

Burkholderia pseudomallei and Burkholderia mallei: Melioidosis and Glanders

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The genus *Burkholderia* is currently composed of many species, but only three are notable pathogens for humans or animals: the former *cepacia* complex (described in Chapter 220) *pseudomallei* (the agent of melioidosis), and *mallei* (the agent of equine glanders). All three are aerobic, nonsporulating, straight or slightly curved gram-negative bacilli that were formerly placed in the genus *Pseudomonas*.

Melioidosis

Melioidosis is a disease of humans and animals; it has enormous clinical diversity, spanning asymptomatic infection, localized skin ulcers or abscesses, chronic pneumonia mimicking tuberculosis, and fulminant septic shock with abscesses in multiple internal organs. Most disease is from recent infection, but latency with reactivation is described up to 62 years after exposure. Most cases are reported from Southeast Asia and northern Australia, but melioidosis is increasingly being recognized in people infected in an endemic region who return or travel to Europe and the United States. The causative bacterium, *Burkholderia pseudomallei*, is also considered a potential biologic warfare agent.

HISTORY

In 1912, Whitmore and Krishnaswami described cases of a newly recognized septicemic disease in morphine addicts in Rangoon, Burma.¹ Fatal cases were characterized by widespread caseous consolidation of the lung and abscesses in liver, spleen, kidney, and subcutaneous tissues. The bacillus isolated from tissues was similar to that causing glanders (*Burkholderia mallei*) but was motile. Whitmore noted the clinical similarity to glanders, and Stanton and Fletcher subsequently proposed the name *melioidosis*, derived from the Greek *melis* ("distemper of asses"). Various names were used for the causative bacterium, including *Bacillus whitmori* and, for many years, *Pseudomonas pseudomallei*.² In 1992, seven *Pseudomonas* species were moved to a new genus, *Burkholderia. B. cepacia* is the type species in the genus, which includes the organisms causing melioidosis (*B. pseudomallei*) and glanders (*B. mallei*).

ETIOLOGY

B. pseudomallei is a small, gram-negative, oxidase-positive, motile, aerobic bacillus with occasional polar flagella. On staining, a bipolar "safety pin" pattern is seen. The organism is easily recovered on standard culture medium but may be misidentified as *B. cepacia*, *P. stutzeri*, or other *Pseudomonas* species.

The organism is present in soil and surface water in endemic regions. Humans and animals are infected by percutaneous inoculation, inhalation, or ingestion. Occasional laboratory-acquired infections are described, but person-to-person spread and zoonotic infection are very uncommon.

EPIDEMIOLOGY

After the initial account in Burma, melioidosis was documented in humans and animals in Malaysia and Singapore from 1913 and then

Vietnam from 1925 and Indonesia from 1929.³⁻⁵ Thailand has reported the largest number of cases,⁶⁻⁸ with an estimated 2000 to 3000 cases of melioidosis each year.⁹ Melioidosis is also common in Malaysia¹⁰ and Singapore.^{11,12} Other countries in the region where melioidosis is recognized in humans and animals include China (especially Hong Kong), Taiwan, Brunei, Vietnam, and Laos.¹³⁻¹⁷ Melioidosis is also likely to occur in Cambodia and the Philippines.^{5,9,18} Melioidosis has been increasingly recognized in India, although reports that some of the "plague" scares of 1994 may have been cases of melioidosis have been disproved.^{19,20} Cases have been reported from Sri Lanka, Bangladesh, and Pakistan.⁵ Despite the early documentation of melioidosis in Burma and Indonesia, recent cases had not been reported from Indonesia until after the 2004 Asian tsunami.²¹ Cases of melioidosis have caledonia,²² but the extent of endemicity in the Pacific islands remains to be defined.

Cases of melioidosis are increasingly being documented from outside the classic endemic region of Southeast Asia, Australasia, the Indian subcontinent, and China. These include sporadic human or animal cases or environmental isolates of *B. pseudomallei* from the Middle East, Africa, the Caribbean, and Central and South America. Although some of these reports are from incorrect species diagnosis, others are confirmed, making the endemic limitations of melioidosis very unclear.⁵ Sporadic cases and occasional case clusters have recently occurred in Brazil and elsewhere in the Americas.²³ Despite recent cases from Madagascar,²⁴ the true extent and magnitude of the presence of *B. pseudomallei* in Africa remains entirely unknown. Global warming may well result in expansion of the endemic boundaries of melioidosis.

The two locations where melioidosis is arguably the most important single bacterial pathogen for humans are some northeast provinces in Thailand and the Top End of the Northern Territory of Australia. In northeast Thailand, 20% of community-acquired septicemic cases are caused by melioidosis, which accounts for 39% of fatal septicemias⁷ and 36% of fatal community-acquired pneumonias.²⁵ In the Top End of the Northern Territory, melioidosis has been the most common cause of fatal community-acquired bacteremic pneumonia.²⁶

In addition to endemic melioidosis, there are several documented situations where melioidosis became established in nontropical locations. In France, in the 1970s, cases of melioidosis occurred in animals in a Paris zoo, with spread to other zoos and equestrian clubs.³ In addition to fatal animal and human cases, there was extensive soil contamination persisting for some years. *B. pseudomallei* was considered likely to have been introduced by importation of infected animals. A cluster of cases occurred over a 25-year period in southwestern Western Australia (31°S), involving animal cases and one human infection in a farmer. Ribotyping of the farm animal and human isolates and one isolate from the soil showed identical patterns.²⁷ This supports the suggestion of clonal introduction of *B. pseudomallei* into this temperate region, probably via an infected animal, with environmental contamination, local dissemination, and persistence over 25 years.



