

## Cases of melioidosis in a university teaching hospital in Malaysia

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**Background and Purpose:** Melioidosis is an infectious disease caused by *Burkholderia pseudomallei* that is endemic in Southeast Asia and northern Australia and has also been reported from non-endemic areas of the world. Little is known about the antimicrobial susceptibility pattern and the demography of melioidosis patients in Malaysia.

**Methods:** This was a retrospective study of 83 patients with culture-proven *B. pseudomallei* infections from the University of Malaya Medical Centre, Kuala Lumpur, Malaysia from May 1995 to June 2005. Antimicrobial susceptibility of *B. pseudomallei*, age, gender and race of patients, nature of specimen, serological evidence and monthly distribution of cases were evaluated.

**Results:** All isolates were susceptible to piperacillin and piperacillin-tazobactam. The majority of strains were susceptible to imipenem (99%), ceftazidime (94%), amoxicillin-clavulanic acid (95%), ampicillin-sulbactam (94%), tetracycline (89%), chloramphenicol (94%), trimethoprim-sulfamethoxazole (70%), meropenem (88%) and ciprofloxacin (79%). Significant antimicrobial resistance was noted in aminoglycosides and ampicillin. The male-to-female ratio was 3.15:1, and mean age was 43.85 years. The majority of the patients were middle-aged (41-60 years). Malays and Indians made up 39% and 33% of affected patients, while Chinese and others comprised 25% and 3%, respectively. Of 83 patients, 67 were diagnosed by positive blood cultures, and 16 patients were non-bacteremic cases. There were 22 patients in whom *B. pseudomallei* grew in more than one clinical specimen, and there were 6 polymicrobial cases.

**Conclusion:** Melioidosis is expanding in endemicity around the world. Control of the disease requires close monitoring, improved clinical laboratory standards and aggressive therapy.

**Key words:** *Burkholderia pseudomallei*; Malaysia; Melioidosis

### Introduction

Melioidosis is caused by a Gram-negative free living saprophyte, *Burkholderia pseudomallei*, and is endemic in Southeast Asia and northern Australia. It has also been reported from outside the well known endemic areas, such as Mauritius, South America, India, China, the Middle East and Africa. It is a disease of great public health concern and is associated with high case-fatality rates in animals and humans [1-4]. The established portals of entry into human hosts are skin, pulmonary inhalation and alimentary tract [1,2,5]. It is rarely transmitted from person to person and from

mother to child [6,7]. Two cases of maternal transmission of melioidosis have been reported from Australia and both lactating mothers had melioidotic mastitis [7].

The person-to-person route of transmission is very rare, and only standard infection control measures have been recommended for clinical care of patients with melioidosis. *B. pseudomallei* not only affects apparently healthy individuals, but also causes infections in patients with pre-existing diabetes mellitus, impaired cellular immunity, renal impairment, leukemia/lymphoma and alcoholism [8]. The clinical spectrum of melioidosis ranges from asymptomatic, acute, chronic suppurative forms to acute septicemia. Acute septicemia is usually fatal.

Other presentations include skin or soft tissue abscesses, genitourinary infections, osteomyelitis, arthritis, peritonitis and neurological melioidosis [2,9]. Limited

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treatment options are available for melioidosis, because *B. pseudomallei* is resistant to penicillin, aminoglycosides and rifamycin and relatively resistant to quinolones and macrolides [10].

Melioidosis is an emerging life-threatening disease; the true incidence remains unknown in many parts of the world due to lack of awareness of the disease and a lack of laboratory diagnostic tools. In Malaysia, few extensive studies have been done on melioidosis [11], and little is known about the microbiological features and antimicrobial susceptibility pattern of *B. pseudomallei*. We reviewed the microbiological features of melioidosis cases and antibiotic susceptibility of clinical isolates from the University of Malaya Medical Centre (UMMC), Kuala Lumpur, Malaysia.

## Methods

### Patients

Patients with culture-proven melioidosis between May 1995 and June 2005 were identified from the computerised microbiology statistics programme and the laboratory information system of the Medical Microbiology Laboratory, UMMC. This medical center has 900 beds and is a major teaching hospital.

### Selection of patients

Cases of *B. pseudomallei* infection were classified as having bacteremic or non-bacteremic melioidosis, depending on whether *B. pseudomallei* was isolated from blood or other body site sample. Cases of polymicrobial infections, i.e., those with the isolation of any organism in addition to *B. pseudomallei*, were also included in this study.

