PRACTITIONERS' SECTION

MELIOIDOSIS: A REVIEW OF ORTHOPEDIC MANIFESTATIONS, CLINICAL FEATURES, DIAGNOSIS AND MANAGEMENT

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ABSTRACT

Melioidosis is an infectious disease caused by gram-negative soil-dwelling bacillus Burkholderia pseudomallei. Musculoskeletal melioidosis mimics other infections both clinically and radiologically. An extensive literature review has been performed over musculoskeletal melioidosis through various search engines such as Pubmed, Embase, Medscape, Altavista and Google. Diagnosis requires a high index of clinical suspicion and is dependent on microbiological confirmation. Prompt treatment with long-term combination antibiotics in high dosages and surgical drainage of abscesses improves survival

Key words: ***Burkholderia pseudomallei, melioidosis, musculoskeletal, orthopedics***

Melioidosis is a saprophytic infectious disease caused by gram-negative soil-dwelling bacillus *Burkholderia pseudomallei*. Synonyms include Pseudoglanders, Vietnamese time bomb, Whitmore's disease and Rangoon beggar's disease.[1,2] Alfred Whitmore and C. S. Krishnaswami first described melioidosis as a 'glanders-like' disease in morphia addicts.[3,4] An extensive literature review has been performed over melioidosis through various search engines such as Pubmed, Embase, Medscape, Altavista and Google. This disease, now termed melioidosis, was named from the Greek *melis* (distemper of asses) and *eidos* (resemblance) by Stanton and Fletcher.[5] A wide variety of animal species have been shown to be susceptible to melioidosis.[6] Human melioidosis does not appear to be a zoonosis.[7] Any delay in diagnosis and treatment of this infection may be harmful, because the disease possesses the potential for recurrence and may become an acute, fulminant and fatal infection.[8,9] In melioidosis, recurrent infections can occur in about 2-9% of cases, due to either relapse (same strain, unknown mechanism) in two-thirds of cases, especially in the first year; and the rest due to re-infection with new strain.[10] The first case of human melioidosis in Australia was described in a young diabetic adult from Townsville in 1950, who died of septicemic melioidosis.[11] Recent study, using molecular technique called multilocus sequencing typing

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(MLST), shows that both environmental and clinical strains of *B. pseudomallei* from Australia are much different from those from Thailand.[12] Melioidosis is increasingly recognized around the world. It has been noted that published case reports and series are likely to represent only the 'tip of the iceberg' - i.e., melioidosis is far more common than previously recognized, as culture facilities for bacterial isolation are not available in most of the rural tropics, where the infection is likely to be prevalent.[13] There have been concerns of *B. pseudomallei* being thought of as a potential biological warfare agent.[14]

CAUSATIVE ORGANISM

Burkholderia pseudomallei, also termed previously as *Bacillus pseudomallei*, *Bacillus whitmorii* (or *Bacille de Whitmore*), *Malleomyces pseudomallei* and *Pseudomonas pseudomallei,*[15] closely resembles common contaminant *Pseudomonas* species and is easily misidentified in microbiology laboratories.[7] *B. pseudomallei* is visualized as a small gram-negative aerobic, motile, non-spore-forming bacillus with bipolar staining and is vacuolated and slender and has rounded ends; it is often described as having a 'safety pin' appearance.[16,17] The organisms are commonly found in water and soil; *B. pseudomallei* is a resilient bacterium that can survive in a variety of hostile conditions, including nutrient deficiency, acid and alkali pH, disinfectant and antiseptic solutions (including detergents and chlorine), exposure to many antibiotics and extremes of temperature.[6,18] *B. pseudomallei* produces a glycocalyx polysaccharide capsule, which is probably an important virulence determinant.[19]

GEOGRAPHIC DISTRIBUTION

Melioidosis is regarded as endemic to Southeast Asia and northern Australia, corresponding approximately to the tropical latitudes between 20°N and 20°S.[20] The highest rates of disease are currently noted in Thailand and Australia, and sporadic cases are reported in India,[21-24] Indonesia, Bangladesh, Japan, Philippines, Pakistan, Sri Lanka[6] and Malaysia.[25]