Figure 221-1 Natural history of infection with Burkholderia pseudomallei. GIT, gastrointestinal tract.

Melioidosis was an important cause of morbidity and mortality in foreign troops fighting in Southeast Asia. Dance has noted that at least 100 cases occurred among French forces in Indochina between 1948 and 1954.³ By 1973, 343 cases had been reported in American troops fighting in Vietnam. Concerns of reactivation of latent infection in soldiers returning from Vietnam, with estimates from serology studies of approximately 225,000 potential cases, resulted in melioidosis being called the "Vietnamese time bomb."²⁸ However, although occasional cases of reactivation of *B. pseudomallei* still occur in Vietnam veterans, it is rare in comparison to the numbers exposed.

TRANSMISSION

Figure 221-1 summarizes the natural history of infection with B. pseudomallei. Studies from Malaysia, and more recently from Thailand²⁹ and Australia,30 have found that the organism is more common in cleared, irrigated sites such as rice paddies and farms. It has been suggested that the increase in melioidosis cases in Thailand may partly be the consequence of the increased number of bacteria in such environments and partly the consequence of increased exposure to bacteria resulting from changes in behaviors, such as farming techniques.¹³ In Australia, B. pseudomallei has been found most commonly in clay soils to a depth of 25 to 45 cm, and it has been proposed that the bacteria move to the surface with the rising water table during the wet season.³¹ An alternative explanation for the variable bacterial presence found is that during times of stress, such as in prolonged dry seasons, B. pseudomallei may persist in soil in a viable but nonculturable state.³² Differential gene activation may allow such environmental bacteria to respond and adapt to different environmental conditions. This possibility is also relevant to the pathogenicity, latency, and reactivation of infection with B. pseudomallei in humans. The role of biofilms in the persistence of B. pseudomallei in the environment, as well as in animal and human hosts, requires further study.³³ There is increasing interest in the intracellular survival of B. pseudomallei, and it has been proposed that an ecologic niche for the bacteria in the environment may be in environmental protozoa or fungi.32

In most endemic regions, there is a close association between melioidosis and rainfall. In northeast Thailand³⁴ and northern Australia,³⁵ 75% and 85% of cases, respectively, have occurred in the wet season. Although early animal studies showed infection with *B. pseudomallei* through oral or nasal exposure and from ingestion, more recent reviews have considered that most human cases are from percutane-

ous inoculation of B. pseudomallei after exposure to muddy soils or surface water in endemic locations.^{2,5,26} Ingestion and sexual transmission have been suggested as unusual modes of transmission of B. pseudomallei. Presentations of melioidosis pneumonia after presumptive inoculating skin injuries have been documented in patients with soil-contaminated burns and are also common in tropical Australia.²⁴ This suggests hematogenous spread to the lung rather than inhalation or spread from the upper respiratory tract. However, under certain epidemiologic conditions, the inhalation route may predominate, as suggested for soldiers exposed to dusts raised by helicopter rotor blades in Vietnam.³⁶ Melioidosis after near-drowning is well documented, with the probable infecting event being aspiration.¹⁴ Intensity of rainfall is an independent predictor of melioidosis manifesting as pneumonia and of a fatal outcome,37 suggesting that heavy monsoonal rainfall and winds may result in a shift toward inhalation as the mode of infection with B. pseudomallei. Several outbreaks of melioidosis in Australia have been linked to contamination of potable water with *B. pseudomallei.*^{38,39} The water supplies involved were unchlorinated or the chlorination was below standard. The contamination of the water supply has been attributed to soil disturbance during excavations.

The incubation period for melioidosis is influenced by inoculating dose, mode of infection, host risk factors, and probably differential virulence of infecting *B. pseudomallei* strains. Onset of melioidosis within 24 hours has been seen in presumed aspiration after near-drowning and, in some cases, after severe weather events. In 25 cases of acute melioidosis in which a clear incubation period could be determined between the inoculating injury and the onset of symptoms, the incubation period was 1 to 21 days (mean, 9 days),⁴⁰ which is consistent with a series of nosocomial cases from Thailand, in which the incubation period was 3 to 16 days (mean, 9.5 days).⁴¹

PATHOGENESIS

Serology studies have shown that most infection with *B. pseudomallei* is asymptomatic.^{42,43} In northeast Thailand, most of the rural population is seropositive by indirect hemagglutination (IHA),³⁴ with most seroconversion occurring between 6 months and 4 years of age.⁴³ Although melioidosis occurs in all age groups, severe clinical disease such as septicemic pneumonia is seen mostly in those with risk factors such as diabetes, renal disease, and alcoholism.