### Data collection

Demographic data and monthly incidence of both bacteremic and non-bacteremic cases were recorded retrospectively. The microbiology data collected included the antimicrobial susceptibility patterns of all clinical isolates of *B. pseudomallei*.

### Microbiology

Blood specimens and clinical specimens, such as sputum or pus from suspected sites of infection, were sent to the microbiology laboratory for culture and antibiotic susceptibility testing. Blood samples for serology were also performed. Blood cultures were processed by the BACTEC 9240 system (BD Diagnostics, Becton, Dickinson and Company, Sparks, MD,

USA). Sputum, pus or urine samples were processed by inoculating the samples on blood agar, MacConkey agar and chocolate agar plates incubated in aerobic chamber and 5-10% carbon dioxide, respectively, at 37°C for two days.

*B. pseudomallei* was identified by conventional bacteriological methods, and confirmed by API 20NE biochemical identification system (bioMérieux, Marcy l'Etoile, France) and latex agglutination test (All Eight Sdn Bhd, Selangor Darul Ehsan, Malaysia).

### Antimicrobial susceptibility tests

Antimicrobial susceptibility testing by the disk diffusion method was performed on Mueller-Hinton agar plates in accordance with the Clinical and Laboratory Standards Institute (CLSI) [12]. The CLSI does not validate susceptibility testing of *B. pseudomallei* by the disk diffusion method and interpretation of zone sizes has never been established. The interpretation of results of zone sizes was based on the CLSI guideline for zone sizes used for non-*Enterobacteriaceae*. The following fresh antibiotic-containing disks were employed: ampicillin (10 µg/mL), trimethoprim-sulfamethoxazole (25 µg/mL), ampicillin-sulbactam (20 µg/mL), amoxicillin-clavulanic acid (30 µg/mL), gentamicin (10 µg/mL), netilmicin (30 µg/mL), amikacin (30 µg/mL), cefoperazone (75 µg/mL), ceftazidime (30 µg/mL), ciprofloxacin (5 µg/mL), imipenem (10 µg/mL), piperacillin (100 µg/mL), tetracycline (30 µg/mL), chloramphenicol (30 µg/mL) and piperacillin-tazobactam (110 µg/mL).

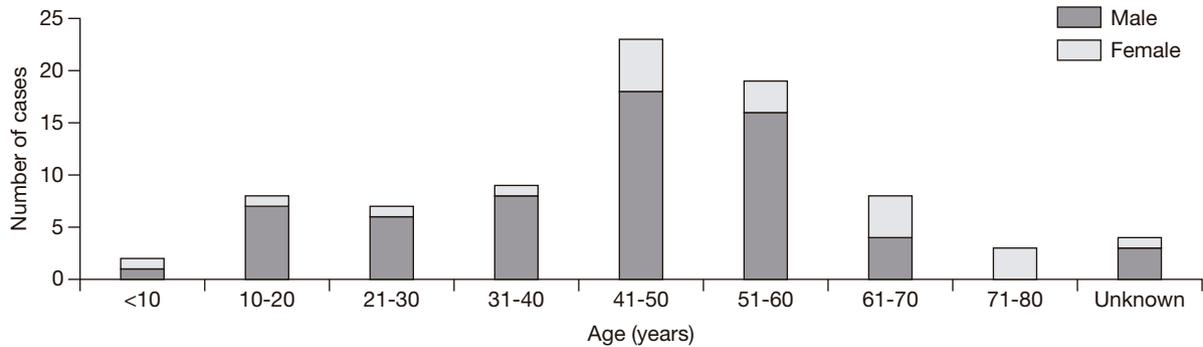
### Serological tests

Serum antibodies of *B. pseudomallei* (immunoglobulin M and immunoglobulin G) were measured in the majority of patients using immunofluorescent antibody assay test, as described previously [12-14].

## Results

### Demography

Eighty three patients fulfilled the inclusion criteria. The mean and median ages of the patients were 43.9 years and 45 years (range, 2 to 73 years), while the ages of four patients could not be ascertained from the laboratory information system. There were 63 males and 20 females with a male-to-female ratio of 3.15:1. The ethnic breakdown of patients was as follows: 32 Malays (38.6%), 27 Indians (32.5%), 21 Chinese (25.3%), and 3 others (3.6%). The age and gender



**Fig. 1.** Age and gender distribution of *Burkholderia pseudomallei*-infected patients.

distribution of patients is shown in Fig. 1. Most (47/83, 56.6%) cases of melioidosis occurred during October to April, the rainy season in Malaysia.

