle category. Involvement of more than one location was 28.0% (7/25) in bone category and 16.7% (4/24) in muscle category.

We analyzed the numbers of involved areas and the associated risk factors, clinical course and outcome in Table 16. We regarded the infection of adjacent joint, bone or muscle as the contiguous process of infection and counted them as the one-site involvement from clinical viewpoint. DM patients had significantly more involvements of more than one site (P=0.002). In survival analysis, patients with more than one-site rheumatological involvements had significantly longer median duration of parenteral antibiotics compared with one-site involvement group (22 vs. 16 days, respectively; P=0.006, log-rank test). There were no significant differences in duration of symptoms and signs, complication, mortality, switching of antibiotics and hospital stay between two groups. In multiple logistic regression analysis adjusted for DM, thalassemia, sex, age, complication, switching of antibiotics, and duration of S/S, we found DM (OR; 8.64, 95% CI; 1.51-49.6, P=0.015) was the only independent risk factor for multiple-site rheumatological involvement. There were nine diabetes patients who had extensive infection (involving joint, adjacent bone, muscle and soft tissue) but were classified to the one-site of infection. Median duration of symptoms and signs before admission for these nine cases was 21 days (range 7-150 days), which was considered to be longer than median duration of symptoms and signs in overall rheumatological patients (n=96, median 14 days, range 0-150 days); in another word, these nine patients had delayed medical attention.

In addition to parenteral treatment, rheumatological cases received local intervention for adjunctive treatment (Table 17). Intervention included aspiration, arthrotomy and incision/drainage. Overall, 65.3% (64/98) of rheumatological cases received local intervention and 26.6% (17/64) of them had interventions more than two times. Intervention included 18.7% (17/91) of patients receiving needle aspiration and 55.1% (54/98) surgical treatments, of which comprised arthrotomy (31) and incision/drainage (31). Patients with intervention had significantly higher survival outcome than no intervention group (P<0.001). From analysis of survived rheumatological cases, we found there were no differences in the hospital stay, total parenteral treatment duration, antibiotics switch, and FCT between two groups (Table 18). Sixty nine percents (68/98) of rheumatological cases had initial leukocytosis and 3.0% (3/97) suffered from weight loss. Local rheumatological complications included limited ROM 35.6% (16/45), sinus tract 8.9% (4/45) and deformity 4.4% (2/45).

Table 1 Demographic profile

	Number of cases (%)			*P*-value
	Total (n=679)	Non-rheumatological (n=581)	Rheumatological (n=98)	
Male Female	410(60.0) 269(40.0)	360 (62.0) 221 (38.0)	50 (51.0) 48 (49.0)	**0.04**
Age-year Median (range)	49(1-86)	47 (1-86)	48 (3-86)	0.95
Age category-yr 0-20 21-40 41-60 61-80 > 81	 72(10.6) 129(19.0) 327(48.2) 140(20.6) 11(1.6)	 67 (11.5) 112 (19.3) 266 (45.8) 126 (21.7) 10 (1.7)	 5 (5.1) 17 (17.3) 61 (62.2) 14 (14.3) 1 (1.0)	**0.03** 0.06 0.65 **0.003** 0.09 1.00
Rice farmer	494/656(75.0)	415/566 (74.0)	79/90 (83.0)	0.05

Table 2 Past medical history and risk factors

	Number of cases (%)			*P*-value
	Total	Non-rheumatological	Rheumatological	
No known risk factor	126/679(23.0)	147/581(25.3)	9/98(9.2)	**<0.001**
DM	307/613(50.1)	246/524(46.9)	61/89(68.5)	**<0.001**
Thalassemia	11/679(1.6)	5/581(0.9)	6/98(6.1)	**0.002**
CRF	56/679(8.2)	51/581(8.8)	5/98(5.1)	0.22
Steroid	38/679(5.6)	30/581(5.2)	8/98(8.2)	0.23
Renal calculi	37/679(5.4)	31/581(5.3)	6/98(6.1)	0.75
TB	29/679(4.3)	28/581(4.8)	1/98(1.0)	0.11
CLD	13/679(1.9)	10/581(1.7)	3/98(3.1)	0.42
Trauma	13/679(1.9)	9/581(1.5)	4/98(4.1)	0.10
COPD	10/679(1.5)	9/581(1.5)	1/98(1.0)	1.00
SLE	7/679(1.0)	6/581(10.0)	1/98(1.0)	1.00
Hematological malignancy	7/679(1.0)	4/581(0.7)	3/98(3.1)	0.07
Gout	4/679(0.6)	2/581(0.3)	2/98(2.0)	0.10
Near drowning	4/679(0.6)	3/581(0.5)	1/98(1.0)	0.58

Table 3 Presenting symptoms and signs (S/S) and physical examination

	Number of cases (%)			*P*-value
	Total	Non-rheumatological	Rheumatological	
Duration of S/S N Median(range)	 674 9(0-365)	 578 7(1-365)	 96 14(0-150)	 **0.002**
Fever	579/678(85.4)	498/581(85.7)	81/97 (83.5)	0.57
Cough	254/679(37.4)	232/581(39.9)	22/98 (22.4)	**0.001**
Dyspnea	241/679(35.5)	232/581(39.9)	9/98 (9.2)	**<0.001**
Sputum	158/677(23.3)	149/580(25.7)	9/97(9.3)	**<0.001**
Chill	140/678(20.6)	122/580(21)	18/98(18.4)	0.55
Abdominal Pain	126/678(18.6)	118/580(20.3)	8/98 (8.2)	**0.004**
Abscess	120/678(17.7)	91/580 (15.7)	29/98 (29.6)	**0.001**
Anorexia	81/678 (11.9)	79/580 (13.6)	2/98 (2.0)	**0.001**
Diarrhea	51/678 (7.5)	48/580 (8.3)	3/98 (3.1)	0.07
Myalgia	48/678 (7.1)	42/580 (7.2)	6/98 (6.1)	0.69
Deterioration	36/678 (5.3)	33/580 (5.7)	3/98 (3.1)	0.28
Loin Pain	34/678 (5.0)	33/580 (5.7)	1/98 (1.0)	**0.047**
Dysuria	33/678 (4.9)	32/580 (5.5)	1/98 (1.0)	0.07
Jaundice	32/678 (4.7)	27/580 (4.7)	5/98 (5.1)	0.80
Headache	31/678 (4.6)	27/580 (4.7)	4/98 (4.1)	0.53
Chest pain	24/678 (3.5)	23/580 (4.0)	1/98 (1.0)	0.23
Confused	24/678 (3.5)	20/580 (3.4)	4/98 (4.1)	0.77
Back pain	17/678 (2.5)	14/580 (2.4)	3/98 (3.1)	0.72
Cellulitis	11/678 (1.6)	10/580 (1.7)	1/98 (1.0)	1.00
Convulsion	11/678 (1.6)	10/580 (1.7)	1/98 (1.0)	1.00
Highest BT N median (range)	 672 39.5 (35.0-43.0)	 577 39.5(35.0-43.0)	 95 39.9(3.0-41.0)	 **0.01**

BT: body temperature

Table 4 Duration of symptoms and signs before admission

	Number of cases (%)			*P*-value
	Total (n=674)	Non-rheumatological (n=578)	Rheumatological (n=96)	
Acute(< 2 weeks)	381 (56.5)	340(58.8)	41(42.7)	**0.003**
Subacute (2-4 weeks)	166(24.6)	134(23.2)	32(33.3)	0.03
Chronic (> 4 weeks)	127(18.8)	104(18.0)	23(24.0)	0.17