In addition to infection by inhalation, bacterial load on exposure (inoculating dose) and virulence of the infecting strain of B. pseudomallei are also likely to influence the severity of disease. However, it has been noted that despite the large bacterial load in severely ill patients with septicemic pulmonary melioidosis, person-to-person transmission is extremely unusual. This, together with the rarity of fulminant melioidosis in healthy people, supports the primary importance of host risk factors for development of melioidosis. Furthermore, although it is clear from laboratory studies of isolates of B. pseudomallei from animals, humans, and the environment that virulence differs among B. pseudomallei isolates,44 the importance of this variation in virulence in determining clinical aspects of melioidosis remains uncertain. Molecular typing that shows clonality of isolates in animal and human clusters has revealed that the same outbreak strain can cause different clinical presentations, with host factors being most important in determining the severity of disease.³⁹ Whole-genome sequencing and subsequent molecular studies have shown that B. pseudomallei has two chromosomes, multiple genomic islands that are variably present in different strains and have a great propensity for horizontal gene transfer.45 Further studies are required to unravel the global phylogeny and evolutionary history of B. pseudomallei and related species and to determine which genes or gene clusters may be critical for pathogenesis and disease presentation and outcome.46

B. pseudomallei is a facultative intracellular pathogen that can invade and replicate inside various cells, including polymorphonuclear leukocytes and macrophages and some epithelial cell lines.⁴⁷ Animal models have been unable to confirm a clinically relevant exotoxin for *B. pseudomallei.*⁴⁸ However, resistance to human serum (conferred by lipopolysaccharide [LPS])⁴⁹ and the ability of *B. pseudomallei* to survive intracellularly (conferred in part by capsular polysaccharide) appear to be critical in the pathogenesis of melioidosis.⁵⁰⁻⁵² Type III secretion systems in *B. pseudomallei* have also been found to be important in cell invasion and intracellular survival.^{53,54} Quorum sensing may play an important role in many aspects of virulence of *B. pseudomallei*, including cell invasion, cytotoxicity and antimicrobial resistance.^{55,56} Other putative virulence factor candidates include flagella, type IV pili and other adhesins, a siderophore, and secreted proteins such as hemolysin, lipases, and proteases.⁵⁶

Intracellular survival of *B. pseudomallei* in human and animal hosts is likely to explain the ability for latency. After internalization, *B. pseudomallei* escapes from endocytic vacuoles into the cell cytoplasm, and induction of actin polymerization at one bacterial pole leads to membrane protrusions, with cell-to-cell spread involving these actin tails.^{54,56,57} Additional survival factors are the ability of *B. pseudomallei* to form antibiotic-resistant small-colony variants⁵⁸ and the ability of mucoid variants with large extracellular polysaccharide glycocalyx structures to form biofilm-encased microcolonies that are also relatively antibiotic-resistant.

There have been a number of studies showing elevated levels of various endogenous inflammatory mediators and cytokines to be associated with severity and outcomes of melioidosis. Nevertheless, whether these elevated cytokines are a cause or result of severe disease is not established. In Thailand, there was an association of severe melioidosis with tumor necrosis factor (TNF)- α gene allele 2, which is linked to higher constitutive and inducible production of TNF- α .⁵¹ However, in a mouse model of melioidosis, neutralization of TNF- α or interleukin (IL)-12 increased susceptibility to infection in vivo, and interferon- γ (IFN- γ) was found to be important for survival, with mice treated with monoclonal anti-IFN-7 dying more quickly.60 A role for Toll-like receptors in the innate immune response in melioidosis has been proposed.⁶¹ There are, therefore, important host protective mechanisms against B. pseudomallei in cytokine responses as well as potentially detrimental ones, with the timing of cytokine release and the balance between pro- and anti-inflammatory responses likely to determine the severity of disease and outcome of infection.^{56,62} The extent to which host polymorphisms in immune response contribute in comparison to differences in organism virulence, infecting dose of B. pseudomallei, and defined host risk factors such as diabetes remains to be clarified. Nevertheless, the predominant association with fatal melioidosis is the presence of defined patient risk factors.

Although a vigorous cell-mediated immune response may protect against disease progression,⁶³ there is no definitive evidence for the development of immunity from melioidosis after natural exposure to *B. pseudomallei*, and reinfection can occur with a different strain of *B. pseudomallei* after successful treatment of melioidosis.⁶⁴

Table 221-1 summarizes the risk factors for melioidosis. The most important risk factors are diabetes, alcohol excess, and renal disease.^{2,35,65} In Thailand, the adjusted odds ratios for diabetes and renal disease (chronic renal impairment or renal or ureteric calculi) in cases of melioidosis versus controls were 12.9 (95% confidence interval [CI], 5.1 to 37.2) and 2.9 (95% CI, 1.7 to 5.0), respectively.⁶⁵ Other risk factors for melioidosis include chronic lung disease (including cystic fibrosis), thalassemia (odds ratio in Thailand, 10.2; 95% CI, 3.5 to 30.8), malignancies, steroid therapy, iron overload, and tuberculosis.⁶⁵ Severe disease and fatalities are uncommon in those without risk factors who are diagnosed and treated early, with only one death in 51 patients without risk factors in one study.³⁵ Risk factors are less common in children than in adults.^{66,67}

Evidence suggests that there may be a predisposition to melioidosis in those with diabetes, alcohol excess, or chronic renal disease, which may reflect impairment of their neutrophil and other phagocytic cell functions, such as mobilization, delivery, adherence, and ingestion.^{35,68} Melioidosis has also been described in chronic granulomatous disease.⁶⁹

TABLE 221-1	Risk Factors for Melioidosis									
Risk Factor*		Thailand (%	of cases)	Australia (% of cases)						
Diabetes		23-60	0	37						
Alcohol excess		12		39						
Renal disease		20-22	7	10						
Chronic lung disease		NR	NR		27					
Thalassemia		7	7		Nil					
No risk	factors	24-30	6		20					
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*Not listed: malignancy, steroid therapy, iron overload, cardiac failure. NR, not reported.