Multiple cases have been reported from disparate regions of India but have been largely restricted to a few large medical centers, presumably where identification is possible.[6] Cases in travelers returning to Europe from the Indian subcontinent have been reported, suggesting poor ascertainment of cases locally.[26] In addition, one sero survey revealed a seroprevalence of 7% in a rural rice-growing area near Vellore.[27]

Further, John *et al*. reported Tripura, Kerala Orissa, Tamil Nadu and Maharashtra as potentially endemic areas for melioidosis.[27] Moreover, involvement in the tsunami of December 2004 is a risk factor for melioidosis, and the risk may extend to individuals who were uninjured bystanders.[28,29]

PREDISPOSING FACTORS

1. Surface water: There is a strong relationship between surface water and melioidosis.[30,31]
2. Moist clay: Moist clay soils seem to be favored by the organism. Melioidosis is seasonal in the tropics, where most cases occur during the rainy season. This can be explained by increased contact with the organism. Although the main mode of acquisition of disease is through inoculation, the association of prior heavy rainfall with both pneumonia and more severe disease may well reflect a shift towards inhalation as the mode of acquiring *B. pseudomallei*. The periods of intense monsoon rainfall are usually also associated with heavy winds; therefore, aerosolization of bacteria from surface soil and water under such conditions is probable.[32] Moreover, both increased environmental bacterial load and increased virulence of environmental *B. pseudomallei* may possibly result from periods of heavy rainfall.[31,33,34]
3. Physical factors that may influence the distribution of *B. pseudomallei* in the environment include rainfall, humidity, UV radiation and temperature.[6]
4. Chemical factors such as soil composition, other vegetation, the use of fertilizers, soil digging and plowing also flourish the growth of organism.[35]

RISK FACTORS

Melioidosis is often associated with other underlying diseases such as diabetes,[30,36,37] thalassemia,[7,38] chronic renal failure and high alcohol consumption.[6]

Kosuwon *et al*. found diabetes and thalassemia were the two most common concurrent diseases in the melioidotic patients.[7,39] The presence of specific risk factors for infection, such as diabetes, suggests that functional neutrophil defects are important in the pathogenesis of melioidosis.[40,41] Other risk factors are chronic granulomatous disease, splenectomy, aplastic anemia, febrile neutropenia, mycobacterial disease, dengue hemorrhagic fever, AIDS, porphyria cutanea tarda, cystic fibrosis, hemosiderosis, glucose-6-phosphatase deficiency, systemic lupus erythematosus, steroid use and renal transplantation.[6] A population-based study in Australia defined adjusted relative risks of melioidosis as 4.0 for those aged ≥45 years, 2.4 for males, 3.0 for Aboriginal race.[35]

MODE OF TRANSMISSION

Infection is acquired through three modes of acquisition, viz., inhalation, ingestion and cutaneous inoculation.[6,30] The skin is the usual portal of entry, and organisms enter through preexisting lesions, including penetrating wounds. Kosuwon *et al.* reported that two patients who had wound of the knee and heel cord while working in wet rice field subsequently became infected with *Burkholderia pseudomallei*.[7]

Human-to-human sexual transmission of melioidosis has been rarely seen.[42] Infection in the neonates has been postulated to arise from the birth canal infection or amniotic fluid contamination.[43] In addition, laboratory-acquired infection through contaminated equipments and inhalation has been reported in the literature.[44-45]

INCUBATION PERIOD

In natural infection, the incubation period varies from 2 days to months or years, with the longest incubation period documented being 62 years. Infection may remain latent for years.[46-47]

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CLINICAL FEATURES

In terms of clinical classification, six types of melioidosis were introduced by Punyagupta:[48]

1. Disseminated septic melioidosis
2. Non-disseminated septic melioidosis
3. Localized melioidosis
4. Transient bacteremic melioidosis
5. Probable melioidosis
6. Subclinical melioidosis