Table 5 Laboratory parameters

	Number of cases analyzed Median(range)			*P*
	Total	Non-rheumatological	Rheumatological	
WBC(cell/mm^3)	664 1210 (500-52720)	570 12010 (500-52720)	94 13100 (800-28500)	**0.046**
Hb(g/dl)	667 10.0(1.6-18.9)	573 10.1(1.6-18.9)	94 9.8(4.7-17.8)	0.11
PLT(x10^{5}cell/mm^3)	652 2.2 (0.1-10.0)	561 2.1 (0.1-9.7)	91 2.7 (0.3-10.0)	**0.003**
% Neutrophils	655 83 (24-99)	562 83(24-99)	93 84 (48-96)	0.85
% Lymphocytes	654 12(1-55)	561 12(1-55)	93 11(1-51)	0.73
% Eosinophils	669 0(0-14)	574 0(0-12)	95 0(0-14)	0.05
% Monocytes	668 2(0-18)	574 2(0-18)	94 2.7(0-14)	0.12
Na(mmol/L)	617 134(115-155)	528 134(115-155)	89 133(119-151)	0.07
K(mmol/L)	612 3.8(1.1-9.0)	524 3.8(1.1-9.0)	88 3.8(1.5-5.9)	0.25
HCO3(mmol/L)	609 18(3-39)	522 18(3-39)	87 20(5-34)	**0.007**
BUN(mg/dl)	620 27(3-302)	530 28(3-302)	90 22(4-212)	0.12
Cr(mg/dl)	620 1.6(0.3-36.7)	531 1.7(0.3-36.7)	89 1.5(0.5-8.9)	**0.038**
Glucose(mg/dl)	385 166(17-886)	318 164(21-886)	67 79(17-581)	0.48
Bil(T) (mg/dl)	300 1.4(0.1-38.5)	256 1.4(0.1-38.5)	44 1.4(0.1-21.6)	0.80
Bil(D) (mg/dl)	294 1.0(0.3-39.0)	250 1.0(0.3-39.0)	44 0.8(0.1-19.0)	0.80
SGOT(U/L)	307 78(19-107)	261 81(11-107)	46 70(15-250)	0.06
SGPT(U/L)	306 59(12-2315)	260 60(12-2315)	46 51(16-211)	0.08
Alk-P(U/L)	303 249(16-1480)	256 234(16-1480)	47 305(64-1250)	0.08
Albumin(g/dl)	246 2.4(0.8-6.5)	212 2.4(0.8-6.5)	34 2.2(1.4-5.2)	0.50
Globulin(g/dl)	218 4.3(0.5-7.6)	189 4.3(0.5-7.1)	29 4.5(1.2-7.6)	0.87
B/C (+) n(%)	380/674(56.4)	323/576(56.1)	57/98(58.2)	0.70

B/C: blood culture

Table 6 Complications

	Number of cases (%)			*P*-value
	Total	Non-rheumatological	Rheumatological	
Complication	560/671(83.5)	483/578(83.6)	77/93(82.8)	0.85
Anemia	256/499(51.3)	210/427(49.2)	46/72(63.9)	**0.02**
Hypotension	229/648(35.3)	207/557(37.2)	22/91(24.2)	**0.02**
Resp. failure	207/670(30.9)	188/577(32.6)	19/93(20.4)	**0.02**
MV	101/665(15.2)	96/571 (16.8)	5/94 (5.3)	**0.004**
ARF	187/671(27.9)	164/578(28.4)	23/93(24.7)	0.47
Jaundice	110/671(16.4)	96/578(16.6)	14/93(15.1)	0.71
Pancytopenia	15/490(3.1)	14/419(3.3)	1/71(1.4)	0.71

Resp. failure: respiratory failure; ARF: acute renal failure; MV: mechanical ventilation

Table 7 Initial parenteral antibiotics regimens

	Number of cases (%)		
	Total (n=526)	Non-rheumatological (n=437)	Rheumatological (n=89)
CAZ-based	432(82.0)	360(82.4)	72(80.9)
AUG-based	84(16.0)	67(15.3)	17(19.1)
IMP-based	10(2.0)	10(2.3)	0

1. CAZ (Ceftazidime); AUG (co-amoxiclav.); IMP (Imipenem); Doxy (Doxycycline); B (Bactrim or cotrimoxazole); CM (Chloramphenicol)
2. **Case number in each arm of initial parenteral antibiotics:**

CAZ-based regimens: only CAZ (381), CAZ+B(38), CAZ+CM(3), CAZ+Doxy (1), CAZ+AUG (9); **AUG-based**: only AUG(83), AUG+CM(1); **IMP-based:** only IMP(9); IMP+B(1)

Table 8 Antibiotics (ATB) switching, and total duration of parenteral antibiotics among survived cases

	Number of cases (%)			*P*-value
	Total	Non-rheumatological	Rheumatological	
Switching of ATB	64/331(19.3)	43/268(16.0)	21/63(33.3)	**0.002**
CAZ or IMP	18/64 (28.1)	10/43 (23.3)	8/21 (38.1)	
AUG or others	46/64 (71.9)	33/43 (76.7)	13/21 (61.9)	
Total duration of parenteral ATB				
N	330	267	63	
Median(range)	12(1-93)	12(1-93)	13 (2-52)	0.19

Table 9 Oral antibiotics regimens among survived cases

	Total(343)	Non-rheumatological(280)	Rheumatological(63)	*P*
None	42(12.2)	40(14.3)	2(3.2)	**0.02**
Dual therapy	133(38.8)	101(36.1)	32(50.8)	NS
Conventional	39(11.4)	30(10.7)	9(14.3)	NS
Cotrimoxazole	14(4.1)	11(3.9)	3(4.8)	NS
Co-amoxiclav	100(29.2)	84(30.0)	16(25.4)	NS
Doxycycline	15(4.4)	14(5.0)	1(1.6)	NS

Dual therapy (cotrimoxazole+doxycycline); conventional therapy (chloramphenicol+ cotrimoxazole+doxycycline); NS: non-significant

Table 10 Mortality, fever patterns and FCT (fever clearance time)

	Total	Non-rheumatological	Rheumatological	*P*-value
Mortality No (%)	285/651(43.8)	258/556(46.4)	27/95(28.4)	**0.001**
No fever	98/648(15.1)	89/556(16.0)	9/92(9.8)	0.12
Never defeverence	372/550(67.6)	325/467(69.6)	47/83(56.6)	**0.02**
FCT(days) N Median (range)	339※ 8.0 (0-81.3)	277 7.2 (0-56.0)	62 12.8 (0-81.3)	0.058*

* *P*-value from log-rank test by Kaplan Meier survival analysis

※ Survived cases: Median and range from Mann-Whitney test ($P<0.001$)

