

Melioidosis : Recognition and Treatment[†]

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Abstract

Melioidosis, an infection caused by *Burkholderia pseudomallei*, is endemic in Southeast Asia and northern Australia. Thailand has the greatest number of recorded cases. Melioidosis has been called "a great imitator" because of its protean manifestations. The infection can also remain quiescent for a long period after initial acquisition, and patients present with the disease many years later. The most dramatic presentation is fulminant septicemia with a case fatality rate of up to 80 percent. Another common presentation is severe pneumonia, which is also associated with a high fatality rate. Other localized infection has been reported in almost every organ or organ system. Making the diagnosis depends on the physicians' awareness of its various clinical presentations and the epidemiologic settings in which the disease is likely to occur. In suspected cases of severe disease, antibiotic treatment needs to be started before the culture result becomes available. Serologic tests for antibody to *B. pseudomallei* give a result faster but cannot differentiate the disease from past infection. There have been very few attempts to standardize and to make comparison among the various serologic tests available. Treatment of severe disease requires 2-4 weeks of potent antibiotics such as a combination of ceftazidime and cotrimoxazole, followed by 3-6 months of oral agent such as doxycycline or cotrimoxazole. Localized infection may be treated with oral antibiotic (s) for similar duration. Even after this prolonged treatment regimen relapses are not uncommon. (*J Infect Dis Antimicrob Agents* 1997;14:105-11.)

INTRODUCTION

Melioidosis, an infection caused by *Burkholderia pseudomallei*, was first described in 1912 in Burma by Whitmore and Krishnaswami (1). The first two cases in Thailand were reported in 1947 in European prisoners of war (2,3). In 1955, The first case in a Thai patient was reported (4). In the 1960's and 1970's during the Vietnam conflict, melioidosis became an important problem in military medicine (5,6), resulting in several studies of the distribution of *B. pseudomallei* and subclinical melioidosis in Thailand (7,8). However, it was not until 1976 that 10 more cases of melioidosis were reported in Thai patients (9). Following the modernization of microbiology laboratories in hospitals outside the big cities, 686 cases were reported at a national workshop on melioidosis in Bangkok in 1985 (10). Since 1985, it has been recognized that melioidosis

is highly endemic in Thailand especially in the northeastern part of the country bordering Laos and Cambodia, where approximately 100 cases of culture-proven melioidosis are seen each year in a typical large provincial hospital such as Ubon Ratchathani and Khon Kaen (11,12). It is estimated that the number of cases of melioidosis in the northeastern part of Thailand alone may reach 2,000 to 5,000 per year (13). Thailand has by far the greatest number of recorded cases. Besides Thailand, the major endemic area of infection by *B. pseudomallei* in human includes northern Australia, Indonesia, Singapore, Malaysia, Burma, southern China, Laos, Cambodia, and Vietnam (14,15).

CLINICAL MANIFESTATION

Three important features characterize the manifestation of melioidosis. The disease has a notoriously protean

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manifestation that it is called "a great imitator" (16,17). Secondly, the infection can remain quiescent for a long period after initial acquisition, and patients can present with disease many years later (18,19). In one report, symptomatic melioidosis in a patient was documented 26 years after leaving the endemic area (20). Hence, melioidosis had been dubbed "the medical time-bomb" (21). Lastly, patients who do respond initially to antibiotics remain at risk of subsequent relapse. In one study, it was found that the relapse rate was 15 percent per year despite a total of 8 weeks' antibiotic treatment (22).

In the endemic area, *B. pseudomallei* is widely distributed in the environment, including fields, streams, ponds, and rice paddies. Infection is thought to be acquired by inoculation, inhalation or aspiration and possibly ingestion of environmental organisms (18). Incubation can be as short as 3 days, but sometimes the disease is latent, and becoming evident months or years later. It is not clear what proportion of symptomatic infections are recently acquired or reactivation of a latent focus (11). Primary sites of infection develop in the skin and subcutaneous tissue, or lungs. Infection at the secondary sites most likely develops *via* the blood stream. Virtually any organ system can be affected: lungs, skin and subcutaneous tissues, bones and joints, liver, spleen, pancreas, kidneys, bladder, prostate, genital organs, brain and meninges, parotid glands, lymph nodes, and pericardium (10). Parotitis is an especially common manifestation in children (23,24). When the bacteria cannot be contained at either the primary or

secondary sites of infection, septicemia occurs.

