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Melioidosis: a clinical overview

Direk Limmathurotsakul[†,‡] and **Sharon J. Peacock**[‡,¶,§*]

[†]*Department of Tropical Hygiene, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand;* [‡]*Mahidol-Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand;* [¶]*Department of Microbiology and Immunology, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand, and* [§]*Department of Medicine, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK*

Introduction: melioidosis, an infection caused by the environmental Gram-negative bacillus *Burkholderia pseudomallei*, has emerged as an important cause of morbidity and mortality in Southeast Asia and northern Australia.

Sources of data: a review of the literature using PubMed.

Areas of agreement: approaches to diagnosis and antimicrobial therapy.

Areas of controversy: whether seroconversion signals the presence of a quiescent bacterial focus and an increase in long-term risk of melioidosis.

Areas timely for developing research: melioidosis is potentially preventable, but there is a striking lack of evidence on which to base an effective prevention programme. An accurate map defining the global distribution of *B. pseudomallei* is needed, together with studies on the relative importance of different routes of infection. There is a marked difference in mortality from melioidosis in high-income versus lower income countries, and affordable strategies that reduce death from severe sepsis (from any cause) in resource-restricted settings are needed.

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Melioidosis is an infection caused by the Gram-negative bacillus *Burkholderia pseudomallei*. This disease has emerged over the past 25 years as an important cause of morbidity and mortality in Southeast Asia and northern Australia, and is also endemic in other tropical regions. *B. pseudomallei* has been classified as a Category B agent by the US Centers for Disease Control.

*Correspondence address. Department of Medicine, University of Cambridge, Box 157, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ, UK. E-mail: sharondt@tropmedres.ac

Geographical distribution

Melioidosis results from exposure to *B. pseudomallei* in the environment, and so the geographical distribution of disease largely mirrors the distribution of the organism. Table 1 lists the countries where endemic or sporadic human melioidosis has been documented.[1] This is incomplete since diagnosing melioidosis or detecting environmental *B. pseudomallei* requires relatively sophisticated microbiology laboratory facilities, a patchy resource worldwide. There is a need for systematic mapping of the geographic distribution of *B. pseudomallei*, an essential baseline for preventive strategies on a global scale.

Routes of infection

Melioidosis predominantly affects people in regular contact with soil and water. The commonest routes of *B. pseudomallei* infection are thought to be inoculation, inhalation and ingestion.[2] The prevailing assumption that most disease occurs as a result of percutaneous inoculation is based on the observations that people at high risk such as agricultural workers do not wear protective clothing and suffer repeated minor injuries. In addition, disease incidence increases during the rainy season when rice farmers have regular and prolonged contact with contaminated soil and water.[3] This is intuitively compelling but not supported by published evidence. A retrospective study performed in northern Australia found that less than one-quarter of people presenting with melioidosis recalled an injury in the preceding weeks,[4] and a case–control study conducted in the same setting found that exposure to soil was not associated with melioidosis.[5] Inoculation as a route of

Table 1 List of countries reporting endemic or sporadic melioidosis.*

Continents	Countries
Africa	Gambia, Kenya, Madagascar, Sierra Leone and Uganda
Asia	Bangladesh, Brunei, Burma (Myanmar), Cambodia, China, Hong Kong, India, Indonesia, Iran, Laos, Malaysia, Pakistan, Philippines, Singapore, Sri Lanka, Taiwan, Thailand and Vietnam
Europe	France
North America	Costa Rica, El Salvador and Panama
Oceania	Australia, Fiji, New Caledonia and Papua New Guinea
South America	Brazil, Colombia, Ecuador and Venezuela
Others	Aruba, Guadeloupe, Guam, Haiti, Martinique, and Puerto Rico

*Does not include cases of melioidosis in returning travellers who acquired infection elsewhere.

infection also fails to take account of disease in people who have no regular contact with soil. The lack of data on the relative importance of inoculation as the route of infection represents an important knowledge gap.

Inhalation of *B. pseudomallei* suspended in aerosols may have been an important mode of infection in US combatants during the conflict with Vietnam, particularly in helicopter crewmen.[6] Published evidence for inhalation as a route of infection in the general population is limited. Several studies from northern Australia reported a shift towards a higher frequency of pneumonia and severe disease during the rainy season or following heavy monsoon rains and winds.[2] However, pneumonia is not an accurate indicator for inhalation as the route of infection since lung involvement is also common in patients who develop infection after a defined inoculation event, and in those who relapse from a persistent nidus of infection after a course of antimicrobial therapy.[7] There is no evidence to support direct human-to-human transmission via the respiratory route, but no studies have been performed to determine whether aerosols generated by patients with pulmonary melioidosis contain viable *B. pseudomallei*, or if close contacts of cases are at increased risk.