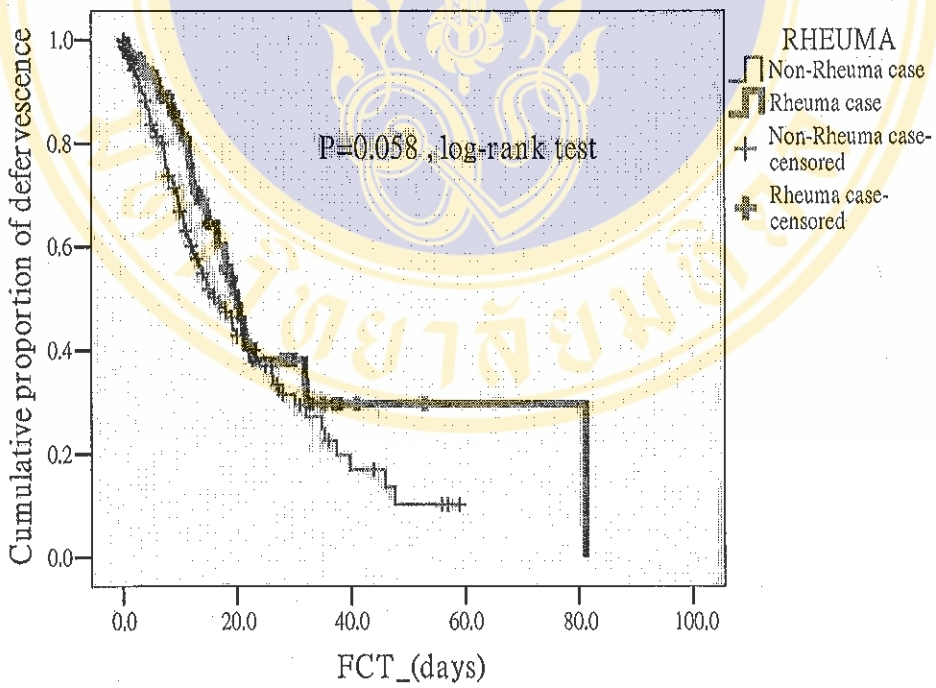

Figure 1. Kaplan-Meier survival curve for fever clearance time (FCT) comparing between rheumatological and non-rheumatological melioidosis groups

Table 11 Hospital stay, survival, recurrent infection and nosocomial infection

	Total	Non-rheumatological	Rheumatological	*P*-value
Nosocomial infection of melioidosis No (%)	14/643(2.2)	13/554(2.3)	1/89(1.1)	0.702
Survived	366/651(56.2)	298/556(53.6)	68/95(71.6)	**0.001**
Hospital stay(days) N Median(range)	360※ 14.0(1.0-93.0)	293 12.0(1.0-76.0)	67 20(3.0-93.0)	**<0.001***
Recurrent infection No (%)	19/366(5.2)	10/298(3.4)	9/68(13.2)	**0.005**

* *P*-value from log-rank test by Kaplan Meier survival analysis
※Survived cases: Median and range from Mann-Whitney test (*P*<0.001)

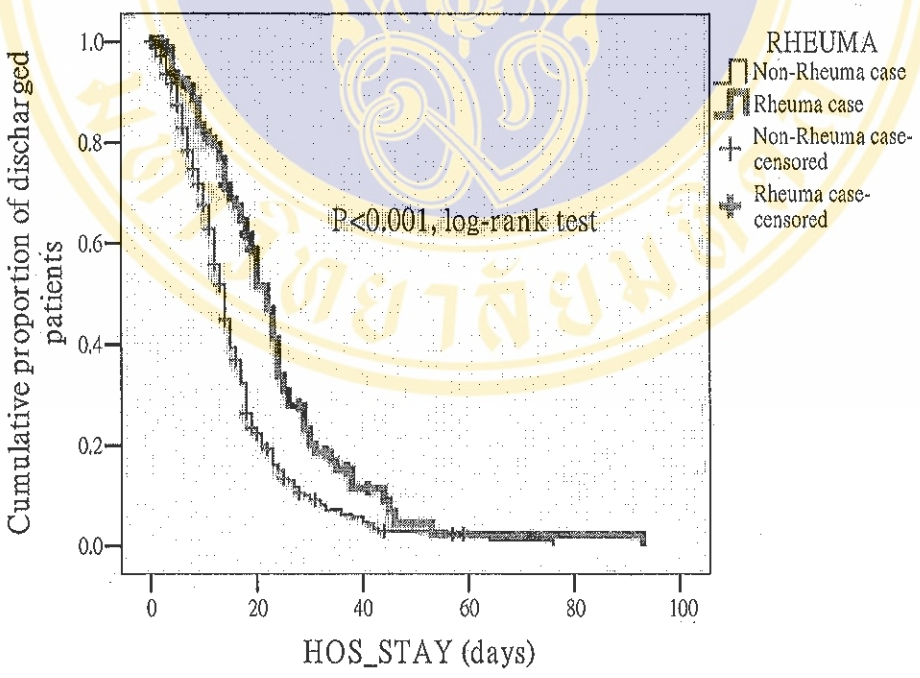

Figure 2 Kaplan-Meier survival curve for the duration of hospital stay comparing between rheumatological and non-rheumatological melioidosis groups

Table 12 Co-infections found in any specimens, including blood, sputum, urine, etc.

	Total (n=93)	Non-rheumatological (n=71)	Rheumatological (n=22)	*P*-value
Acinetobacter spp.	25(26.9)	18(25.4)	7(31.8)	NS
Klebsiella spp.	22(23.7)	18(25.4)	4(18.2)	NS
Pseudomonas spp.	18(19.4)	14(19.7)	4(18.2)	NS
Yeast	9(9.7)	6(8.5)	3(13.6)	NS
Staphylococcus spp.	8(8.6)	6(8.5)	2(9.1)	NS
Enterococcus spp.	5(5.4)	3(4.2)	2(9.1)	NS
Streptococcus spp.	2 (2.2)	2(2.8)	0	NS
E. coli	4(4.3)	4(5.6)	0	NS

Table 13 Joint, bone and muscle involvements in 98 rheumatological cases

Involved site	Number of cases (%)
Only joint	52(53)
Only bone	5(5.1)
Only muscle	12(12.2)
Joint & bone	17(17.4)
Joint & muscle	9(9.2)
Joint & bone & muscle	3(3.1)

Table 14 Bone involvement in melioidosis arthritis patients and duration of joint symptoms and signs (S/S) before admission

Duration of joint S/S	Number of cases (%)			*P* value
	Total (n=41)	Bone infection (n=12)	No Bone infection (n=29)	
Acute (<2 weeks)	26(63.4)	4(33.3)	22(75.9)	**0.02**
Non-acute (≧ 2 weeks)	15(36.6)	8(66.7)	7(24.1)	

Table 15 Involved location in rheumatological cases

	Joint(n=81)	Bone(n=25)	Muscle(n=24)
Lower extremity	65(76.0) Knee 41(40.6) Ankle 20(19.8) Hip 15(14.9) Foot 3(3.0)	19(76.0) Femur 12(48.0) Tibia 9(36.0) Foot 2(8.0)	17(70.8) Leg 9(37.5) Thigh 7(29.0) Calf 2(8.3) Buttock 1(4.2)
Upper extremity	18(21.0) Shoulder 10(9.9) Elbow 4(4.0) Wrist 4(4.0) Hand 1(1.0)	4(16.0) Humerus 2(8.0) Radial 1(4.0) Hand 2(8.0)	4(16.7) Around elbow 3(12.5) Forearm 2(8.3)
Others	3(3.0) Sacroiliac joint 2(2.0) Sternoclavicular joint 1(1.0)	3(12.0) T 10 spine 1(4.0) L4-5 spine 1(4.0) Skull 1(4.0)	3(12.5) Psoas 3(12.5)

* All numbers expressed as no (%)
T 10: 10th thoracic spine; L4-5: 4th -5th lumbar spine

