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REVIEW

Burkholderia Pseudomallei Causing Bone and Joint Infections: A Clinical Update

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ABSTRACT

Burkholderia pseudomallei (*B. pseudomallei*), a causative agent of an emerging infectious disease melioidosis, is endemic in the tropical regions of the world. Due to increased international travel, the infection is now also seen outside of the tropics. The majority of patients with identified risk factors such as diabetes mellitus, heavy alcohol use, malignancy, chronic lung and kidney disease, corticosteroid use, thalassemia, rheumatic heart disease, systemic lupus erythematosus and cardiac failure acquire this organism through percutaneous inoculation or inhalation. The clinical manifestations are variable, ranging from localized abscess formation to septicemia. Melioidotic bone and joint infections are rarely reported but are an established entity. The knee joint is the most commonly affected joint in melioidosis, followed by the ankle, hip and shoulder joints. Melioidosis should be in the differential diagnosis of bone and joint infections in residents or returning travelers from the endemic area. Melioidosis diagnosis is missed in many parts of the world due to the lack of awareness of this infection and limited laboratory training and diagnostic techniques. It also mimics other diseases such as tuberculosis. Delay in the diagnosis, or the initiation of appropriate and effective treatment against melioidosis, could worsen the outcome. Initial therapy with ceftazidime, or carbapenem with or without cotrimoxazole is recommended, followed by the oral eradication therapy (based on the antimicrobial susceptibility) with amoxicillin/clavulanic acid or cotrimoxazole. Surgical intervention remains important. This paper reviews current literature on the epidemiology, clinical features, diagnosis, and management of melioidotic bone and joint infections.

Keywords: Bone and joint infections; *Burkholderia pseudomallei*; Melioidosis

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INTRODUCTION

Burkholderia pseudomallei (*B. pseudomallei*) is a causative agent of a severe and fatal infectious disease which is called melioidosis. *B. pseudomallei*, a Gram-negative bacterium, is a water and soil pathogen in Eastern Asia and Northern Australia. Melioidosis has emerged as an important cause of morbidity and mortality for the last several decades in the Southeast hemisphere. Melioidosis has expanded its occurrence from the tropics to other parts of the world such as other Asian regions, South America and the Caribbean [1–5]. *B. pseudomallei* can infect healthy individuals, but it is seen more commonly in patients with co-morbidities such as diabetes mellitus, malignancy and immunosuppression. Clinical manifestations of melioidosis range from latent infection, localized cutaneous lesions, sub-acute pneumonia, bone and joint infections, abscesses in body organs and cranial abscesses to life-threatening septicemia [1, 3, 6, 7].

The clinical presentations of bone and joint infections due to *B. pseudomallei* are indistinguishable from other infectious causes. Melioidosis should be considered in the differential diagnosis in patients from the disease endemic area, or who are returning from these areas. Early diagnosis can be made using the laboratory and clinical parameters to prompt administration of appropriate antimicrobial therapy, and achieve better prognostic outcome [5]. Mortality in acute severe melioidosis even with appropriate treatment still remains considerably high, ranging from 30% to 47% [8]. This article reviews the microbiology, epidemiology, clinical features, diagnosis, management and aspects of melioidosis particularly associated with bone and joint infections. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

MICROBIOLOGY

Burkholderia pseudomallei, previously known as *Pseudomonas pseudomallei*, is an aerobic, motile, non-spore forming, intracellular, soil saprophyte which can be found in wet soil and surface water [9, 10]. It is an oxidase-positive, Gram-negative bacillus with bipolar staining, (appears as a safety pin in the Gram stain film) which grows easily on commonly used media in the microbiology laboratory at 37 °C. Variation in the colonial morphology can be noted; smooth colonies appear in young culture, while wrinkled and dry colonies appear in old culture [11, 12]. *B. pseudomallei* is able to resist hostile conditions such as extreme temperature, nutrient deficiency, acidic and alkaline conditions, dehydration and antiseptics and disinfectants [11, 12]. *B. pseudomallei* is resistant to different groups of antibiotics, for example, aminoglycosides, penicillins, cephalosporins (first and second generations), and rifamycins.