Septicemia is the most common clinical presentation of melioidosis; 50-70 percent of patients with *B. pseudomallei* infection are bacteremic at the time of admission to the hospital (25). In most patients, septicemic melioidosis was characterized by a fulminant course with high fever, chills, severe prostration, lethargy or stupor, and tachypnea. Acute respiratory failure and shock often developed. Multiple liver and spleen abscesses were common. Superficial skin lesions, when present, were valuable diagnostic clues, as aspirates stained by Gram's stain usually showed bipolar gram-negative rods (Fig. 1). The chest roentgenogram often showed disseminated nodular lesions characteristic of blood-borne pneumonia (12) (Fig. 2). The mortality was as high as 87 percent due to shock, respiratory failure, and multiorgan failure (10,26). These patients usually died within 2-3 days of presentation. However, there were patients who had positive blood cultures and usually a positive culture from one other anatomic site, whose clinical manifestations were less severe and whose mortality rate was less than 20 percent (10). In a few unusual cases, the patients who had positive blood culture presented with little evidence of systemic disease other than fever (26,27). Some patients even recovered without treatment with antibiotic that was active against *B. pseudomallei* (27). To differentiate between these two groups of patients with septicemic melioidosis but with significantly different clinical manifestation including prognosis, the Infectious Disease Association of Thailand had used the terms



Fig. 1 This 47-year-old woman who had chronic renal failure presented with fever, chest pain, cough, and a soft tissue mass in the neck. Aspirates from the skin lesion showed many gram-negative rods and grew *B. pseudomallei* on culture. She died 12 days after admission from septicemic melioidosis.

“Disseminated septicemic melioidosis” and “Non-disseminated septicemic melioidosis” respectively in its clinical classification of melioidosis (10). This classification was modified and adopted by another important group of researchers in this field (22).

Localized melioidosis refers to disease at either the primary or secondary sites of infection. Pulmonary infection is the most common localized melioidosis. The clinical manifestation may be acute lobular pneumonia or subacute/chronic pulmonary melioidosis. Patients with acute pneumonia have acute illness manifested by high fever, chills, cough, chest pain, dyspnea, and occasionally hemoptysis. The chest roentgenogram shows alveolar infiltrates and consolidation (Fig. 3). Patients with subacute/chronic pulmonary melioidosis present with insidious onset of fever, cough, weight loss, and occasionally chest pain and blood-streaked sputum. The prodromal period varies from several weeks to months. The chest roentgenogram is characterized by fibronodular lesions with or without cavities (Fig. 4). They are prevalent in the upper lobes but usually spare the apices (12). In northeastern Thailand, melioidosis is one of the leading causes of community-acquired pulmonary infection (28). Other common forms

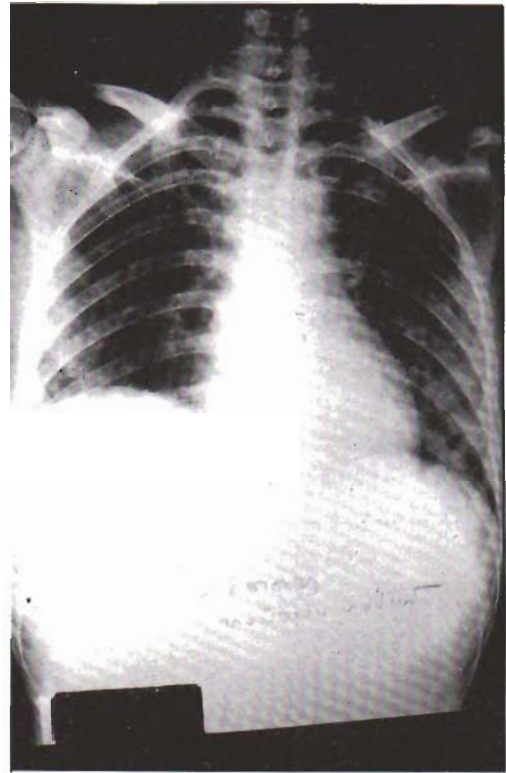


Fig. 2 This 29-year-old diabetic woman presented with septicemic shock and died within 24 hours of admission. The chest roentgenogram showed diffuse nodular lesions of both lungs, particularly in the lower lung fields.