Table 16 Risk factors, clinical course and the number of involved sites

	Number of cases (%)		*P*-value
	One site	More than one site	
Female	34/69 (49.3)	14/29 (48.3)	0.93
Age Median (range)	69 48 (3-71)	29 54 (26-86)	0.05
Duration of S/S Median (range)	68 14 (0-150)	28 14 (2-90)	0.44
DM	42/68 (61.8)	27/29 (93.1)	**0.002**
Thalassemia	5/69 (7.2)	1/29 (3.4)	0.67
Complication	54/66 (81.8)	23/27 (85.2)	0.77
Outcome			
Mortality	21/66 (31.8)	6/29 (20.7)	0.27
Antibiotics switch	14/62 (22.6)	9/26 (34.6)	0.24
Hospital stay Median (range)	45※ 19.0 (3.0-46.0)	22 23.0 (23.0-93.0)	0.07*
PT duration Median (range)	41※ 16.0 (2.0-40.0)	22 22.0 (9.0-81.0)	**0.006***

* *P*-value from log-rank test by Kaplan Meier survival analysis
※ Survived cases; Median and range from Mann-Whitney test (hospital stay, *P*=0.09; PT duration, *P*=0.01)

Table 17 Intervention of rheumatological cases

	No (%)	Number of intervention No (%)
Aspiration	17 /91(18.7%)	Once 16/17(94.1) Twice 1/17(5.9)
Surgical (arthrotomy or incision/drainage)	54/98(55.0%)	Once 51/54(94.4) More than once 3/54(5.6)
Overall intervention	64/98 (65.3%)	Once 47/64(73.4) More than once 17/64(26.6)

Table 18 Intervention and clinical outcome in rheumatological group

		Median (range)		*P*-value
		Intervention (n=63)	No intervention (n=30)	
Survived	N(%)	52/63(82.5)	14/30(46.7)	**<0.001**
Hospital stay (days) Median (range)	N	51※ 20 (3-93)	14 20 (5 -53)	0.83*
Total PT duration (days) Median (range)	N	48※ 17(3.0-81.0)	13 19.0(2.0-49.0)	0.53*
Antibiotics switch	N(%)	15/48(31.3)	5/13(38.5)	0.74
FCT(days) Median (range)	N	27※ 13.1(0.1-81.3)	9 12.2(8.2-32.2)	0.83*

* *P*-value from Wilcoxon test by Life table survival analysis

※ Survived cases: Median and range from Mann-Whitney test (P>0.05)

CHAPTER VI
DISCUSSION

Our study was the first to compare rheumatological and non-rheumatological groups among the melioidosis patients. There were several distinct features between two groups which were never reported before.

Age and gender distribution were different between rheumatological and non-rheumatological groups. Melioidosis may present at any age; peak incidence is in the fourth and fifth decades of life (White, 2003). A prospective population-based study about melioidosis epidemiology in Australia defined adjusted relative risks of 4.0 (3.2 to 5.1) for those aged more than 45 years and 2.4 (1.9 to 3.0) for males (Currie et al., 2004). Our rheumatological patients aged 41-60 years which were significantly more than those in non-rheumatological group. All series in Thailand, Australia, Malaysia, and Singapore demonstrate male preponderance in melioidosis cases (Cheng et al., 2005). Whereas, in our rheumatological melioidosis group, we observed female was significantly more predominant than non-rheumatological group. But from multiple logistic regression analysis of risk factors for rheumatological involvement, sex and age became confounding factors, which might coincide with development of underlying predisposing illness (White, 2003).

Melioidosis mainly affects people who have directly contacted with wet soils and have an underlying predisposition to infection. For soil/water exposure, rice farmers constitute 81% of patients in Thailand; relative risk in case-control study estimated at 3.3 (Suputtamongkol et al., 1999; Suputtamongkol et al.,1994〔i〕). 75.0% of our melioidosis cases were rice farmer and rheumatological melioidosis cases even up to 83.0%. Risk factors for melioidosis include diabetes mellitus, renal disease, cirrhosis, thalassemia, alcoholism, or those who are immunosuppressed as the result of either disease or drug treatment (Cheng et al., 2005). The most common underlying disease in melioidosis patients was diabetes mellitus (White, 2003). Between 37 to 60% of patients are diabetic, mainly type 2; case-control and

population-based studies in Thailand and Australia give estimated relative risk of 5.9 to 13.1 (Currie et al., 2000; Currie et al., 2004; Merianos et al., 1993; Suputtamongkol et al., 1999; Suputtamongkol et al., 1994〔i〕). α -thalassemia, beta-thalassemia and the hemoglobin variants E and Constant Spring (CS) are common in Thailand especially in the northeast part. These abnormal globin genes in different combinations lead to over 60 thalassemic syndromes. The frequency of α -thalassemia reaches 20-30% in some part of Thailand and that of beta-thalassemia varies between 3 and 9%. The frequency of HbE is attaining 50-60% at the junction with the Laos People's Democratic Republic and Cambodia. Case-control studies in Thailand estimate that patients with thalassemic diseases had relative risk of 10.2 for melioidosis infection (Suputtamongkol et al., 1999; Suputtamongkol et al., 1994〔i〕; Wanachiwanawin et al., 2000). From case-control studies of Kosuwon (1993 & 2003) comparing melioidosis musculoskeletal or septic arthritis (MSA) cases with non-melioidosis musculoskeletal or septic arthritis (non-MSA) cases, Kosuwon (1993) found 5/13 (38.4%) of MSA patients with thalassemia, 7/13 (54%) of MSA patients with DM, but no DM or thalassemia in non-MSA patients; Kosuwon (2003) found 72% (18/25) of MSA patients with DM (OR 15.7, 95% CI 4.50 to 55.6) compared with non-MSA patients (11.5%, 6/52).

Based on above reports, DM and thalassemia were very well-established risk factors for melioidosis; this study was the first to find both diseases contributing even higher risks to rheumatological melioidosis cases, compared with non-rheumatological melioidosis cases. From our study, 50% of our patients with melioidosis had diabetes mellitus. Up to 68.5 % of patients with rheumatological melioidosis had DM in comparison with non-rheumatological melioidosis cases (46.9%) and the odds ratio was 2.49 (95% CI 1.41 to 4.39). 6.1% of patients with rheumatological melioidosis had thalassemia disease in comparison with non-rheumatological melioidosis cases (0.9%) and the odds ratio was 9.56 (95% CI 2.47 to 37.07). It meant melioidosis patients with DM and thalassemia had 2.5 and 10 times independent risks, respectively of rheumatological involvement than non-rheumatological involvement.

The explanation for this strong association could be speculated from systemic and local factors of both diseases. DM, which would cause systemic compromised immunity, was also the important predisposing factor for bacterial

arthritis (Ross, 2005; Kaandorp CJ et al., 1995), osteomyelitis (Mader et al., 1997; Ramsey et al., 1999) and pyomyositis (Montserrat Chimeno et al., 1996). Thalassemia disease was also the risk factor for septic arthritis (Kosuwon, 1993) and hematogenous osteomyelitis (Strecker et al., 2004). The foremost risk factor for septic arthritis is pre-existing joint disease. Up to 47% of patients have prior joint problems (Kaandorp et al., 1997). A high index of suspicion for septic arthritis should be maintained in patients with other rheumatological conditions, such as RA, osteoarthritis, gout, pseudo-gout, recent trauma, prior joint surgery, and SLE (Ross, 2005).