EPIDEMIOLOGY

Melioidosis was first diagnosed in intravenous morphine users with septicemia in Burma (now Myanmar) in 1912 by Whitmore and Krishnaswami [13]. The majority of cases are reported from Southeast Asia and Northern Australia, corresponding to tropical latitudes between 20°N and 20°S, and sporadic cases have been reported from Malaysia, Pakistan, Indonesia, Japan, Bangladesh, India, Sri Lanka and Indonesia [3, 14–16]. It is thought that *B. pseudomallei* may be brought up from a clay

layer and distributed in the environment during the rainfall, as it resides in the clay layer 25–30 cm underneath the soil surface [17–19]. Between 75% and 85% melioidosis cases from northeast Thailand and northern Australia occur during the wet season [18]. One study from Malaysia reported that 57% of melioidosis cases occurred during the rainy season, which usually takes place every year between October and April [20]. It is thought that there may be a shift from inoculation to inhalation of *B. pseudomallei* during the monsoon stormy weather, hurricanes, typhoons and cyclones, as pneumonia is a predominant presenting feature in melioidosis [21].

Bone and joint infections due to *B. pseudomallei* are a well-recognized entity of this disease. The majority of the melioidotic bone and joint infections are found in the case reports from different regions of the world [5]. One study [22] from an endemic area in Northern Australia reported a 7.6% incidence of bone and joint infections in melioidosis patients, which was much less than a melioidosis case series of bone and joint infections from Thailand (14–27% incidence) [4, 23, 24]. A total of 29% patients with melioidosis in Brunei had bone and joint infections [5].

MODES OF TRANSMISSION

Hematogenous spread after percutaneous inoculation is thought to be an important mode of transmission in bone and joint infections. The organism may also reach directly from other organs, or from soft tissue infection over bones or joints. Septic arthritis and osteomyelitis, one or both, can be the primary manifestation in patients with melioidosis. Other important routes of spread of melioidosis are ingestion and inhalation especially during heavy rainfall and cyclones [4, 25].

RISK FACTORS

A number of environmental and patient-related host factors have been defined in several studies from the endemic areas. Many cases have been linked to occupational and recreational exposure to surface water, for example, in rice paddy farmers in Thailand, [26] and outdoor work, landscaping and gardening in Australia [22]. Melioidosis usually affects patients with underlying illnesses such as diabetes mellitus, heavy alcohol consumption, chronic lung disease, renal disease, malignancy, corticosteroid use, thalassemia, previous trauma, rheumatic heart disease and/or cardiac failure, and surgery [4, 22, 27–29]. Other risk factors include splenectomy, aplastic anemia, cystic fibrosis, glucose 6 phosphate dehydrogenase deficiency, and systemic lupus erythematosus (SLE) [1]. Diabetes mellitus is the most important predisposing risk factor, and it increases the risk of melioidosis by 100-fold [19, 22, 23, 29]. The underlying comorbidities lead to immune dysfunction such as impaired polymorphonuclear phagocyte functions, so impaired phagocytic cells fail to clear this organism. It is thought that the immune deficiency increases the risk of melioidosis [30, 31]. One study reported that there is a 5.7 times higher risk of septic arthritis in melioidotic patients with diabetes mellitus, SLE and chronic renal failure [24]. Melioidosis in bone and joint infection is more common in males [4, 23]. This may be the case because males are exposed to *B. pseudomallei* while working in the rice paddies and they may be more involved in other outdoor activities.