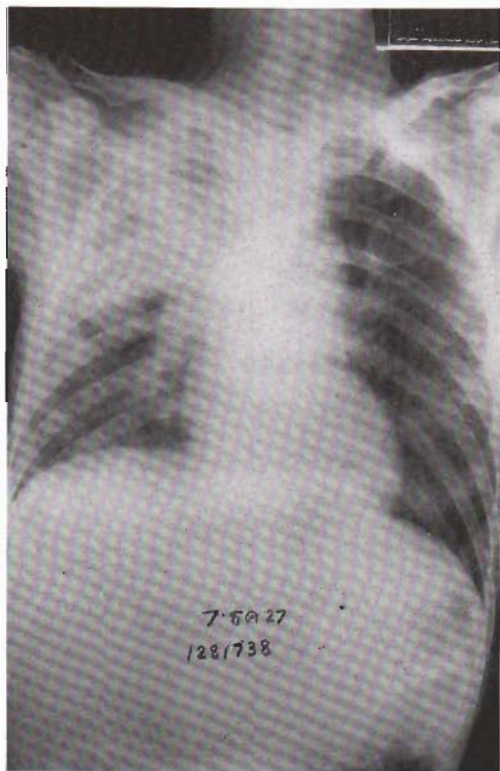


Fig. 3 This 42-year-old diabetic man presented with fever and cough for 3 weeks. The chest roentgenogram showed dense infiltrate in the right upper lung field.

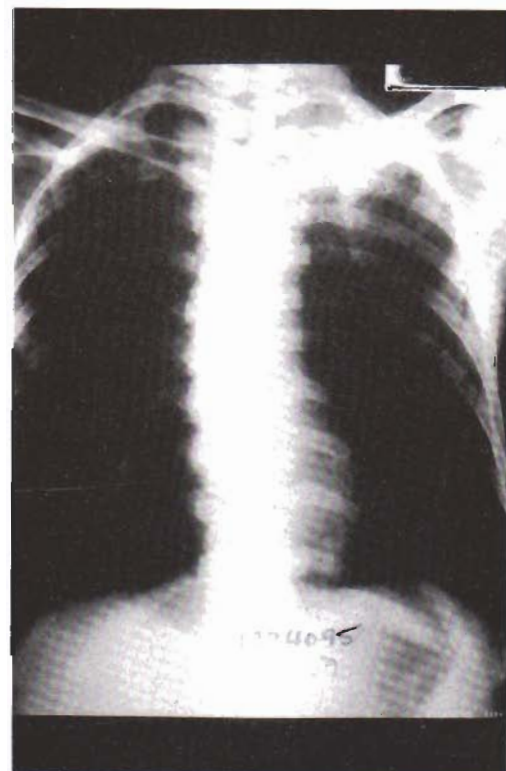


Fig. 4 This 68-year-old man who had chronic renal failure presented with fever and cough. The chest roentgenogram showed findings of chronic obstructive pulmonary disease and fibronodular lesion in the left upper lung field.

of localized melioidosis are infection of the skin and soft tissue, lymphadenitis, infection of the bones and joints, liver abscess, splenic abscess, and infection of the genito-urinary system (10). In many instances, the infection has spread to the blood stream and the patients present with symptoms and signs of both the original localized melioidosis and septicemia.

Table 1 shows the demographic and clinical characteristics of 51 consecutive patients with melioidosis at Maharaj Hospital, Chiang Mai between October 1980

and September 1985 (Sirisanthana T, unpublished data). Chiang Mai does not have as many cases of melioidosis as provinces in the northeast. The first case of melioidosis was diagnosed in 1979. After the physicians and laboratory staff became more familiar with the disease, about 15-20 cases per year were diagnosed at this hospital. The majority of cases were in farmers who acquired the infection during the rainy season. Forty-three per cent of cases had one or more pre-existing illnesses. Twenty-one patients had septicemic melioidosis. Thirty had the localized form of

Table 1. Demographic and clinical characteristics of 51 consecutive patients with melioidosis at Maharaj Hospital, Chiang Mai.