In addition to systemic factors, DM and thalassemia disease themselves will cause arthropathy which might contribute to pre-existing joint disease and thus increase higher risk for septic arthritis. DM would cause osteoarthropathy, osteoporosis, osteoarthritis, and pseudo-gout (Hochberg et al., 2003). Thalassemia arthropathy is associated with hemochromatosis; the basic pathological change is resulted from osteoporosis. Osteoarthritis and pseudogout are the main clinical features in hemochromatosis-associated arthropathy (Faraawi et al., 1993; Schumacher et al., 1988; Pawlotsky et al., 1999). The chiefly involved sites for osteoarthritis or pseudogout are knee, ankle and shoulder (Hochberg et al., 2003), which are quite similar to the distribution in our melioidosis arthritis group. The peak age range for either DM arthropathy or hemochromatosis is within 40-60 yrs, which might explain the same peak age distribution in our rheumatological patients (Takabayashi, 2005; Hochberg et al., 2003; Sinigaglia et al., 1997; Faraawi et al., 1993). From these evidences, the combined effects of systemic and local factors might highly predispose patients to rheumatological involvement in melioidosis patients. It requires further study to prove.

57.3% of our rheumatological cases presented with subacute or chronic illness prior to admission, and in contrast, 58.8% of non-rheumatological cases manifested with acute illness, such as dyspnea, cough, sputum, anorexia, abdominal pain and mechanical ventilation. Over 50% of non-rheumatological cases had involvements of lung, liver and spleen, which could conform to the above acute illness. From Kosuwon (1993) report, the mean duration of the symptoms among their musculoskeletal melioidosis patients was 37 days (range, 5-210 days). For our rheumatological patients, the most common symptoms were fever (83.5%), and joint

symptoms (42.0%) of arthralgia or swollen joint; the median duration of the symptoms was 14 days (range, 0 -150 days). Our rheumatological cases had significantly higher skin or soft tissue abscess than non-rheumatological cases, because we enrolled pyomyositis into our rheumatological group; therefore it would be biased upon selection of cases regarding associated abscess.

Non-rheumatological cases had more significant acute and severe complications and thus resulted in higher mortality than rheumatological cases. The more frequent complications in non-rheumatological cases were hypotension, respiratory failure, elevated serum creatinine level and depressed HCO3 level. Whereas, chronic complication of anemia was found more in rheumatological cases significantly; which might be associated with more prolonged duration of illness, and more underlying diseases or known risk factors. Our rheumatological cases with known risk factors or underlying diseases (90.8%) were significantly higher than non-rheumatological group (74.7%). We found melioidosis patients with DM had significantly more survived cases (64.9%, 192/296) than melioidosis patients without DM (54.1%, 159/294) (P=0.008); which was also observed significantly in rheumatological group〔83.1% (49/59) vs. 63.0% (17/27)〕 (P=0.041), but not significant in non-rheumatological group. Though DM contributed to rheumatological involvement, it might also be related with more survival among this group. Only 58.2 % of the rheumatological cases could be diagnosed from blood culture, whereas from local pus culture, it was up to 91.8% positive rate. Prolonged existence of bacteria in the local pus could be cultivated even up to two months despite effective antibiotics treatment. If we analyzed 50.0% (41/81) of melioidosis arthritis cases with joint symptoms, we found 66.7% of positive blood culture and 80.6% of positive local pus culture irrespective of duration of illness. In addition to blood culture, it is imperative to obtain the specimens of local synovial fluid or pus aggressively for higher diagnostic yield in order to make earlier and appropriate management.

In this study, compared to initial parenteral treatment with CAZ or IMP, initial parenteral treatment with co-amoxiclav or others antibiotics caused significantly more antibiotics switch in either rheumatological or non-rheumatological group. Co-amoxiclav is frequently used as the empirical therapy for patients with suspected melioidosis and other infections which could not be ruled out, but once patients have

confirmed the diagnosis with melioidosis, the treatment will be changed to high dose ceftazidime as standard recommendation and this may be in part explain the high rate of switching treatment in our patients and this could not be interpreted as treatment failure of co-amoxiclav. However, data from previous clinical trial of co-amoxiclav in intensive therapy demonstrated a similar mortality as that of CAZ but a higher treatment failure rate requiring a change in antibiotics regimens (Suputtamongkol et al., 1994). The use of co-amoxiclav in intensive treatment of melioidosis especially in patients with rheumatological involvement should be avoided, since this group of patients is more likely to have treatment failure when compared with non-rheumatological melioidosis. This could be possibly associated with poor penetration of antibiotics, and prolonged hospital stay which might be prone to nosocomial infections. It needs further evaluation.

In addition to PT, rheumatological cases received local intervention for adjunctive treatment. Patients with intervention had significantly higher survival outcome than no intervention group. Nevertheless, if patients were in critical condition or expired very rapidly, they might have fewer chances to receive any intervention. Therefore we analyzed the survived rheumatological cases; we found there were no difference in the hospital stay, total PT duration, treatment failure, and FCT. The study of Kosuwon (2003) showed 88.0% (22/25) of patients with MSA responded to treatment which consisted of six months of antibiotics therapy combined with arthrotomy (64.0%, 16/25), as well as needle aspiration (36.0%, 9/25). There were 55.1% (54/98) of our patients receiving surgical intervention (arthrotomy or incision/drainage) and 18.7% (17/91) needle aspiration. The limitation of this study about intervention was we could not have the complete data about the total duration of oral antibiotics and drug adherence; therefore, it was restricted to evaluate the true impact of intervention upon long term outcome. The role and optimal indication of intervention for rheumatological melioidosis, from our result of limited cases, were still obscure.

Septic arthritis is managed with antibiotics combined with joint drainage by arthroscopy, arthrocentesis, or arthrotomy. Joint drainage decompresses the joint; improves blood flow; and removes bacteria, toxins, and proteases. Arthrocentesis should be repeated daily until effusions resolve and cultures are negative (Ross, 2005).

There is general agreement that surgical drainage is indicated for septic arthritis of the hip, failure to respond after 5 to 7 days of antibiotics and arthrocentesis, and soft tissue extension of infection. The shoulder joint should be drained either surgically or under radiological guidance (Pioro et al., 1997; Smith et al., 1995). Retrospective data suggest that patients with rheumatoid arthritis have better functional outcomes with surgical management (Gardner et al., 1990). No good data show a superiority of surgical drainage over arthrocentesis. In fact, one meta-analysis, and a more recent retrospective study, demonstrated better functional outcomes with arthrocentesis compared with surgery, although mortality was higher in patients treated with arthrocentesis (Weston et al., 1999; Broy et al., 1986). Selection bias probably explains these differences. Critically ill patients are poor surgical candidates, whereas otherwise stable patients with severe septic arthritis are more likely to undergo surgical drainage. Randomized, clinical trials of arthrocentesis compared with surgical or arthroscopic drainage are needed.

Our non-rheumatological group had more cases that never cleared fever than those in rheumatological group. But from Kaplan-Meier survival analysis for FCT, there was no difference between two groups. For analysis of survived melioidosis cases, rheumatological group had significantly longer hospital stay and more recurrent infections than non-rheumatological group. But there were no difference regarding antibiotics resistant strains and co-infections of other bacteria in both groups. 13.7% (93/679) of melioidosis patients with co-infections of other bacteria, among which 84.0% were gram-negative bacilli (*Acinetobacter spp. ,Klebsiella spp., Pseudomonas spp., E. coli*) and yeast, which seemed to be common nosocomial pathogens. The judgments between co-infections and nosocomial infections should be based on NNIS (national nosocomial infections surveillance system) from CDC of the United States (Emori et al., 1991), and it should be audited and interpreted by the trained staff of infection control. Under the pressure of prolonged strong and higher generations of antibiotics for melioidosis, it could be highly predisposed to nosocomial super-infections. But from this study, we cannot tell whether these co-infections exactly came from nosocomial infections for lacking of the standardized appropriate interpretation. It deserves further prospective study to investigate the true associations.