CLINICAL FEATURES

Melioidotic bone and joint infections remain uncommon and are usually difficult to differentiate from other causative agents such as *Staphylococcus*, *Streptococcus* and others, unless microbiologically proven in cultures. Acquisition in bone and joint infections is usually via direct spread through small skin abrasions, wound infections and abscess or hematogenous spread in patients who presented with another primary diagnosis, such as pneumonia or septicemia. There is no specific clinical presentation, and it mimics different forms of osteomyelitis, septic arthritis infections and rheumatoid disorders. Prominent features in septic arthritis are swelling, tenderness, redness, and heat around joints [21, 24]. In melioidotic bone and joint infections, the presentation picture is usually chronic in nature, such as persistent fever rather than shock or respiratory failure, and overall mortality is low in this group [23]. Either single or multiple bone or joint involvement is observed in the past in musculoskeletal infections due to melioidosis. *B. pseudomallei* mainly causes infections in knee and hip joints (Table 1). It also affects the shoulder and other joints. Increased vascular supply in the metaphyseal regions of long bones helps it spread easily to bones and joints.

One recent study [32] from Australia revealed that 25.4% patients (16/63 episodes) and 31.7% patients with melioidosis (20/63 episodes) presented with septic arthritis and osteomyelitis as the primary illness, respectively. More than one focus of infection was present in more than half of the patients (32/50). In this study, knee (15), tibia (11) and ankle (11) joints were the most affected, followed by metatarsal (4), femur (3), and lumbar spine (3) (Table 1). Teparrakkul et al. [23] from Thailand reported that of 679 patients, 98 had musculoskeletal melioidosis. Among joints, knee joints (41 patients) were the most affected joint; followed by ankle (20), hip (15), and shoulder (10) joints. Among bones, the femur and tibia were more involved than upper limb bones. This study also showed three patients suffering with discitis. The high incidence of knee joint involvement was recorded in these two studies [23, 32]. On the contrary, Kosuwon et al. [24] reported the shoulder joint being more commonly infected by *B. pseudomallei*. Morse et al. [4] from Northern Australia presented a 20-year study of osteomyelitis and septic arthritis due to *B. pseudomallei*, in which 41/536 patients with melioidosis had suffered with osteomyelitis or septic arthritis. Of the 41 patients, primary melioidosis was identified in 13 patients with septic arthritis and 7 patients with osteomyelitis while 14 had melioidosis of the bone/joint secondary to primary melioidosis elsewhere. Seven patients showed signs of both bone and joint involvement. Saravu et al. [33] reported 25 culture-confirmed adult cases of melioidosis, of which 48% (12/25) had osteomyelitis or septic arthritis. This proportion was higher than the 14–33% reported in studies from Malaysia and Thailand [23, 24, 34].

DIAGNOSIS

Lack of awareness about the disease, limited laboratory resources to isolate the organism, and confusion with other infectious diseases such as *Mycobacterium tuberculosis*, may lead to the misdiagnosis of melioidosis. Melioidosis is diagnosed on the basis of the clinical and laboratory parameters, and radiology. The majority of patients have increased or low white blood cell and neutrophil cell counts, increased C-reactive protein or procalcitonin or

Table 1 Summary of *B. pseudomallei* causing bone and joint infections

References	Country	Number of patients with bone/joint infections/total patients	Mean age	Important risk factors	Bone/joint involved (patients)	Isolate source involvement	Treatment	Mortality
Shetty et al. [32]	Australia	63/781, only 50 were included	48	DM, alcohol use, CLD, CKD, malignancy, immunosuppression	Knee (15), ankle (11), hip (2), elbow (2), shoulder (1) MTP (1), tibia (11), tarsal (4), femur (3), lumbar (3), humerus (1), hand (1), thoracic (1), pelvis (1)	Bone and joint infection, bacteremia, pneumonia, abscess	Ceftazidime and or meropenem, then oral cotrimoxazole or doxycycline for 3–6 months	4/50
Morse et al. [4]	Australia	41/536 (20 primary, 21 secondary bone and joint infections)	41 in 20 patients and 47 years in 21 patients	DM, alcohol use, renal impairment, occupational exposure	Lower limb (37) Upper limb (3), both (1)	Pneumonia, bacteraemia, genitourinary infection, abscess,	Ceftazidime or meropenem, for 4–8 weeks IV, then oral Cotimoxazole plus fusidic acid for 3 months	Primary: 2 (10%) Secondary: 2 (4.5%)
Pande et al. [5]	Brunei Darussalam	8/48	45 years	DM, CKD, cirrhosis, idiopathic membranous nephropathy	Knee (4) Tibia (3) Elbow (1)	Septicemia, joint infection	Not mentioned	No mortality