### Microbiology

*B. pseudomallei* was isolated from blood specimens of 67 patients (80.7%). In total, 120 strains of *B. pseudomallei* were isolated during the study period. *B. pseudomallei* grew from more than one clinical sample in 22 patients. The microbiological findings are summarized in Table 1.

### Serological tests

Twenty five patients were not tested for serology. Of a total of 58 patients, 57 (98.2%) had significant serum titers of antibodies to *B. pseudomallei* (total antibody level  $\geq 1:80$ ).

### Antimicrobial susceptibility

According to disk diffusion tests, all *B. pseudomallei* isolates were sensitive to piperacillin and piperacillin/tazobactam. Ceftazidime, imipenem, amoxicillin-clavulanic acid, chloramphenicol (94%), tetracycline and trimethoprim-sulfamethoxazole appeared to be the most effective antimicrobials tested on these isolates. The antibiotic susceptibility of 120 isolates of *B. pseudomallei* is summarized in Table 2.

### Discussion

Melioidosis was initially reported in patients from Burma and was later linked with the Vietnam War, where helicopter crews showed a high incidence rate of melioidosis. It was then reported from Indonesia,

**Table 1.** Microbiological characteristics of 83 patients with culture-proven *Burkholderia pseudomallei* infections

Characteristic	Number of patients
Source	
Blood	67
Skin (wound, ulcer, etc.)	22
Bone	3
Urine	2
Liver	2
Spleen	2
Brain	1
Pericardial fluid	1
Synovial fluid	1
Respiratory system	10
Sputum	6
Tracheal secretion	3
Bronchoalveolar lavage	1
Growth	
Monomicrobial	77
Polymicrobial (co-existing pathogens)	6
Gram-negative bacilli ( <i>Pseudomonas aeruginosa</i> , <i>Klebsiella pneumoniae</i> , <i>Citrobacter</i> spp., <i>Acinetobacter baumannii</i> )	3
Gram-positive bacilli ( <i>Bacillus</i> spp.)	2
Gram-positive cocci ( <i>Enterococcus</i> spp., methicillin-resistant <i>Staphylococcus aureus</i> )	1

**Table 2.** Antimicrobial susceptibility of clinical isolates of *Burkholderia pseudomallei*

Antibiotic (no. of isolates tested)	Isolates No. (%)		
	Susceptible	Intermediate	Resistant
Ampicillin (n = 105)	1 (1)	0 (0)	104 (99)
Ampicillin-sulbactam (n = 113)	106 (94)	1 (1)	6 (5)
Amoxicillin-clavulanic acid (n = 114)	108 (95)	0 (0)	6 (5)
Piperacillin (n = 74) <sup>a</sup>	74 (100)	0 (0)	0 (0)
Piperacillin-tazobactam (n = 28) <sup>a</sup>	28 (100)	0 (0)	0 (0)
Ceftazidime (n = 120)	113 (94)	1 (1)	6 (5)
Cefoperazone (n = 117)	110 (94)	2 (2)	5 (4)
Imipenem (n = 118)	117 (99)	0 (0)	1 (1)
Meropenem (n = 32) <sup>a</sup>	28 (88)	0 (0)	4 (12)
Gentamicin (n = 113)	2 (2)	1 (1)	110 (97)
Netilmicin (n = 86)	7 (8)	3 (4)	76 (88)
Amikacin (n = 100)	15 (15)	6 (6)	79 (79)
Trimethoprim-sulfamethoxazole (n = 120)	84 (70)	4 (3)	32 (27)
Ciprofloxacin (n = 115)	91 (79)	7 (6)	17 (15)
Tetracycline (n = 115)	102 (89)	2 (1)	11 (10)
Chloramphenicol (n = 114)	107 (94)	1 (1)	6 (5)

<sup>a</sup>Meropenem, piperacillin-tazobactam and piperacillin were tested at the request of clinicians.

Thailand and Australia [15]. Melioidosis has increasingly been recognized as a common infectious disease in Malaysia and Singapore. The increase in incidence of melioidosis cases and new reports from non-endemic regions have raised alarms [1,16,17].

*B. pseudomallei* survives in the clay layer, 25 to 30 cm underneath the soil surface. It may be brought up and distributed to the surface by water seeping through the clay layer during the rainfall season. The association between rainfall and melioidosis has been established. Most melioidosis cases (75-85%) occur during or after the wet season in northeast Thailand and northeast Australia. In Australia, melioidosis-related pneumonia and deaths were more common during the rainy season when rainfall and winds were intense [18-20]. In Malaysia, the monsoon starts in early October and ends in April, and rainfall and winds are usually intense from October to January. Our data demonstrated that 57% of all cases occurred during the rainy season.