In Thailand, the prevalence of rheumatological involvements in melioidosis ranged from 5-27% (Punyagupta, 1989; Simpson et al., 1999; Chetchotisakd et al., 2001). From our study, the prevalence of rheumatological patients among melioidosis population was 14.4% (98/679) which was lower than 27.0% (27/100) of the study in Khon Kaen (Chetchotisakd et al., 2001) and the prevalence of joint or bone infection was 12.7% (86/679) which was higher than 9.8% (21/214) of the study in Ubon Ratchathani (Simpson et al., 1999). The latter study was performed at the same site of our study but done in severely ill patients only. According to our findings, patients with severe disease seemed to have less rheumatological involvement, so this might explain our higher prevalence of rheumatological involvement. The prevalence of our rheumatological cases by year was quite stable and ranged from 13.3% to 15.2%. There was 15.2% (26/171) in 2002, 13.3% (30/226) in 2003, and 14.7% (35/238) in 2004. The prevalence of joint involvement (arthritis) was 11.9% (81/679) bone (osteomyelitis) 3.6% (25/679) and muscle (pyomyositis) 3.5% (24/679). Among rheumatological cases, arthritis comprised 82.7% (81/98), osteomyelitis 25.6% (25/98) and pyomyositis 24.5% (24/98).

There was up to 20.5 % (20/98) of melioidosis arthritis patients simultaneously with bone infection. 50.6% of patients with melioidosis arthritis manifested with swollen joint (24.7%) or arthralgia (33.3%) before admission, within which we found patients with duration of joint symptoms more than two weeks were significantly prone to have simultaneous bone infection as well. Cartilage is avascular, and highly dependent on diffusion of oxygen and nutrients from the synovium. As purulent exudates accumulates, joint pressure increases, and synovial blood flow is tamponaded, resulting in cartilage anoxia and ischemia (Stevens et al., 1991). The joint infection can spread in the sub-chondral bone without treatment after one week and the tissue changes become irreversible (Goldenberg et al., 1985; Lane Smith et al., 1987). In acute osteomyelitis, the penetration of antibiotic therapy is impaired as the intraosseous pressure rises and the blood vessels become occluded by edema and micro-thrombi. At the time when an abscess has developed, the access of antibiotics to the infectious focus is very limited. Therefore, the antibiotics should be instituted within 2-3 days of onset of the clinical symptoms (Vaughan et al., 1987). For our findings, the spread of infection from joint to bone could be possibly associated

with the delayed appropriate management but still should be further elucidated.

In Kosuwon (2003) study, 44.0% (11/25) of MSA patients had the involvements of an upper-extremity joint, in contrast to only 21% (18/81) of those of our arthritis patients. This study showed lower extremity was the main target lesion site in each three categories with more than 70% of involvements. Knee (40.6%), ankle (19.8%), hip (14.9%) and shoulder (9.9%) were frequently involved sites in melioidosis arthritis patients. Actually the knee is the principal target of bacterial septic arthritis (Ross, 2005). 45% of septic arthritis cases in adults involve the knee (Kaandorp et al., 1997). Presumably, this is a consequence of the imperfect human adaptation to bipedal locomotion. The enormous stresses about the knee particularly predispose it to injury (Jones, 1995). Our result showed femur (48.0%) and tibia (36.0%) were the most frequently involved sites for melioidosis osteomyelitis; leg (37.5%) and thigh (29.0%) were the most frequently involved sites for melioidosis pyomyositis. Patients with melioidosis arthritis of the lower extremity were more prone to have more than one-site involvement (22.0%) than those of the upper extremity (5.6%). 80.0% (20/25) of patients with bone infection were also associated with arthritis and the predominant sites located in the femur and tibia, which conformed to the common involved sites on knee and ankle in melioidosis arthritis. The close association of anatomic relationships between joint and bone could be possibly the continuous process from joint to bone or vice versa (Alderson et al., 1986).

If we regarded the infection of adjacent joint, bone or muscle as the contiguous process of infection and counted them as the one-site involvement from clinical point of view. 30.0% (29/98) of rheumatological cases have two or more locations involved. Rheumatological patients with more than one-site involvements had a significantly longer median duration of total parenteral treatment. With multiple logistic regression, DM was the independent risk factor and showed 9-fold risk of more than one-site involvement for rheumatological melioidosis patients. From Dubost (1993), major risk factors for poly-articular septic arthritis are DM, SLE, RA and steroid therapy.

CHAPTER V II
CONCLUSION

This study comprised a retrospective review of culture-proven melioidosis cases at Sappasithiprasong Hospital, Ubon Ratchathani, northeastern Thailand, for the period February 2002-May 2005. The prevalence of rheumatological patients among the melioidosis population was 14.4% (98/679). Rheumatological patients tended to occur among females and those aged 41-60 years. Melioidosis patients with diabetes mellitus (DM) and thalassemia had 2.5 and 10 times independent risks, respectively of rheumatological involvement than non-rheumatological involvement. DM also showed 9-fold risk of more than one-site involvement for rheumatological melioidosis patients. Compared with non-rheumatological cases, rheumatological cases tended to have less severe clinical course—less mortality and less severe complications, including shock and respiratory failure. They also tended to have more chronicity— with subacute or chronic duration of symptoms, and with the complication of anemia. They were prone to prolonged hospital stay, changes in antibiotic therapy, and recurrent infections. Rheumatological patients with more than one-site involvement had prolonged treatment duration with parenteral antibiotics.

Melioidosis arthritis cases comprised most of the rheumatological patients (82.7%). Involvements of joint, bone and muscle overlapped; 80% of bone infections also had joint involvement, and 50% of muscle infections also had joint involvement. Melioidosis arthritis cases, like septic arthritis, were prone to involvement of the lower extremities. 21% of patients with melioidosis arthritis had bone infections, especially those with joint symptoms or signs > 2 weeks. Therefore, patients with melioidosis arthritis should be meticulously evaluated by X-ray of the adjacent long bones, or bone scans, to detect any occult metastatic bone infection during the course of hospital stay. In endemic areas, with presentation of fever, arthralgia and swollen joints, blood or local pus/synovial fluid for culture should be obtained aggressively for early diagnosis and the institution of appropriate antibiotics, to prevent adjacent bone infection.