Table 1 continued

References	Country	Number of patients with bone/joint infections/total patients	Mean age	Important risk factors	Bone/joint involved (patients)	Isolate source involvement	Treatment	Mortality
Currie et al. [22]	Australia	20/540	49 years	DM, alcohol use, CKD, CLD, malignancy	Not mentioned	Pneumonia, splenic abscess	Not mentioned	2/20
Saravu et al. [33]	India	12/25	Age range 18–67	DM, alcoholism, CLD, HIV, CKD, malignancy and chemotherapy, farming	Not mentioned	Pneumonia, chronic osteomyelitis, abscess, septicamia	Ceftazidime or carbapenem for 14 days followed by co-amoxiclav plus cotrimoxazole or co-amoxiclav plus doxycycline around 5–6 weeks	Not mentioned
Ahmed et al. [34]	Malaysia	11/33	Range 40–65 years	DM,	Not mentioned	Pneumonia, foot abscess	Ceftazidime or meropenem plus co-amoxiclav for 4 weeks, then oral amoxi clavulanate plus trimethoprim or doxycycline for 6 months	2/11
Teparrakkul et al. [23]	Thailand	98/679	49	DM, malignancy, renal insufficiency, liver disease, steroids	Mostly lower extremities (65) Fewer upper extremities (18), others (3)	Pneumonia, sepsis, abscess,	IV therapy (ceftazidime etc.) between 9 and 18 days and oral therapy between 50 and 145 days	27/98

Table 1 continued

References	Country	Number of patients with bone/joint infections/total patients	Mean age	Important risk factors	Bone/joint involved (patients)	Isolate source involvement	Treatment	Mortality
Kosuwon et al. [24]	Thailand	25/104	53.5	DM, CKD, SLE, Farmer	Mostly upper extremity, knee (6)	Synovial fluid, blood	Ceftazidime, cotrimoxazole, or doxycycline, chloramphenicol, cotrimoxazole	Not mentioned
Subhadrabandhu et al. [31]	Thailand	10/64	46.8	DM, renal calculi, AIDS	Proximal humerus (4), femur (1), tibia (1), spine (4)	Pus, blood culture	Chloramphenicol plus tetracycline or chloramphenicol plus cotrimoxazole or ceftazidime plus cotrimoxazole IV therapy for six weeks followed by oral therapy for one year 7	2/10

CLD chronic lung disease; *CKD* chronic kidney disease; *DM* diabetes mellitus; *IV* intravenous; *SLE* systemic lupus erythematosus

erythrocyte sedimentation rate, impaired renal or liver functions, and in some cases organ failure. Accurate and timely diagnosis remains crucial to initiate prompt definitive antimicrobial therapy, to reduce the mortality. Several factors play a pivotal role in the laboratory diagnosis of melioidosis: (1) collection of an appropriate sample; for example, needle aspiration from the abscess, such as a psoas abscess, or bone in the case of osteomyelitis, tissue or bone in discitis, tissue from ulcers or wounds, and blood cultures, (2) transportation of the samples in appropriate media, or in a sterile container, to the microbiology laboratory without any delay, (3) handling of the samples by trained and experienced laboratory staff, (4) processing using appropriate media, incubating and using the best methods to identify this organism, (5) use of specific antimicrobial discs which are used as intravenous or oral therapy for the treatment of melioidosis. Breach of any of the above-mentioned steps may lead to low chances of isolation of *B. pseudomallei* [1, 3, 35–37].