Thailand data from Punyagupta S. Melioidosis: Review of 686 cases and presentation of a new clinical classification. In: Punyagupta S, Sirisanthana T, Stapatayavong B, eds: *Melioidosis*. Bangkok: Bangkok Medical; 1989:217-229; Chaowagul W, White NJ, Dance DA, et al. Melioidosis: A major cause of community-acquired septicemia in northeastern Thailand. J Infect Dis. 1989;159:890-899; Suputtamongkol Y, Chaowagul W, Chetchotisakd P, et al. Risk factors for melioidosis and bacteremic melioidosis. *Clin Infect Dis*. 1999;29:408-413; and Limmathurotsakul D, Chaowagul W, Chierakul W, et al. Risk factors for recurrent melioidosis in northeast Thailand. *Clin Infect Dis*. 2006;43:979-986.

Australia data from Currie BJ, Fisher DA, Howard DM, et al. Endemic melioidosis in tropical northern Australia: A 10-year prospective study and review of the literature. *Clin Infect Dis.* 2000;31:981-986.

CLINICAL MANIFESTATIONS

The earliest descriptions of melioidosis documented the fulminant end of the clinical spectrum, with abscesses throughout both lungs and in many organs.¹ At the other end of the spectrum are asymptomatic infections and localized skin ulcers or abscesses without systemic illness. Howe and colleagues have classified melioidosis as acute, sub-acute, and chronic.³⁶ The Infectious Disease Association of Thailand has summarized 345 cases in these categories^{2.6}:

- 1. Multifocal infection with septicemia (45% of cases, 87% mortality)
- 2. Localized infection with septicemia (12% of cases, 17% mortality)
- 3. Localized infection (42% of cases, 9% mortality)
- 4. Transient bacteremia (0.3%)

More recent bacteremia and overall mortality rates have been, respectively, 60% and 44% in Thailand,³⁴ 46% and 19% in Australia,³⁵ and 43% and 39% in Singapore.⁵

Table 221-2 summarizes the clinical presentations of patients with melioidosis in northern Australia. Pneumonia is the commonest clinical presentation of patients with melioidosis in all studies, accounting for around half of cases. Secondary pneumonia after another primary presentation occurs in around 10% of cases. Acute melioidosis pneumonia has a spectrum from fulminant septic shock (mortality up to 90%; Figs. 221-2 to 221-5) to mild undifferentiated pneumonia, which can be acute or subacute in nature, with little mortality. Septicemic patients present acutely unwell with high fevers and prostration and often little initial cough or pleuritic pain. On chest radiographs, diffuse nodular infiltrates often develop throughout both lungs and they coalesce, cavitate, and progress rapidly, consistent with the caseous necrosis and multiple metastatic abscess formation seen at autopsy. Nonsepticemic patients with pneumonia and some with septicemic pneumonia have a more predominant cough, with productive sputum and dyspnea, and their chest radiographs show discrete but progressive consolidation in one or more lobes (Fig. 221-6). In endemic regions, acute pneumonia with upper lobe consolidation warrants consideration of melioidosis, although lower lobe infiltrates are also common.

In 12% of cases in northern Australia, patients present with chronic melioidosis, defined as illness with symptoms for longer than 2 months' duration on presentation. Many of these patients have features mimicking tuberculosis, with fevers, weight loss, productive cough (sometimes with hemoptysis), and classic upper lobe infiltrates, with or without cavitation on chest radiographs (Fig. 221-7). In these patients, disease can be remitting and relapsing over many years, sometimes with an initial misdiagnosis of tuberculosis. Although acute deterioration with septicemia may occur, mortality in this group is low.

221-2 Clinical Presentations and O	utcomes of Melioidosis in Northern Australia
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		Total	Bacteremic		Nonbacteremic	
Parameter	No.	Deaths (Mortality)	No.	Deaths (Mortality)	No.	Deaths (Mortality)
Septic Shock	111	59 (53%)	99	49 (49%)	12	13 (81%)
Pneumonia	85	44 (52%)	75	36 (48%)	10*	8 (80%)
Genitourinary	9	5 (56%)	8	4 (50%)	1^{\dagger}	1 (100%)
Osteomyelitis, septic arthritis	4	2 (50%)	4	2 (50%)	0	0 (0%)
No focus	13	8 (62%)	12	7 (58%)	1	1 (100%)
No Septic Shock	403	17 (4%)	181	13 (7%)	222	4 (2%)
Pneumonia	177	9 (5%)	78	8 (10%)	99	1 (1%)
Genitourinary	64	2 (3%)	39	2 (5%)	25	0 (0%)
Skin abscess(es)	64	0 (0%)	1	0 (0%)	63	0 (0%)
Soft tissue abscess(es)	14	0 (0%)	1	0 (0%)	13	0 (0%)
Neurologic	14	3 (21%)	3	0 (0%)	11	3 (47%)
Osteomyelitis, septic arthritis	12	0 (0%)	6	0 (0%)	6	0 (0%)
Other	58	3 (5%)	53	3 (6%)	5	0 (0%)
Total	514	76 (15%)	280	62 (22%)	234	14 (6%)

*Seven blood cultures not done, three blood cultures negative.

[†]Blood culture not done.

Updated from Currie BJ, Fisher DA, Howard DM, et al. Endemic melioidosis in tropical northern Australia: A 10-year prospective study and review of the literature. *Clin Infect Dis.* 2000;31:981-986.

Until recently it was thought that a colonization state did not exist for *B. pseudomallei*, with presence in sputum or throat always reflecting disease. However, it has more recently become evident that *B. pseudomallei* can both colonize airways and cause disease in patients with cystic fibrosis (CF) and bronchiectasis. The similarity to infection with *B. cepacia* complex in CF is of concern, given the association of *B. cepacia* complex with more rapid deterioration in lung function. Furthermore, likely transmission of *B. pseudomallei* between two siblings with CF has been reported.⁷⁰ Patients with CF traveling to melioidosis-endemic locations should be warned of the risk of melioidosis, which should be considered if they become sick after returning.