Several clusters of melioidosis cases have been reported from Australia in which a strain of *B. pseudomallei* isolated from a common water source was a genetic match for the strain causing disease in the cluster.[8,9] The probability of this occurring by chance is small since *B. pseudomallei* is genetically extremely diverse.[10] *B. pseudomallei* has also been isolated from public water supplies in 11 locations in the Northern Territory of Australia, genotyped and implicated as a source of infection in 6 locations.[11] Acute suppurative parotitis caused by *B. pseudomallei* is common as a presentation in Thai children and probably results from direct entry of organisms in the mouth.[12] There are major knowledge gaps in Asia regarding the frequency with which water supplies are contaminated with *B. pseudomallei*, how often such water is consumed, and the relative contribution made by ingestion compared with other routes of infection.

Rare cases of melioidosis occur as a result of alternative routes.[2] Melioidosis in two infants in northern Australia was related to breastfeeding by mothers with mastitis caused by *B. pseudomallei*, and the wife of a Vietnam veteran with chronic prostatitis caused by *B. pseudomallei* developed an antibody response to the organism in the absence of clinical manifestations of melioidosis.[13] Person-to-person transmission occurred between two siblings with cystic fibrosis[14] and may have occurred between a diabetic brother and sister living in Northeast Thailand,[15] and a case of nosocomial infection from a suspected environmental source has been reported from an endemic

area.[16] There is no evidence that insect vectors play a role in transmission.

Clinical epidemiology

Most cases of melioidosis are reported from Thailand and northern Australia. It is the third most frequent cause of death from infectious diseases in northeast Thailand (after HIV/AIDS and tuberculosis),[17] and is the most common cause of community-acquired bacteraemic pneumonia in parts of northern Australia.[2] Reported incidence rates are summarized in Table 2.[17–23] Incidence in Thailand and neighbouring countries appears to parallel the bacterial counts of *B. pseudomallei* in soil. Incidence may increase in a given region following natural disasters, as occurred following the tsunami in 2004,[24] and Typhoon-Haitang which was associated with an increased incidence of culture-confirmed melioidosis from 0.7 to 70 per 100 000 person-years in South-west Taiwan in 2005.[25]

All age groups can develop melioidosis, but incidence peaks between the ages of 40 and 60 years. Melioidosis is markedly seasonal in most settings with ~75% of cases presenting during the rainy season. Predisposing conditions in adults include the presence of diabetes mellitus, chronic renal failure, immunosuppressive treatments, including steroids, thalassemia, chronic liver disease, chronic lung disease (including cystic fibrosis) and kava consumption, one or more of which are found in 60–90% of cases.[2] The association with diabetes mellitus is particularly strong and may increase the relative risk of infection by

Table 2 Incidence of melioidosis in endemic areas.

Countries (area)	Year reported	Incidence of melioidosis (per 100 000 person-years)	Mortality rate (%)
Southeast Asia			
Thailand[17] (Ubon Ratchathani)	1997–2006	12.7	43
Malaysia[18] (Pahang)	2005–2006	4.3	44
Singapore[19]	1998–2007	1.3*	16
Oceania			
Australia[20] (northern Australia)	1990–2002	19.6	16
Torres Strait islands[21]	1995–2000	42.7	22
Papua New Guinea[22] (Balimo district)	1994–1995 and 1998	20.0	40
Emerging areas			
Taiwan[23]	2001–2006	0.7†	Not available

*Average incidence rate was calculated from the total number of culture-confirmed melioidosis cases reported divided by the total number of Singapore population from year 1998 to 2007.
†Average incidence was calculated from reported incidence and total number of population in northern, central and southern Taiwan.

up to 20-fold.[17] Human immunodeficiency virus infection does not appear to predispose to melioidosis.[26] Infection in children often occurs in the absence of a known risk factor. The possibility that some people are genetically predisposed to melioidosis awaits investigation.

Seroconversion and sub-clinical infection

The majority of exposure events to *B. pseudomallei* do not lead to active infection. For example, ~80% of children living in northeast Thailand have antibodies to *B. pseudomallei* by the time they are 4 years old.[27] While seroconversion is indicative of exposure, it is a matter of debate as to whether this amounts to sub-clinical infection. Some investigators have suggested that exposed individuals may harbour a quiescent bacterial focus and are at risk of melioidosis, akin to seroconversion following contact with an individual with active tuberculosis. While case reports of people developing melioidosis many years after exposure provide some support for this idea, such cases are very rare.[28] Longitudinal studies are required to determine the long-term risk of melioidosis in people with serological evidence of exposure to *B. pseudomallei*.

Clinical melioidosis

The period between *B. pseudomallei* exposure and onset of clinical manifestations is highly variable and often difficult to define. In one study, 25% of cases that recalled a specific inoculation event had an incubation period of 1–21 days (mean 9 days).[4] Aspiration may be associated with a large bacterial inoculum, the associated incubation period for which may be very short.[24] The incubation period may also be very prolonged, the maximum recorded being 62 years.[28] The time from onset of clinical features to hospital presentation is highly variable, reflecting the broad range in disease severity. In northern Australia, 13% of patients presenting for the first time had symptoms for more than 2 months.[29] In our experience, around a third of patients have symptoms for <7 days, one-half report being unwell for 7–28 days, and the remainder have symptoms for more than 28 days.