Isolation of *B. pseudomallei* from the clinical specimens is considered to be the gold standard in the diagnosis of melioidosis. Isolation of *B. pseudomallei* from clinical samples is regarded as a significant isolate. Use of selective media for processing samples from non-sterile sites is helpful in suppressing commensal organisms, which otherwise can overgrow and give a false-negative result. A modified Ashdown media which contains colistin is currently used in the laboratories for the isolation of this organism [1, 36, 37]. Serology may be helpful in cases of culture-negative results, or in the absence of clinical samples from patients with melioidosis. However, the serology results should be interpreted cautiously in endemic areas, where local populations have raised melioidosis antibody levels. A group of researchers from north eastern Thailand reported that the indirect hemagglutination assay has a 95% sensitivity but the specificity is low (59%). In this study, patients with bacterial infections had a high titer of 1:1280 [38]. One Malaysian group developed an indirect immunofluorescence test using whole-cell antigen for the detection of total antibodies to *B. pseudomallei*. They found this test quite rapid and reliable [39]. A raised *B. pseudomallei* antibody titer in healthy individuals is probably due to repeated natural exposure to this saprophytic organism during outdoor activities. Molecular methods, for instance Polymerase Chain Reaction, or Pulsed Field Gel Electrophoresis, are being employed in the clinical and research laboratories; these are less sensitive than gold-standard culture results [40].

TREATMENT

Normally systemic antimicrobial therapy active against *B. pseudomallei*, vigorous and repeated washouts, and several extensive debridements of infected bone are the cornerstones of treatment of bone and joint infections. Prompt administration of antibiotics remains important to reduce morbidity and mortality. Inflammatory markers and clinical signs of improvement are used to gauge the response to the specific therapy for melioidotic bone and joint infections. Intravenous antimicrobial therapy should be prolonged for deep-seated infection or complicated infections from four to eight weeks followed by the oral maintenance therapy for a minimum of 12 weeks (Tables 2, 3) [1, 4, 28, 31, 41]. Mortality was quite high before the antibiotic era. In an open-labeled randomized trial, the group compared the efficacy of ceftazidime (120 mg/kg/day) with

Table 2 Antimicrobial therapy for treating severe melioidosis [11, 21, 32, 37, 41]

Patients	Drug	Dosage/route	Frequency
Severe melioidosis			
With no complications	Ceftazidime	IV 50 mg/kg/day (maximum 2 g) Or 6 g/day by continuous infusion after 2 g bolus	8 hourly
With neuromelioidosis, persistent bacteraemia, or in intensive care unit	Meropenem	25 mg/kg (maximum 2 g)	8 hourly
Severe melioidosis			
	Ceftazidime plus cotrimoxazole	Ceftazidime; 100–120 mg/kg/day, cotrimoxazole (8–12 and 40–60 mg/kg/day)	Ceftazidime: 8 hourly Cotrimoxazole: 12 hourly
OR	Ceftazidime plus ciprofloxacin	Ceftazidime as above ciprofloxacin (500 mg)	Ceftazidime as above Ciprofloxacin: 12 hourly for two weeks
OR	Meropenem plus cotrimoxazole	As above	As above
Duration of IV antimicrobial therapy in acute phase is usually 4–8 weeks. Not less than 2 weeks from last operative intervention			
The therapy should be rationalized after the availability of culture and sensitivity results			

IV Intravenous

"conventional therapy" (chloramphenicol 100 mg/kg/day, doxycycline 4 mg/kg/day, trimethoprim 10 mg/kg/day, and sulphamethoxazole 50 mg/kg/day) in the treatment of severe melioidosis. Ceftazidime was associated with 50% (74–37%) reduction in mortality rate than the conventional therapy [42]. Ceftazidime has become the drug of choice for intensive therapy after this study. Ceftazidime, or a member of the carbapenem group, is the drug of choice to treat this infection, followed by oral cotrimoxazole as a monotherapy or amoxicillin–clavulanic acid [41, 43, 44]. On the other hand, Inglis suggests the use of ceftazidime, meropenem or imipenem and trimethoprim–sulfamethoxazole and folic acid in the acute phase followed by any two antibiotics from the group of trimethoprim–sulfamethoxazole, doxycycline, and amoxicillin–clavulanic acid, as eradication therapy in deep-seated infections [11]. One study from Malaysia showed a low-level resistance to the commonly used antibiotics for the treatment of melioidosis. In this study, all isolates (170) of *B. pseudomallei* appeared

Table 3 Oral maintenance therapy for melioidosis [32, 37, 41]