The clinical spectrum of melioidosis is variable and includes latent infection, local cutaneous lesions, subacute pneumonia, focal organ abscesses, musculoskeletal infection and lethal fulminant septicemia.[6,49-52] Melioidosis affects all ages but peak incidence is mainly between 40 and 60 years of age, with male-to-female ratio of 1.4:1.[53] The higher incidence rate among men is related to higher occupational exposure to organism in the soil and water through farming, stock keeping and field work.[54]

The clinical course may be acute, subacute or chronic. The acute illness presents as a pulmonary infection, which varies from mild tracheobronchitis to overwhelming cavitary pneumonia. Some patients may come with septic shock without any focal lesion. Fulminant septicemia, shock, coma and death may be the culminating events. Subacute melioidosis mimics tuberculosis and also occurs as a self-limited febrile disease. Chronic infection is a localized suppurative infection involving lungs, skin or bones.[55] It may resemble TB clinically and radiologically. Therefore, *B. pseudomallei* has been called the 'great mimicker' of other infectious diseases such as TB, syphilis and typhoid fever.[7,55-57] There are no reliable pathognomonic features of acute or subacute melioidosis. Chronic melioidosis may follow a mild acute illness or it may lie dormant for months or years, only to appear suddenly - hence the term 'Vietnamese time bomb'.[58]

Musculoskeletal infection

Melioidosis can involve bone and joint. There are case reports of orthopedic infection published in English literature, and most of the cases of musculoskeletal melioidosis are in localized form without other organ involvement.[7,39]

Clinical manifestations of articular melioidosis are not diagnostic. It can mimic acute or chronic arthritis from other infectious or rheumatic disorders. Articular melioidosis is relatively uncommon and predominantly mono- or poly-articular. Melioidosis involves the large weight-bearing joints, especially knees. Often soft tissue abscess with osteomyelitis is associated with septic arthritis in many patients. Pui *et al.* retrospectively analyzed imaging studies in 26 patients of musculoskeletal melioidosis. They found that septic arthritis is more common than soft tissue abscess and osteomyelitis in melioidotic patients.[59] Saengnipanthkul *et al.* reported only 9 cases of articular melioidosis in 44 years in endemic zone of melioidosis.[55] The clinical presentation of musculoskeletal melioidosis has been reported in most of the bones of the body. According to Pui *et al.,* knee is the most commonly affected, followed by ankle, foot, shoulder, thoracic or lumbar spine and the pelvis.[59] Other reported sites are femur, humerus, hip, elbow, sacroiliac joint, tibia, sternomanubrial joint, rib and mandible.[60-62] Nandurkar and Lau described a case of multifocal melioidotic osteomyelitis.[63] First case of *B. pseudomallei* involving the posterior

elements of the spine and causing extensive osteomyelitis of three vertebrae (T9-T11) was described by Nather *et al.*[64]

Osteoarticular melioidosis is characterized by localized pain over underlying bone or joint, associated swelling, painful movements with fever; and if the spine is involved, truncal rigidity and muscle spasm, with or without neurological signs. Bartley *et al.*[65] reported a case of acute melioidosis which predominantly affected the spinal cord to produce paraplegia-mimicking acute epidural abscess. Bone and joint infections may be difficult to differentiate from infections caused by other causes, except that the systemic features of the illness may be more prominent in melioidosis. Currie *et al.,* in their 10-year prospective study on endemic melioidosis in northern Australia, reported 252 cases, of which only 4% had osteomyelitis or septic arthritis.[35] Further, according to reviews by Sookpranee *et al.* and Cowsuwon and Shaikitpinyo, bone and joint involvement was rare and accounted for 8% of the case series.[66,67] Subhadrabandhu *et al.* reviewed 10 patients of localized melioidotic osteomyelitis and found it as an uncommon infection.[68] Sirikulchayanonta *et al.* considered melioidosis as a differential diagnosis of granulomatous osteomyelitis, since the lesions are indistinguishable from tuberculosis and treatment is quite different from the same.[56] Subsequently, Wilairatana & Wilairatana reported melioidotic spondylitis which mimicked tuberculous spondylitis.[57] Recently, Kosuwon *et al*. compared melioidotic septic arthritis with nonmelioidotic septic arthritis and concluded that a diagnosis of melioidotic septic arthritis should be considered when septic arthritis is seen in an individual who is indigenous to, or has recently visited, Southeast Asia. The infection is more likely to be melioidotic septic arthritis if it involves an upper-extremity joint and if the patient has diabetes mellitus.[39] A case of chest wall melioidotic osteomyelitis resulting from localized extension of a splenic abscess has also been described.[62]