It is common for patients to present with skin ulcers or abscesses (Figs. 221-8 and 221-9).⁷¹ Occasionally, they present with septic arthritis or osteomyelitis, or one of these can develop after the patient has presented with another primary diagnosis, usually pneumonia (Fig. 221-10). Also well recognized, whatever the clinical presentation, are abscesses in internal organs, especially spleen, kidney, prostate, and liver (Figs. 221-11 to 221-15). Where available, abdominopelvic computed tomography (CT) scanning is useful in all melioidosis patients to detect internal abscesses.

Three differences have been noted between Thailand and tropical Australia. First, suppurative parotitis accounts for up to 40% of melioidosis in children in Thailand^{66,72} but is very rare in Australia. Second, prostatic melioidosis is well recognized but uncommon, except in



Figure 221-2 Multiple pustules in a 46-year-old diabetic man with fatal septicemic melioidosis.

Australia, where routine abdominopelvic CT scanning of all melioidosis cases has shown prostatic abscesses to be present in 18% of all male patients with melioidosis (Fig. 221-16).³⁵ Some were incidental in patients presenting with pneumonia or septicemia, but a primary genitourinary presentation was common with fevers, abdominal discomfort, dysuria, and sometimes diarrhea and urinary retention. Third, neurologic melioidosis accounts for around 4% of cases in northern Australia, with the distinctive clinical features being brain stem encephalitis, often with cranial nerve palsies (especially the seventh nerve), together with peripheral motor weakness, or occasionally just flaccid paraparesis alone. The CT scan is often normal, but dramatic changes are seen on magnetic resonance imaging (MRI), most notably a diffusely increased T₂-weighted signal in the midbrain, brain stem, and spinal cord (Fig. 221-17).⁷³ Direct bacterial invasion of the brain and spinal cord occurs with this melioidosis encephalomyelitis.⁷⁴



Figure 221-3 Chest radiograph of patient in Figure 221-2, showing multiple pulmonary abscesses.



Figure 221-4 CT scan of the chest of a 26-year-old woman with fatal melioidosis, showing large pulmonary abscess.

Neurologic melioidosis is occasionally seen outside Australia, although mostly as macroscopic brain abscesses.^{6,75}

Unusual foci of melioidosis infection described in case reports or case series include mycotic aneurysms, lymphadenitis resembling tuberculosis, mediastinal masses, pericardial collections, and adrenal abscesses.

It has long been recognized that *B. pseudomallei*, like tuberculosis, has the potential for reactivation from a latent focus, usually in the lung—hence the concern of the "Vietnamese time bomb" in returned soldiers. Latent periods from exposure to *B. pseudomallei* in an endemic



Figure 221-6 Extensive left upper lobe consolidation in 54-yearold man with fatal melioidosis pneumonia.

region to onset of melioidosis in a nonendemic region have been documented as being as long as 62 years.⁷⁶ However, cases of reactivated *B. pseudomallei* appear to be very uncommon, accounting for only 3% of cases in northern Australia. The vast majority of cases of melioidosis occur in the monsoonal wet seasons of the various endemic regions, supporting the concept that in endemic areas, most patients with melioidosis have recent infections that appear with acute illness.



Figure 221-5 Multiple lung abscesses seen at autopsy of patient with acute melioidosis pneumonia.



Figure 221-7 Radiograph showing right upper lobe cavitation of a 62-year-old man with nonfatal chronic melioidosis.



Figure 221-8 Cutaneous melioidosis seen on the right forearm of a 50-year-old man.



Figure 221-9 Cutaneous melioidosis of the right thigh in an 11-year-old boy.



Figure 221-10 Radiograph of large lucent areas in proximal tibia of a 43-year-old man.



Figure 221-11 Right psoas abscess in a 17-year-old girl with melioidosis.



Figure 221-12 The patient in Figure 221-11 developed an L3 osteomyelitis 6 weeks later.



Figure 221-13 CT scan showing splenic abscesses in a 60-year-old diabetic.



Figure 221-14 Abscesses seen at splenectomy performed on the patient in Figure 221-13.

Reactivation of melioidosis has been associated with influenza, other bacterial sepses, and development of known melioidosis risk factors such as diabetes. It remains unknown what proportion of asymptomatic seropositive people actually have latent infection with the potential for reactivation.

LABORATORY DIAGNOSIS

Definitive diagnosis of melioidosis requires a positive culture of B. pseudomallei. Melioidosis must be considered in febrile patients in or returning from endemic regions to enable appropriate samples to be tested. B. pseudomallei readily grows in commercially available blood culture media, but it is not unusual for laboratories in nonendemic locations to misidentify the bacteria as a Pseudomonas species, especially because some commercial identification systems are poor at identifying B. pseudomallei.77 Culture from nonsterile sites increases the likelihood of diagnosis but can be problematic. The rate of successful culture is increased if sputum, throat swabs, ulcer or skin lesion swabs, and rectal swabs are placed into Ashdown's medium, a gentamicin-containing liquid transport broth that results in the selective growth of *B. pseudomallei*.^{78,79} *B. pseudomallei* can be identified by combining the commercial API 20NE or 20E biochemical kit with a simple screening system involving the Gram stain, oxidase reaction, typical growth characteristics, and resistance to certain antibiotics.8



Figure 221-16 Melioidosis prostatic abscesses in a 31-year-old man who presented with fever and urinary retention.