Drug	Patient characteristics	Dose/frequency	Duration
Trimethoprim–sulfamethoxazole	Adult >60 kg	160 mg/800 mg tablets; two tablets every 12 h	For osteomyelitis: the recommended duration is a minimum of 6 months
	Adult, 40–60 kg	80 mg/400 mg tablets; three tablets every 12 h	
	Adult, <40 kg	160 mg/800 mg tablets; one tablet every 12 h OR	
		80 mg/400 mg tablets; two tablets every 12 h	
	Child	8 mg/40 mg per kg; maximum dose 320 mg/1600 mg every 12 h	
OR			
Amoxicillin/clavulanic acid (co-amoxiclav)	Adult, 40–60 kg	500 mg/125 mg tablets; three tablets every 8 h	For septic arthritis: the recommended duration is a minimum of 3 months
	Adult, <40 kg	500 mg/125 mg tablets; two tablets every 8 h	
	Child	20 mg/5 mg per kg every 8 h; maximum dose 1000 mg/250 mg every 8 h	
OR			
Doxycycline	Adult	100 mg tablets, 12 hourly	

sensitive to meropenem and piperacillin/tazobactam, while less than 1% resistance was recorded in ceftazidime, imipenem, and amoxicillin–clavulanic acid. Of 170 isolates, 98 were resistant to ciprofloxacillin [45]. Table 1 summarizes the antibiotic therapy. No specific vaccine is available for melioidosis.

Out-of-hospital intravenous antimicrobial treatment in clinically stable patients, or those who do not require intensive care support or hospitalization, has become popular in many parts of the world. This service saves not only hospital bed days, and healthcare costs, but also healthcare workers' time. These patients are closely monitored by specialist staff during the treatment period [46, 47]. One study from Southeast Asia looked at outpatient antimicrobial therapy in 56 patients with confirmed melioidosis who were treated in two large tertiary care hospitals. Patients received ceftazidime 100–200 mg/kg/day via a peripherally inserted central catheter (PICC) and elastomeric infuser. Eighty-six percent of patients (47/56) completed the course. Of the nine patients who did not complete the therapy, four patients experienced adverse

reactions, two needed surgical intervention, and in three patients the underlying illness worsened. The overall outcome was good [47].

RELAPSE

High relapse rates in *B. pseudomallei* infections are mentioned in the literature [4, 48–50]. It remains important to complete therapy (Table 1), including the maintenance therapy, to prevent relapse in melioidosis. Patients treated with appropriate antibiotics require long-term follow-up, as this organism remains latent for up to 26 years in the body. One recent study on melioidotic bone and joint infections reported relapse in 10 patients. Of the 10 patients, seven received less than 4 weeks of antibiotics [32]. The average time between discharge from the hospital and relapse is approximately 21 weeks [49]. A higher relapse rate (30%) has been noted if the overall duration of antimicrobial therapy is less than eight weeks [50]. Relapse should be considered and treated as a first episode [50].

CONCLUSION

In endemic areas, *B. pseudomallei* should be considered as one of the causative agents of bone and joint infections because of its rising incidence and high rate of morbidity and mortality if not diagnosed and treated early on. A high index of suspicion of melioidosis is required to make the diagnosis. Isolation of *B. pseudomallei* from clinical specimens is considered to be the gold standard; however, to achieve this, samples must be processed carefully and in the appropriate media. Treatment of melioidosis affecting bones and joints consists of antimicrobial therapy coupled with surgical management including washouts of joints and debridement of infected bone. Those patients with deep-seated or complicated infections require intravenous antibiotics for 4–8 weeks, followed by oral antibiotics for a minimum of 12 weeks. Ceftazidime is usually the intravenous antibiotic of choice, which is followed by oral therapy such as cotrimoxazole. Some countries are now using outpatient antimicrobial therapy for their clinically stable patients. Unfortunately no vaccine has yet been developed for this disease, which makes the awareness and understanding of melioidotic bone and joint infections, and the need for timely diagnosis and treatment, all the more relevant to microbiologists today.

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