INVESTIGATION

Plain radiograph

There are no specific radiographic features described that are pathognomonic of melioidosis of bones or joints. However, common imaging findings that should arouse suspicion of joint involvement or septic arthritis include soft tissue swelling, joint effusion and periarticular osteoporosis on plain radiograph.[59]

Osseous lesions usually involve the red marrow of long bones and the vertebral bodies, in which radiographic appearance cannot be differentiated from that of tuberculous lesion.[56]

Long bone: The imaging features of osteomyelitis in long bone are soft tissue swelling, increased marrow density, osteoporosis or osteosclerosis and bone destruction; osteolytic or cystic lesions or circumscribed, saucer-shaped erosion of cortical bone with scalloped border may be evident. This mimics conditions like neoplasm, sarcoidosis and other granulomatous infections. Any part of bone may be involved, like epiphysis, metaphysis or diaphysis; but metaphyseal region is most commonly involved. Sequestrum, periosteal new bone formation and periostitis are rarely seen.[7,39,55,56,59,63,68]

Vertebral lesions: Shows destruction of vertebral bodies with varying degree of collapse with scalloping of anterior vertebral margin, para-

vertebral abscess and decreased vertebral disc spaces on plain radiography. Often, multiple bones are involved in the spine.[7,68,55,59,63]

Subhadrabandhu *et al.* also reported pathological fracture in one case. It is noteworthy that isolated bone lesions caused by melioidosis may closely mimic neoplasm or cysts radiologically.[68]

White cell scanning

White cell scanning is a quick and effective way of assessing the extent of musculoskeletal, visceral and soft tissue disease in melioidosis.[69] Septic arthritis and osteomyelitis showed hyperemia and increased bone uptake on bone scintigraphy.[59]

Computerized tomography (CT) scan

Soft tissue abscess appeared as mass with central attenuation and peripheral contrast enhancement on CT scan.[59] 'CT'-guided needle biopsy is recommended to investigate causative microorganisms.[64]

Magnetic resonance imaging (MRI)

Septic arthritis showed hyperintensity relative to muscle on T2-weighted MR images and hypointensity on T1-weighted MR images with contrast enhancement; and findings of osteomyelitis include hyperintensity of bone marrow on T2-weighted MR images and hypointensity on T1-weighted MR images with contrast enhancement.[59]

DIAGNOSIS

General

General tests of inflammation are neither specific nor completely reliable. However, Erythrocyte Sedimentation Rate, Total Leukocyte Count and C-reactive protein levels are elevated.

Microbiology

Confirmation of a diagnosis of melioidosis depends heavily on the clinical microbiology laboratory and specifically on recovering *B. pseudomallei* isolate by culture from blood, sputum, cerebrospinal fluid or other bacteriology specimen. Isolation of *B. pseudomallei* from body fluids of patients remains the 'gold standard' in diagnosis. Use of selective media for nonsterile specimens is helpful. Actually, the isolation of this organism can only use routine media in microbiology laboratory. With inexperienced eyes, the organism may be missed easily by the overgrowth of other rapid-growing normal flora; so the use of selective media may facilitate the growth of *B. pseudomallei* and inhibit growth of other gram-negative normal flora, since the media contain gentamicin. A modified Ashdown medium, with colistin, is now commonly used.[6,70,71] Gram stain and other histopathological stains are not specific for the organism. Bacilli showing bipolar (safety pin) staining with methylene blue or Wayson's or Wright's stain may be found in exudates.[20,72] Pseudomonas stains so poorly that its presence can be easily missed. There is difficulty in identifying the organism, which mimics any other nonfermenting gram-negative bacilli (NFGNB) on cursory examination.[72]

Histopathology

Microscopic examination of tissue specimen shows granuloma of closely aggregated epithelioid cells with multinucleated giant cells with some focal necrosis.[73]