There are a variety of locally developed antigen and DNA detection techniques used in endemic regions for early identification of *B. pseudomallei* in culture media and patient blood or urine, but these are not yet widely available.⁸⁰⁻⁸⁴ An indirect hemagglutination test (IHA), various enzyme-linked immunosorbent assays (ELISAs), and other serologic assays are available.^{83,85,86} In endemic areas, their usefulness is limited by high rates of background antibody positivity. In acute septicemic melioidosis, IHA and ELISA are often initially negative, but repeat testing may show seroconversion. A positive IHA or ELISA in a tourist returning from a melioidosis, but definitive diagnosis still requires a positive culture.

TREATMENT

B. pseudomallei is characteristically resistant to penicillin, ampicillin, first- and second-generation cephalosporins, gentamicin, tobramycin, and streptomycin. Before 1989, "conventional therapy" for melioidosis consisted of a combination of chloramphenicol, sulfamethoxazole-trimethoprim, doxycycline, and sometimes kanamycin, given for 6 weeks to 6 months.^{2,87} However, there were also reports of the successful use of sulfamethoxazole-trimethoprim alone and tetracycline or doxycycline alone. These conventional antibiotics are bacteriostatic rather than bactericidal, and in vitro studies have shown various combinations to be antagonistic.



Figure 221-15 Melioidosis orchitis and scrotal ulcer in a 49-yearold man.



Figure 221-17 Melioidosis encephalomyelitis in a 24-year-old man. MRI shows increased T_2 -weighted signal extending through brain stem and into spinal cord.

TABLE 221-3 Antibiotic Therapy for Melioidosis

Initial Intensive Therapy (minimum of 10-14 days) Ceftazidime (50 mg/kg, up to 2 g) every 6 hr

Meropenem (25 mg/kg, up to 1 g) every 8 hr

Imipenem (25 mg/kg, up to 1 g) every 6 hr With or without

Any one of the three may be combined with

Sulfamethoxazole-trimethoprim (40/8 mg/kg up to 1600/320 mg) every 12 hr (recommended for neurologic cutaneous, bone and prostatic melioidosis)

Eradication Therapy (minimum of 3 mo)

Sulfamethoxazole-trimethoprim (40/8 mg/kg up to 1600/320 mg) every 12 hr With or without

Doxycycline (2.5 mg/kg up to 100 mg) every 12 hr

Subsequent studies have shown *B. pseudomallei* to be susceptible to various newer β -lactam antibiotics, especially ceftazidime, imipenem, meropenem, piperacillin, amoxicillin-clavulanate, ceftriaxone, and cefotaxime, with various degrees of bactericidal activity. Table 221-3 summarizes recommended antibiotic treatment.

Initial Intensive Therapy for Melioidosis

The most important therapeutic study for melioidosis was an openlabel randomized trial in Thailand comparing ceftazidime (120 mg/kg/ day) with conventional therapy, which showed that ceftazidime is associated with a 50% lower overall mortality in severe melioidosis.⁸⁷ Ceftazidime then became the drug of choice for initial intensive therapy for melioidosis. Another study from Thailand showed similar results when ceftazidime was used in combination with sulfamethoxazoletrimethoprim.⁸⁸ Whether sulfamethoxazole-trimethoprim added to ceftazidime is superior to ceftazidime alone has been studied in two randomized controlled trials in Thailand.⁸⁹ Although the addition of sulfamethoxazole-trimethoprim conferred no survival benefit, the excellent tissue penetration of sulfamethoxazole-trimethoprim is the rationale for recommending combination therapy in neurologic, cutaneous, bone and joint, and prostatic melioidosis.

After initial favorable reports of use of amoxicillin-clavulanate, another randomized comparative trial in Thailand showed that initial therapy with high-dose IV amoxicillin-clavulanate is as effective as ceftazidime in preventing deaths in severe melioidosis.⁹⁰ However, when amoxicillin-clavulanate was continued as eradication therapy (see later), treatment failure was more frequent.

The carbapenems imipenem and meropenem have the lowest minimum inhibitory concentrations against *B. pseudomallei*. Furthermore, in vitro time-kill studies to measure the rate of bacterial killing has shown the carbapenems to perform better against *B. pseudomallei* than ceftazidime.^{91,92} High-dose imipenem has been shown in another comparative trial from Thailand to be at least as effective as ceftazidime for severe melioidosis, with no differences in mortality between the groups and with fewer treatment failures in those given imipenem.⁹³ Observational data from Australia have suggested that meropenem produces better outcomes in severe melioidosis than ceftazidime, which has led to the recommendation that meropenem be the drug of choice for melioidosis septic shock.⁹⁴

The duration of initial intensive therapy should be 10 to 14 days, with longer treatment required for critically ill patients, or for extensive pulmonary disease, deep-seated collections or organ abscesses, osteomyelitis, septic arthritis, and neurologic melioidosis. Even with the newer regimens, the therapeutic response can be slow, with median time to defervescence up to 9 days, and longer times seen in those with deep-seated abscesses.

Ceftazidime infusions (6 g over 24 hours, adult dose) through a peripherally inserted central catheter (PICC line) using an elastomeric infusion device (Baxter, Sydney) have enabled early hospital discharge for in-home therapy.⁹⁵ The absence of any postantibiotic effect with ceftazidime gives such a continuous infusion a theoretical advantage over intermittent dosing.