The demographic characteristics of this series were similar to those of other studies in endemic and non-endemic areas [21-23]. *B. pseudomallei* can affect all ages [24]. In our study, *B. pseudomallei* was isolated from a wound in a child aged two years, eight months. The majority of patients were elderly (41-60 years old), a previously identified possible risk factor [20]. Male patients accounted for 76% of all melioidosis cases, concurring with other reports from Taiwan

[23] and Thailand [20]. The high prevalence rate in males may be explained by the fact that males were often involved in outdoor activities and have more exposure to the soil and water than females.

White et al demonstrated that ceftazidime could reduce overall mortality by 50% in a randomised clinical trial [25]. Since then, it has become the drug of choice in severe acute melioidosis. In 1987, Puthuchery and Parasakthi reported that all 47 human isolates and 10 isolates from animals were susceptible to ceftazidime [26]. Most *B. pseudomallei* isolates, 94% in this series, are susceptible in vitro to ceftazidime. The emergence of ceftazidime resistance in clinical isolates of *B. pseudomallei* has previously been reported [27], and indeed six isolates (5%) were found to be resistant, and one intermediately resistant to ceftazidime. Other third-generation cephalosporins were less effective [22,25,28-30]. On the other hand, carbapenems have proved to be useful alternatives to ceftazidime in order to avoid resistance in *B. pseudomallei*. Carbapenems have good antibacterial activity against *B. pseudomallei* in vitro, and are active against strains exhibiting reduced susceptibility to ceftazidime or amoxicillin-clavulanic acid [31,32]. It has been shown that imipenem was as effective as ceftazidime for the treatment of severe melioidosis [33]. In our study, the majority of the strains of *B. pseudomallei* tested were sensitive to carbapenems.

Use of tetracycline, chloramphenicol, trimethoprim-sulfamethoxazole or amoxicillin-clavulanic acid has

been recommended as maintenance therapy on the basis of previous in vitro studies [16,34,35]. A combination of chloramphenicol, doxycycline and trimethoprim-sulfamethoxazole has been suggested as maintenance therapy in melioidosis. Chloramphenicol is given for the first eight weeks, followed by doxycycline and trimethoprim-sulfamethoxazole for 12 to 20 weeks [30]. However, a recent study revealed that the combination of trimethoprim-sulfamethoxazole and doxycycline was as effective as, and better tolerated than, the conventional four-drug regimen as maintenance treatment [36]. We found high susceptibility rates to amoxicillin-clavulanic acid (95%), chloramphenicol (94%), and tetracycline (89%) among *B. pseudomallei* clinical isolates, whilst 70% of isolates were susceptible to trimethoprim-sulfamethoxazole.

*B. pseudomallei*, a facultative intracellular organism, can survive in phagocytic cells and polymorphonuclear cells [37]. While ciprofloxacin is able to penetrate such cells, oral quinolones have been reported to be inferior to amoxicillin-clavulanic acid or the combination of trimethoprim-sulfamethoxazole, doxycycline and chloramphenicol as eradication therapy [38]. Clinical experience with ciprofloxacin maintenance therapy has shown poor efficacy for preventing relapse in melioidosis [38,39], but in our center 79% isolates of *B. pseudomallei* were susceptible to ciprofloxacin.

Aminoglycosides, either alone or with other beta-lactam drugs, are used empirically to treat suspected community-acquired infections in the different regions of the world, but these are ineffective against *B. pseudomallei*. High resistance to gentamicin was observed in our data, concurring with previous studies [21,34].

Melioidosis, a major community-acquired infectious disease, is hard to diagnose and eventually fatal. The incidence of melioidosis is increasing in Malaysia. There should be a high suspicion of melioidosis in all cases of sepsis, especially in patients with known risk factors and in the rainy season in endemic areas. It is suggested that all melioidosis cases should be monitored closely for a prolonged period. Melioidosis remains difficult to manage, and consultation with infectious disease specialists and microbiologists is advisable in cases of *B. pseudomallei* infection. In Malaysia, melioidosis could be treated aggressively by use of ceftazidime or a carbapenem for at least two weeks, and then by oral maintenance therapy with trimethoprim-sulfamethoxazole and tetracycline for at least 20 weeks.

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