Serology

Indirect hemagglutination (IHA), latex agglutination and immunofluorescence are currently used clinically. IHA single titer of 1:80 to 1:320 is suggestive of active melioidosis, and a single titer of more than 1:640 is diagnostic of highly active melioidosis.[68,74]

Enzyme linked immunosorbent assay [ELISA] test detects specific IgG and IgM antibodies of *B. pseudomallei* in serum specimens. ELISA is more sensitive and specific as it points to an active disease process and is recommended as a diagnostic serological test when melioidosis is in the differential diagnosis of 'pyrexia of unknown origin' cases.[49,75]

Molecular

Polymerase chain reaction has been developed for bacterial identification. Other molecular biology techniques such as dot immunoassay are also used for rapid diagnosis.[49,76]

TREATMENT

The main objective of treatment is to reduce mortality and morbidity and to prevent recurrent infection in melioidosis. Outcome following melioidosis remains poor despite 20 years of clinical research and the introduction of ceftazidime- and carbapenem-based intravenous treatments; melioidosis is still associated with significant mortality attributable to severe sepsis and its complications. A long course of oral eradication therapy is required to prevent relapse. Treatment is continued over 12-20 weeks or longer if clinically indicated. This is divided into intravenous and oral phases. Ceftazidime or a carbapenem antibiotic for initial parenteral therapy should be administered for at least 10-14 days followed by a prolonged course of oral antimicrobial therapy with trimethoprim-sulfamethoxazole (TMP-SMX) with or without doxycycline. Amoxicillin-clavulanate is an alternative for children, pregnant women and for patients with intolerance to first-line therapy. Resistance of *B. pseudomallei* to these drugs is rare.[1,6,77-79]

The organism is also susceptible to chloramphenicol, doxycycline, ureidopenicillins and is intrinsically resistant to many antibiotics (including penicillin, first- and second-generation cephalosporins, macrolides, rifamycins, colistin and aminoglycosides).

Operative intervention for musculoskeletal melioidosis includes aspiration drainage of pus, curettage debridement, together with combination of antimicrobials. Spinal melioidosis needs debridement with bone grafting for inter-body fusion. Other joints would require debridement with synovectomy and removal of infected and necrotic bone material. Ng *et al.* successfully treated osteomyelitis after debridement and filling the bone gap with calcium hydroxyapatite blocks filled with ceftazidime powder. They concluded that calcium hydroxyapatite appears to be superior to polymethyl methacrylate (PMMA) as a drug delivery system as there is no thermal damage to the drug during the process of preparation.[80] However, Subhadrabandhu *et al.* had reported that the use of gentamicin-impregnated PMMA beads reduces the risk of relapse by achieving a local concentration of gentamicin exceeding the minimal inhibitory concentration (MIC) for *Burkholderia.*[68] However, this study was based on retrospective reports on few patients, and

there was no comparison-controlled trial; so the evidence for this is weak.

Vaccine development

There is no effective vaccine available that protects against *B. pseudomallei* infection. Current approaches under evaluation include conjugate DNA, attenuated and heterologous vaccines, attenuated mutants that are invasive but have a reduced ability to produce an acute, fulminating and often fatal infection.[81]

Follow-up

Accurate diagnosis of this infection is important because a high mortality rate is usually associated with the septicemic form of disease. The infection also has the potential of a prolonged latent period, with reactivation despite adequate treatment. Hence follow-up should probably be lifelong.

CONCLUSION

Diagnosis of melioidosis requires a high index of clinical suspicion and is dependent on microbiological confirmation; the important clue is travel to, or residence in, an endemic area. Infection often, but not always, occurs in well-recognized risk groups, especially diabetics and alcoholics. Melioidosis can involve bone and joint. Clinical manifestations of bone melioidosis are not diagnostic. Musculoskeletal melioidosis mimics other infections both clinically and radiologically. Clinical awareness is therefore crucial, as diagnosis can only be established by bacteriological and immunological studies. Prompt treatment with long-term combination antibiotics in high dosages and surgical drainage of abscesses improves survival.

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