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APPENDIX

APPENDIX

1. PATIENT CODE: ☐☐☐☐

Date of Completion:__/__/__

2. CULTURE PROVEN MELIOIDOSIS ☐

3. RHEUMATOLOGICAL MELIOIDOSIS

☐ (1) yes ☐ (2) no ☐ (9) unknown

4. DEMOGRAPHIC PROFILES

4.1 Age ☐☐ years

4.2 Sex ☐ (1) male ☐ (2) female

4.3 Residence: ☐ (1) Ubon Ratchathani ☐ (2) other ☐ (9) unknown

4.4 Occupation: ☐ (1) farmer ☐ (2) non-farmer ☐ (9) unknown

4.5 Admission to Hospital: ☐☐/☐☐/☐☐

4.6 Discharge from Hospital: ☐☐/☐☐/☐☐

4.7 Duration of symptoms before admission: ☐☐ days

4.8 Chronicity: ☐ (1.acute=0-13 days, 2.subacute=14-28 days, 3.chronic> 29 days; 9 unknown)

5. MEDICATION AND SUBSTANCE

5.1 Antibiotic Treatment prior to admission:

☐ (1) penicillins ☐ (2) macrolides

☐ (3) fluoroquinolones ☐ (4) TMP-SMX

☐ (5) cephalosporin ☐ (6) tetracyclines

☐ (7) other_____ ☐ (9) unknown

5.2 Duration: ☐☐ days

5.3 Current Medication: ☐ (1) insulin ☐ (2) oral hypoglycaemic

☐ (3) steroids ☐ (4) others ☐ (9)unknown

6. PRESENTING SYMPTOMS AND SIGNS

Symptom	Code*	Duration(days)	Comment
6.1 Fever	☐	☐☐	
6.2 Constitutional symptom	☐	☐☐	
6.3 Myalgia	☐	☐☐	
6.4 Arthralgia	☐	☐☐	
6.5 Swollen joint	☐	☐☐	
6.6 Back pain/loin pain	☐	☐☐	
6.7 Skin lesions	☐	☐☐	
6.8 Subcutaneous mass	☐	☐☐	
6.9 Cellulitis	☐	☐☐	
6.10 Muscle abscess	☐	☐☐	
6.11 Genitourinary symptom	☐	☐☐	
6.12 Central Nervous symptom	☐	☐☐	
6.13 Gastrointestinal symptom	☐	☐☐	
6.14 Respiratory symptom	☐	☐☐	

*(1) yes (2) no (9) unknown

Constitutional symptoms include chills, headache and malaise.

7. PHYSICAL EXAMINATION

7.1 Temperature ☐☐.☐ °C

7.2 Mechanically ventilated: ☐ (1) yes ☐ (2) no ☐ (9) unknown

7.3 Lymph nodes ☐ (1) normal ☐ (2) abnormal ☐ (9) unknown

7.4 Bone abnormality ☐ (1) yes ☐ (2) no ☐ (9) unknown

7.5 Joint abnormality ☐ (1) yes ☐ (2) no ☐ (9) unknown

7.6 Muscle abscess ☐ (1) yes ☐ (2) no ☐ (9) unknown

8. PAST MEDICAL HISTORY AND RISK FACTORS

8.1 Diabetes mellitus ☐ (1) yes ☐ (2) no ☐ (9) unknown

8.2 COPD ☐ (1) yes ☐ (2) no ☐ (9) unknown

8.3 Tuberculosis ☐ (1) yes ☐ (2) no ☐ (9) unknown

8.4 Chronic renal failure ☐ (1) yes ☐ (2) no ☐ (9) unknown

8.5 Renal calculi ☐ (1) yes ☐ (2) no ☐ (9) unknown

8.6 Chronic liver disease ☐ (1) yes ☐ (2) no ☐ (9) unknown

8.7 Alcohol/drug abuse	☐ (1) yes	☐ (2) no	☐ (9) unknown
8.8 Malnutrition	☐ (1) yes	☐ (2) no	☐ (9) unknown
8.9 Penetrating injury	☐ (1) yes	☐ (2) no	☐ (9) unknown
8.10 Near drowning	☐ (1) yes	☐ (2) no	☐ (9) unknown
8.11 Trauma	☐ (1) yes	☐ (2) no	☐ (9) unknown
8.12 Thalassemia	☐ (1) yes	☐ (2) no	☐ (9) unknown
8.13 Others	☐ (1) yes	☐ (2) no	☐ (9) unknown
8.14 No known risk factors	☐ (1) yes	☐ (2) no	☐ (9) unknown

9. LABORATORY

	1	2	3	4	5	6	7	8
Date								
9.1 Hemoglobin								
9.2 WBC								
9.3 %Neutrophils								
9.4 %Lymphocyctes								
9.5 %Eosinophills								
9.6 %Monocytes								
9.7 Platelet count								
9.8 BUN								
9.9 Cr								
9.10 Glucose								
9.11 Bilirubin (T)								
9.12 Bilirubin (D)								
9.13 SGOT								
9.14 SGPT								
9.15 ALP								
9.16 Albumin								
9.17 Globulin								
9.18 Bicarbonate								
9.19 Lactate								
9.20 Blood sodium								
9.21 Blood potassium								

10. MICROBIOLOGY

10.1 Culture site ☐ (1) Blood ☐ (2) Muscle pus ☐ (3) Bone pus
☐ (4) Synovial fluid ☐ (5) Organ pus ☐ (6) Urine
☐ (7) Sputum ☐ (8) Throat swab
☐ (9) Others ☐ (99) unknown

10.2-10.9 Resistant to effective drug

10.2 Antibiotics Resistance (Blood) ☐ (1) CAZ ☐ (2) IMP ☐ (3) Chlor ☐ (4) Dox ☐ (5) Co-amoxy ☐ (6) TMP-SMX ☐ (7) None

10.3 Antibiotics Resistance (Muscle pus) ☐ (1) CAZ ☐ (2) IMP ☐ (3) Chlor ☐ (4) Dox ☐ (5) Co-amoxy ☐ (6) TMP-SMX ☐ (7) None

10.4 Antibiotics Resistance (Bone pus) ☐ (1) CAZ ☐ (2) IMP ☐ (3) Chlor ☐ (4) Dox ☐ (5) Co-amoxy ☐ (6) TMP-SMX ☐ (7) None

10.5 Antibiotics Resistance (Synovial fluid) ☐ (1) CAZ ☐ (2) IMP ☐ (3) Chlor ☐ (4) Dox ☐ (5) Co-amoxy ☐ (6) TMP-SMX ☐ (7) None

10.6 Antibiotics Resistance (Organ pus) ☐ (1) CAZ ☐ (2) IMP ☐ (3) Chlor ☐ (4) Dox ☐ (5) Co-amoxy ☐ (6) TMP-SMX ☐ (7) None

10.7 Antibiotics Resistance (Urine) ☐ (1) CAZ ☐ (2) IMP ☐ (3) Chlor ☐ (4) Dox ☐ (5) Co-amoxy ☐ (6) TMP-SMX ☐ (7) None

10.8 Antibiotics Resistance (Respiratory) ☐ (1) CAZ ☐ (2) IMP ☐ (3) Chlor ☐ (4) Dox ☐ (5) Co-amoxy ☐ (6) TMP-SMX ☐ (7) None

10.9 Antibiotics Resistance (Others) ☐ (1) CAZ ☐ (2) IMP ☐ (3) Chlor ☐ (4) Dox ☐ (5) Co-amoxy ☐ (6) TMP-SMX ☐ (7) None

11. NOSOCOMIAL INFECTION OR CONCOMITANT INFECTION

11.1 Possible nosocomial infection ☐ (1) yes ☐ (2) no ☐ (9) unknown

11.2 Pathogens ☐ (1) ESBL *Enterobacteriaceae* ☐ (2) *Acinetobacter spp.*
☐ (3) *Stenotrophomonas maltophilia*
☐ (4) MRSA ☐ (5) MSSA
☐ (6) *Candida spp.* ☐ (7) other Gram negative bacteria
☐ (8) other Gram positive bacteria ☐ (9) unknown