Subsequent Eradication Therapy for Melioidosis

After initial intensive therapy, using ceftazidime, imipenem, or meropenem, possibly in combination with sulfamethoxazole-trimethoprim, subsequent eradication therapy is considered necessary for preventing recrudescence or later relapse of melioidosis. Both duration of eradication therapy and the best antibiotics to use remain uncertain. Molecular typing of isolates from patients with recurrent melioidosis has confirmed that most cases are true relapses from failed eradication rather than new infection.⁶⁴

There are a number of reasons for failure of eradication therapy:

- The most important factor responsible for most recrudescences or relapses of melioidosis is poor compliance with eradication therapy.
- Relapses were found to be 4.7 times (95% CI, 1.6 to 14.1) more common in patients with severe disease than in those with localized melioidosis.⁹⁶ Positive blood cultures and multifocal disease were also associated with relapse.⁶⁴
- 3. Use of ceftazidime in the initial intensive therapy was also associated with a halving of relapses.⁹⁶
- 4. Duration of eradication therapy is also critical, with relapses after oral therapy of 8 weeks or less more likely than if eradication therapy is given for longer than 12 weeks.^{64,96}
- 5. The choice of agents for the eradication therapy is important. Both amoxicillin-clavulanate and oral quinolones (ciprofloxacin or ofloxacin) have been found to be less effective in preventing relapse than the former conventional eradication with chloramphenicol (given usually only for the first 4 to 8 weeks), sulfamethoxazole-trimethoprim, and doxycycline.⁶⁴ Amoxicillin-clavulanate is recommended for eradication therapy in pregnancy and is an alternative to sulfamethoxazole-trimethoprim in children or those intolerant of sulfamethoxazole-trimethoprim or with a B. pseudomallei isolate confirmed as resistant to sulfamethoxazole-trimethoprim, with dosing guidelines recently published.⁹⁷ Quinolones should not be considered as first-line agents for melioidosis, with in vitro susceptibility testing generally showing resistance or intermediate results. A trial of eradication therapy involved a comparison of doxycycline alone versus conventional chloramphenicol (first 4 weeks only), sulfamethoxazole-trimethoprim, and doxycycline combination therapy.⁹⁸ Relapses were significantly more common in the doxycyclinealone group, resulting in a recommendation that doxycycline not be used alone as first-line eradication therapy.

A randomized trial has found no benefit in adding chloramphenicol to sulfamethoxazole-trimethoprim plus doxycycline for the eradication phase.⁹⁹ It has been suggested that sulfamethoxazole-trimethoprim is the critical component for eradication therapy, and prospective studies in Australia using sulfamethoxazole-trimethoprim alone have supported this because relapses occurred almost exclusively in non-compliant patients. Interpretation of disk diffusion sensitivity testing has been problematic for sulfamethoxazole-trimethoprim, and agar dilution methods have confirmed that most *B. pseudomallei* isolates are sensitive to sulfamethoxazole-trimethoprim. Ongoing studies will ascertain whether it is still beneficial to have combination therapy for the eradication phase of melioidosis treatment or whether sulfamethoxazole-trimethoprim without doxycycline is adequate.

Adjunctive Therapy

Surgical drainage of large abscesses is indicated, but this is usually not necessary or possible for multiple small abscesses in the spleen and liver. Parotid abscesses require careful incision and drainage. Prostatic abscesses can often be drained under ultrasound guidance using a rectal probe, with transurethral resection reserved for failures of the simpler procedure.

State-of-the-art intensive care management has resulted in decreased mortality in patients with melioidosis septic shock. The possible primary role of neutrophil function in containing *B. pseudomallei* has led to the empirical use of granulocyte colony-stimulating factor (G-CSF) in patients with strictly defined septic shock, with observational data from Australia showing a significant improvement in survival with G-CSF.¹⁰⁰ Nevertheless, a randomized controlled trial in Thailand has shown no survival benefit of G-CSF in that location.¹⁰¹

PREVENTION

Primary prevention involves education in endemic areas about minimizing exposure to wet season soils and surface water, especially for diabetics. Footwear and gloves while gardening are recommended in northern Australia, but preventing occupational exposure in rice farmers may be unrealistic in Southeast Asia. Cystic fibrosis patients should consider avoiding travel to high-risk areas.

Laboratory-acquired infections, person-to-person spread, and zoonotic infection are all very uncommon, but secondary prophylaxis with sulfamethoxazole-trimethoprim, doxycycline, or amoxicillin-clavulanate could be considered for exceptional circumstances, especially if the exposed person is diabetic or has other risk factors for melioidosis. Guidelines for the management of accidental laboratory exposure have recently been published.¹⁰² Isolation of patients is recommended only for those with severe suppurative pneumonia with productive sputum.

Concerns of possible bioterrorism using the bacterium or its virulence components in genetically engineered constructs and of exposure of military personnel to *B. pseudomallei* have driven funding for recent work. Development of a melioidosis vaccine could also have substantial benefits for those living in endemic regions and for commercial livestock, although cost will be a major impediment to availability. Preliminary studies have included various conjugate, live attenuated, and heterologous vaccine candidates.⁵⁶

Glanders

Glanders is a highly communicable disease of solipeds (horses, donkeys, and mules) that is caused by *Burkholderia mallei*. It can be transmitted to other animals and to humans.