	No. (%)	
Sex		
Male	33 (64.7)	
Age range, mean (years)		8-70 (43)
Female	18 (35.3)	
Age range, mean (years)		21-67 (38.9)
Time of presentation		
Jun - Nov (rainy months)	36 (70.6)	
Dec - May (dry months)	15 (29.4)	
Occupation		
Farmers	30 (58.8)	
Others	21 (41.2)	
Pre - existing illnesses		
Absent (or not known)	29 (56.9)	
Present (one or more)	22 (43.1)	
Renal failure		7 patients
Urolithiasis		7
Thalassemia		5
Diabetes mellitus		4
Alcoholism		2
Cirrhosis		1
Nephrotic syndrome on glucocorticoid		1
ITP* on glucocorticoid		1
Hodgekin's disease on chemotherapy		1
Carcinoma of the lung		1
Clinical presentation		
Disseminated septicemic	11 (21.6)	
Non-disseminated septicemic	10 (19.6)	
Localized	30 (58.8)	
Skin and soft tissue		11 patients
Pulmonary		7
Bones and Joints		2
Genito-urinary		2
Liver		1
Spleen		1
More than one site		6

*Idiopathic thrombocytopenic purpura

the disease. Unlike reports from other case series (10), infection of the skin and soft tissue was the most common form of localized melioidosis in Chiang Mai. This was because our case series also included patients who were diagnosed and treated as outpatients. Also, many of our patients who had pulmonary infection and infection of the liver and/or spleen presented as septicemic melioidosis and were tallied as such. In other series, pulmonary and hepatosplenic infection accounted for a higher proportion of patients with localized melioidosis (10).

DIAGNOSIS

Definite diagnosis of melioidosis is made by isolation of *B. pseudomallei* from various clinical specimens, including blood in patients with septicemia. Although the organism is not difficult to grow and identify, requiring only a few key tests or commercial kits (29), good communication between the attending physician and laboratory staff may help speeding up and improve the efficacy of the process. High index of suspicion on the part of the attending physician is important. In endemic area, most physicians are already very much aware of the disease given the very high incidence of melioidosis. In northeastern Thailand, for example, *B. pseudomallei* causes about 20 percent of cases and 40 percent of deaths from community-acquired cases of septicemia (26). Similarly, melioidosis is the commonest cause of death from community-acquired pneumonia at Royal Darwin Hospital in northern Australia with only *Streptococcus pneumoniae* responsible for more bacteremic pneumonia admission (30,31). In the non-endemic area, the history of traveling to or having lived in an endemic area is the most important clue to the diagnosis.

In the endemic area, other epidemiological features may also be good clues to the diagnosis. In one study involving 161 patients with melioidosis in northeastern Thailand, all except 14 presented in the rainy season, between June and November (32). Rainfall also appeared to correlate with the severity of disease in these patients (31). In Thailand, since *B. pseudomallei* is widely distributed in water and soil of the rice paddies, melioidosis occurred predominantly in rice farmers of their families (26). Also, the association of melioidosis with pre-existing illness is a well-known fact (14,26). Of the 602 patients with melioidosis admitted to a hospital in northeastern Thailand, 31.6 percent had diabetes mellitus and 14.3 percent had renal failure usually associated with urolithiasis (11,22). Other pre-existing illnesses included malignancies and hematologic diseases especially thalassemia (10).

In one study comparing 21 patients with melioidosis of the musculoskeletal system with 39 patients who had infection due to other organisms, if the patient had one or more of these pre-existing illnesses the odds that *B. pseudomallei* was the cause of the infection were 12 to 1 (33).

Melioidosis can also be diagnosed presumptively by detecting antibody against *B. pseudomallei* in the patients' sera. These tests include the indirect hemagglutination (IHA) test (34,35), the complement fixation test (8), the indirect fluorescent antibody test (36) and the enzyme-linked immunosorbent assay (37). The IHA test, in which and autoclaved culture filtrate or lipopolysaccharides extracted from *B. pseudomallei* are used as antigens (35), remains the most widely used test. Other tests have not been evaluated in large numbers of patients and healthy individuals in endemic areas and are not in routine use. In Thailand, antigens used in IHA test are prepared in several laboratories using different methods. Diagnostic titers vary from one laboratory to another. Also, the usefulness of the IHA as well as other serologic tests is compromised by the high background seropositivity rates in the general population (34,38). In addition, some patients with acute septicemic melioidosis and those during the early stage of infection may not have detectable antibody against *B. pseudomallei* in their sera (34,38,39).