11.3 Concomitant infection

☐ (1) Gram positive bacteria ☐ (2) Gram negative bacteria

☐ (3) fungi ☐ (4) anaerobes ☐ (9) unknown

12-14. MUSCULOSKELETAL SYSTEM

12. Radiology	1	2
	Diagnosis	Location
12.1 Bone/ Joint X-Ray		
12.2 Plain abdomen		
12.3 KUB		
12.4 CT		
12.5 Others		

1. Diagnosis: 1. Normal 2. Osteoporosis/demineralization 3. Joint effusion
4. Soft tissue swelling 5. Fracture 6. Arthritis
7. Muscle abscess 8. Degenerative changes
9. Spondylolithesis 10. other

2. Location

Joint: 1. elbow 2. shoulder 3. wrist 4. hand 5. hip 6. knee
7. ankle 8. foot 9. sacroiliac joint 10. sternoclavicular joint
11. sternomanubrial joint 12. others

Bone: 1. T-spine 2. L-spine 3. C-spine 4. Iliac bone
5. upper extremity long bone
6. lower extremity long bone 7. ribs 8. skull 9. others

Muscle: 1. Psoas muscle 2. upper extremities 3. lower extremities 4. back
5.buttock 6. others

3 – 4 Improved ☐ (1) yes ☐ (2) no ☐ (9) unknown

13. Ultrasonography	1	2
	Date	Location
13.1 Arthritis		
13.2 Pyomyositis		
13.3 Soft tissue abscess		
13.4 Organ abscess		
13.5 Other		

14. SUMMARY OF INVOLVED SITE AND CHARACTER

Summary of Involved site	1.Yes/No	2.Location	3 number of involvement
14.1 Joint			
14.2 Bone			
14.3 Muscle			
14.4 J+B			
14.5 J+M			
14.6 B+M			
14.7 J+B+M			

3. Number of joint involvement:

1. Monoarthritis 2. oligoarthritis (2-4) 3. polyarthritis (more than 5)

15. MELIOIDOSIS SPECIFIC ANTIBIOTICS TREATMENT

15.1 Parenteral antibiotics

Drug	Dose	Interval	Start	Stop

15.1.1 IV Regimens ☐ (1) CAZ ☐ (2) CAZ+TMP-SMX ☐ (3) IMP ☐ (4) co-amoxiclav ☐ (5) others

15.1.2 Duration ☐☐☐ days

15.1.3 Change to ☐ (1) CAZ ☐ (2) CAZ+TMP-SMX ☐ (3) IMP ☐ (4) co-amoxiclav ☐ (5) others

15.1.4 Switch reason ☐ (1) side effect ☐ (2) worsening ☐ (3) Tx failure ☐ (4) others

15.2 Oral antibiotics

Drug	Dose	Interval	Start	Stop

15.2.1 Oral Regimens ☐ (1) Chlor + Dox +TMP-SMX
☐ (2) Dox +TMP-SMX
☐ (3) Co-amoxy ☐ (4) Others

15.2.2 Duration ☐☐☐ days

16 NON-MELIOIDOSIS SPECIFIC TREATMENT

Intervention	1st time (Days after admission)	frequency	complication	location
16.1 Aspiration				
16.2 Arthrotomy				
16.3 Incision/ drainage				
16.4 Others				

17-21 SUMMARY

17. TISSUE INVOLVEMENT

17.1	Joint	☐ (1) yes	☐ (2) no	☐ (9) unknown
17.2	Bone	☐ (1) yes	☐ (2) no	☐ (9) unknown
17.3	Muscle	☐ (1) yes	☐ (2) no	☐ (9) unknown
17.4	Skin	☐ (1) yes	☐ (2) no	☐ (9) unknown
17.5	Soft tissue	☐ (1) yes	☐ (2) no	☐ (9) unknown
17.6	Pericardium	☐ (1) yes	☐ (2) no	☐ (9) unknown
17.7	Lung	☐ (1) yes	☐ (2) no	☐ (9) unknown
17.8	Parotid	☐ (1) yes	☐ (2) no	☐ (9) unknown
17.9	Liver	☐ (1) yes	☐ (2) no	☐ (9) unknown
17.10	Spleen	☐ (1) yes	☐ (2) no	☐ (9) unknown

17.11	Abdomen	☐ (1) yes	☐ (2) no	☐ (9) unknown
17.12	Kidney	☐ (1) yes	☐ (2) no	☐ (9) unknown
17.13	Prostate	☐ (1) yes	☐ (2) no	☐ (9) unknown
17.14	Lymph node	☐ (1) yes	☐ (2) no	☐ (9) unknown
17.15	CNS	☐ (1) yes	☐ (2) no	☐ (9) unknown
17.16	Others	☐ (1) yes	☐ (2) no	☐ (9) unknown

18.1 COMPLICATIONS ☐ (1) yes ☐ (2) no ☐ (9) unknown

18.2	Hypotension	☐ (1) yes	☐ (2) no	☐ (9) unknown
18.3	Respiratory failure	☐ (1) yes	☐ (2) no	☐ (9) unknown
18.4	Pulmonary edema	☐ (1) yes	☐ (2) no	☐ (9) unknown
18.5	Hemoptysis	☐ (1) yes	☐ (2) no	☐ (9) unknown
18.6	ARF	☐ (1) yes	☐ (2) no	☐ (9) unknown
18.7	Jaundice/ liver failure	☐ (1) yes	☐ (2) no	☐ (9) unknown
18.8	CNS involvement	☐ (1) yes	☐ (2) no	☐ (9) unknown
18.9	GI bleeding	☐ (1) yes	☐ (2) no	☐ (9) unknown
18.10	Superinfection	☐ (1) yes	☐ (2) no	☐ (9) unknown
18.11	Anemia	☐ (1) yes	☐ (2) no	☐ (9) unknown

18.11 Rheumatological Complication		☐ (1) yes	☐ (2) no	☐ (9) unknown
18.12	Sinus tract	☐ (1) yes	☐ (2) no	☐ (9) unknown
18.13	Limited ROM	☐ (1) yes	☐ (2) no	☐ (9) unknown
18.14	Deformity	☐ (1) yes	☐ (2) no	☐ (9) unknown

19. Highest Temperature ☐☐.☐ °C

20. Fever Clearance time ☐☐☐ hrs

Time from start of Rx until point at which Temp remains <37.5°C for 48 hrs.

999=no clearance until death 000 never pyrexial

21. OUTCOME

21.1	Early Death	☐ (1) yes	☐ (2) no	☐ (9) unknown
21.2	Late Death	☐ (1) yes	☐ (2) no	☐ (9) unknown
21.2.	Treatment Failure	☐ (1) yes	☐ (2) no	☐ (9) unknown
21.3	Recurrent Infection	☐ (1) yes	☐ (2) no	☐ (9) unknown
21.4	Cure	☐ (1) yes	☐ (2) no	☐ (9) unknown

* Early death: expired within 48 hours after admission

BIOGRAPHY

NAME : Chi-Chun Tsai (also named as Jih-Jin Tsai) M.D.

DATE OF BIRTH : Oct. 07, 1963

PLACE OF BIRTH : Chiayi County, Taiwan

INSTITUTION ATTENDED : Medical Degree of Kaohsiung Medical University (KMU) in 1989
Internal Medicine, Kaohsiung Medical University Hospital (KMUH) from 1989 up to now
Infectious diseases visiting staff of KMUH from 1994 up to now
Specialist for Allergy, Immunology and Rheumatology (AIR) from 1994;
Part-time attending physician of AIR, KMUH from 1994 up to now

POSITION : Director, Division of Infectious Diseases & Section of Infection Control, KMUH from 2003 to 2005
Commissioner of Taiwan CDC
Commissioner of International affairs of Taiwan Infectious Diseases Society

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