HISTORY

Glanders was described by Hippocrates and has long been recognized as an occupational risk for horse handlers, veterinarians, equine butchers, and laboratory workers. Together with anthrax, glanders was involved in the first modern use of microbes as weapons when German agents targeted horses in the United States, Romania, Spain, Norway, and Argentina between 1915 and 1918.¹⁰³

ETIOLOGY

B. mallei is a small, gram-negative, oxidase-positive, aerobic bacillus. Unlike *B. pseudomallei*, it is nonmotile. It is a host-adapted pathogen that, unlike *B. pseudomallei*, does not persist in the environment outside its equine host. The *Burkholderia* genome projects and multilocus sequence typing have supported the idea that *B. mallei* evolved in animals from the environmental pathogen *B. pseudomallei*.^{104,105}

EPIDEMIOLOGY, TRANSMISSION, AND PATHOGENESIS

With quarantine and other control measures, glanders has been eradicated from most countries, but enzootic foci continue in the Middle East, Asia, Africa, and South America. In addition to disease in equines, glanders has occurred in cats and other carnivores eating infected horse meat. Inhalation and percutaneous inoculation also occur. Discharges from the horse respiratory tract and skin are highly infectious. *B. mallei* has much greater potential for zoonotic transmission than *B. pseudomallei*, and the risk of laboratory-acquired infection also appears to be greater for *B. mallei*.^{106,107} The incubation period is from as short as 1 to 2 days (e.g., with inhalation) to many months and, as occurs with melioidosis, reactivation from a latent focus after many years has been described.

There are many parallels with the pathogenesis of *B. pseudomallei*, with studies showing the *B. mallei* extracellular polysaccharide capsule to be a critical determinant of virulence.^{52,108,109} There is differential susceptibility among animals and, although it is likely that diabetics are more susceptible to infection and disease progression with *B. mallei*,¹⁰⁷ the human host risk factors are less well defined than for melioidosis.

CLINICAL MANIFESTATIONS

Knowledge of the disease in horses is useful for understanding the potential for zoonotic transmission to humans. In acute glanders in horses, fever is accompanied by necrotic ulcers and nodules in the nasal passages that result in copious, infectious, sticky yellow discharges. Neck and mediastinal lymph nodes are enlarged, and pneumonia with nodular abscesses and dissemination to internal organs can accompany the progressive deterioration. In cutaneous glanders (known as farcy), nodular lymphatic or skin abscesses (0.5 to 2.5 cm) occur and ulcerate, discharging infectious, oily yellow pus.¹¹⁰

Human glanders, like melioidosis, can be acute or chronic, with mode of infection, inoculating dose, and host risk factors determining the clinical course. With inhaled organisms (respiratory inoculation), acute febrile illness with ulcerative necrosis of the tracheobronchial tree can occur, with mucopurulent discharge involving the nose, lips, and eyes. Lobar or bronchopneumonia, neck and mediastinal lymphadenopathy, pustular skin lesions, and septicemia with dissemination to internal organs can follow.¹¹¹ Historically, without antibiotics, death within 10 days usually occurred, but a more chronic pneumonic illness was also recognized after inhalation of *B. mallei.*¹⁰⁶

After percutaneous inoculation, local skin nodules that can suppurate and regional lymphadenopathy occur, often accompanied by fever, rigors, and malaise.^{107,111} Regional lymphadenopathy is much more common than with melioidosis. Lymphatic tract nodules and suppurating abscesses in the lymph nodes are common after several weeks in untreated cases. Dissemination at 1 to 4 weeks can result in infection in almost any tissue, with spleen and liver abscesses, pneumonia, lung abscesses, pleural nodules, and multiple subcutaneous and muscle abscesses all being common (Fig. 221-18). Central nervous system infection can also occur.



Figure 221-18 CT scan showing abscesses (arrows) in liver and spleen of a patient with laboratory-acquired glanders. (From Srinivasan A, Kraus CN, DeShazer D, et al. Glanders in a military research microbiologist. N Engl J Med. 2001;345:256-258.)

LABORATORY DIAGNOSIS

Definitive diagnosis of glanders requires a positive culture of *B. mallei*. Blood, exudates, and pus from abscesses should be cultured on standard media. Organisms are often very scanty in exudates and pus and are morphologically indistinguishable from those of *B. pseudomallei*. As happens with *B. pseudomallei*, some commercial identification systems may misidentify *B. mallei* as a *Pseudomonas* species, and 16S ribosomal RNA gene-sequenced analysis or a *B. mallei*–specific polymerase chain reaction assay may be required for confirmation.¹⁰⁷ Current serologic assays cannot distinguish *B. mallei* from *B. pseudomallei*, and the mallein skin test used extensively in animal control programs and modified for human diagnosis has poor specificity.¹⁰⁶

TREATMENT

The antibiotic susceptibility profile of *B. mallei* resembles that of *B. pseudomallei*, except that gentamicin and newer macrolides (e.g., cla-

rithromycin, azithromycin) are active against *B. mallei* but not *B. pseudomallei*.¹¹² Although response to treatment with older regimens was often slow, rapid improvement occurred in the recent U.S. military researcher with laboratory-acquired infection who was treated with imipenem and doxycycline.¹⁰⁷ This was the first reported case of glanders in the United States in more than 50 years. Recommended treatment and duration are the same as for melioidosis.

PREVENTION

Prevention depends on control of glanders in the equine species and strict precautions to prevent laboratory-acquired infection.^{106,107} Unlike the case with melioidosis, isolation of all infected persons is recommended to prevent person-to-person spread. Guidelines for the management of accidental laboratory exposure have been published.¹⁰² As with melioidosis, there is much work being done toward a vaccine to prevent disease in humans.¹¹⁰

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