To overcome the problem of high background activity that leads to the lack of specificity of antibody detection, tests to detect *B. pseudomallei* in clinical specimens have been developed (40-42). In a study of 135 patients with acute melioidosis, 40 healthy individuals and 194 patients with illness other than melioidosis, Desakorn and colleagues were able to detect the antigen in unconcentrated urine of 96 and 80 percent of cases of septicemic and localized melioidosis respectively. Antigen was not detected in the urine of healthy individuals. False positive rate was low and was found mainly in patients with significant gram-negative bacteriuria (42). This is potentially a very useful system and its further evaluation should be carried out in a large-scale field trial.

TREATMENT

B. pseudomallei is usually sensitive to chloramphenicol, tetracyclines, cotrimoxazole, ceftazidime and several other third generation cephalosporins, imipenem, piperacillin, ampicillin/sulbactam, ticarcillin/clavulanic acid, and amoxicillin/clavulanic acid (43-46). Table 2 shows the sensitivity to antibiotics of *B. pseudomallei* isolated from

47 consecutive patients with melioidosis at Maharaj Hospital, Chiang Mai between January 1993 and December 1995 (Sirisanthana T, unpublished data). The organism was consistently resistant to the aminoglycosides, first- and second-generation cephalosporins and most quinolones. Compared to a previous report from the same hospital, the percentage of the organism that was sensitive to cotrimoxazole dropped from 78 in 1985 to 14.8 in 1993, that to cefotaxime from 100 in 1985 to 85 in 1993, and that to ceftriazone from 100 in 1985 to 77.3 in 1993 (46).

In an open randomized trial comparing ceftazidime (120 mg/kg/day) with "conventional therapy" (a combination of chloramphenicol, doxycycline, and cotrimoxazole) in patients with severe melioidosis, White and colleagues showed that ceftazidime was associated with a 50 percent lower overall mortality rate than conventional treatment (32). In another multicenter prospective randomized trial comparing ceftazidime (100 mg/kg/day) and cotrimoxazole (trimethoprim, 8 mg/kg/day; sulfamethoxazole, 40 mg/kg/day) with chloramphenicol plus doxycycline and cotrimoxazole for the treatment of severe melioidosis, Sookprance and coworkers found similar reduction in the mortality rate in those treated with the ceftazidime containing regimen (47). Thus ceftazidime, preferably in combination with cotrimoxazole, is the regimen of choice for the treatment of severe melioidosis. The emergence during

treatment of resistance to ceftazidime had been documented (48). Thus there is a need for careful microbiological follow-up of patients with melioidosis during treatment.

One other important issue in the treatment of melioidosis is the tendency of the disease to relapse after an initial successful treatment. Chaowagul and associates followed 118 patients who had been given appropriate antibiotics for 8 weeks and found that the relapse rate was 23 percent. The median time from initial treatment to relapse was 21 weeks; but with longer disease-free intervals, the chance of subsequent relapse fell. Patients with more severe disease i.e. multiple foci of infection or septicemia relapsed 4.7 times more often than patients with localized melioidosis. Pre-existing illness was not a risk factor, but initial treatment with ceftazidime reduced the risk of relapse 2-fold. The mortality in relapse with melioidosis was high and was not significantly different from that in acute infection (22). In a subsequent study by the same group of researchers, one of the objectives was to look at the effect of increasing the duration of total treatment on the relapse rate (49). This prospective study compared oral amoxicillin/clavulanic acid with the combination of chloramphenicol, doxycycline, and cotrimoxazole in preventing relapse. Of the patients who took 12-20 weeks of either treatment, only 7.6 percent relapsed. Amoxicillin/clavulanic acid caused less serious adverse effects and was better tolerated, but seemed to be less effective (although the difference did not reach statistical difference). Thus there is still a need to find an oral antimicrobial drug which is effective in preventing relapse with a shorter duration of treatment, since the patient's compliance with taking any oral antibiotic regimen for 20 weeks was quite poor.

Table 2. Sensitivity to antibiotics by disc diffusion method of *B. pseudomallei* isolated from 47 consecutive patients at Maharaj Hospital, Chiang Mai.

Antibiotic	Per cent sensitive
Chloramphenicol	97.8
Tetracycline	100
Cotrimoxazole	14.8
Gentamicin	2.2
Netilmicin	3.1
Amikacin	0
Cefuroxime	0
Cefoxitin	0
Cefmetazole	0
Cefotaxime	85
Cefodizime	35
Ceftriazone	77.3
Cefoperazone	100
Ceftazidime	92.9
Piperacillin	100
Imipenem	96.7
Norfloxacin	17.6
Ofloxacin	5.9
Ciprofloxacin	68

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