The most frequent clinical picture is a septicaemic illness, often associated with bacterial dissemination to distant sites such that concomitant pneumonia and hepatic and splenic abscesses are common. Bacteraemia and pneumonia occur in ~50% of cases, but not necessarily together. Pulmonary involvement may involve the lung parenchyma and/or pleural cavity and may result in abscess formation. Solitary

or multiple abscesses may develop in the liver and/or spleen. Hepatosplenic abscess formation is reported to be present in a quarter of melioidosis patients in Thailand, but in only 6% of melioidosis patients in Australia. Multiple abscesses are more common than a solitary abscess in either organ. The finding of a 'Swiss cheese' appearance on ultrasonogram or 'honeycomb' appearance on computed tomography (CT) scan are said to be highly suggestive of melioidosis. More than half of the patients with hepatosplenic abscess(es) lack abdominal pain or tenderness.

Osteomyelitis and septic arthritis due to *B. pseudomallei* are well recognized. Superficial pustules, subcutaneous abscesses and pyomyositis are relatively common manifestations (15–25%), and may be the primary site of infection or secondary to haematogenous spread. Genitourinary infection is a common manifestation of melioidosis in Australia, with prostatic abscesses occurring in 18% of male patients. Renal abscesses may be associated with calculi. Infection involving the urinary tract is present in at least one-quarter of Thai patients based on a urine culture positive for *B. pseudomallei*, although only a quarter of cases with urine culture positive for *B. pseudomallei* have urinary symptoms. Neurological melioidosis characterized by brainstem encephalitis and flaccid paraparesis is defined in 4% of melioidosis cases in northern Australia, but not in Northeast Thailand where central nervous system involvement occurs in 2% of cases and is usually associated with abscess formation. Acute suppurative parotitis is a common presentation in Thai children, uncommon in Thai adults, and limited to a single-case report from Australia. Parotitis is bilateral in 10% of patients, and may be complicated by rupture into the auditory canal, facial nerve palsy and necrotizing fasciitis.

Infection involving many other sites has been described, including lymphadenitis, mycotic aneurysm, adrenal gland abscess, mediastinal infection, pericarditis, deep neck abscess, acute otitis media, sinusitis, corneal ulcers, orbital cellulitis, breast abscess and scrotal abscess.

Diagnosis

A high index of suspicion is required in order to diagnose melioidosis in the non-endemic setting. Clinicians should consider the possibility in patients with a fever who have one or more of the following: a history of residency in, or travel to a region where melioidosis is endemic; an occupation or other pursuits associated with contact with soil or water that might contain *B. pseudomallei* (including military personnel who are on exercise or active service); and the presence of risk factors such as diabetes mellitus or renal disease. The variability in clinical features

of infection is such that it is often impossible on clinical grounds to differentiate between melioidosis and other acute and chronic bacterial infections. Confirmation of the diagnosis relies on good practices for specimen collection, laboratory culture and isolation of *B. pseudomallei*.

Culture represents the diagnostic gold standard for melioidosis.[30] *Burkholderia pseudomallei* is not thought to exist as a member of the normal flora, although studies have been restricted to throat carriage.[31] While such evidence falls short of being definitive, patients admitted to Sappasithiprasong Hospital in Ubon Ratchathani, northeast Thailand with a febrile illness over the last 20 years who were culture positive for *B. pseudomallei* invariably, in our experience, have melioidosis. The possibility that individuals living in endemic areas with skin defects or other wounds may become colonized in the absence of signs or symptoms of infection has not undergone systematic study, and the possibility of wound colonization in the absence of disease has not been adequately refuted.[32] Several individuals reported to ProMED who were culture positive for *B. pseudomallei* following injuries sustained during the tsunami of December 2004 did not have symptoms consistent with melioidosis, but follow-up was not reported. Despite this uncertainty, it is prudent to suspect melioidosis in anyone with a positive culture from any site, and investigate accordingly.

Microbiological sampling of patients with suspected melioidosis differs from the investigation of many bacterial infections where culture from a normally sterile site may be the preferred evidence for a definitive diagnosis. The isolation of *B. pseudomallei* from any sample, including those from colonized sites such as urine, respiratory secretions or surface swabs, should be viewed as being highly likely to represent *B. pseudomallei* infection. It is important to perform microbiological culture of all available specimens (blood, urine, throat swab, respiratory secretions, pus and swabs from surface wounds). Samples taken from certain sites that lack signs of active inflammation and are not contiguous with the clinical site of infection may nonetheless be positive. For example, a urine or throat swab culture may be positive for *B. pseudomallei* in a patient with apparently isolated involvement of the liver or spleen.

Early discussion with the clinical microbiology laboratory is important during investigation of suspected cases. This will raise awareness for the presence of a significant pathogen in a mixed culture. In addition, *B. pseudomallei* is classified as a hazard group 3 biological agent and safe handling requires the use of the appropriate containment level. The use of selective agar increases the sensitivity of culture from non-sterile clinical specimens.[33] The medium used in melioidosis-endemic regions is Ashdown agar, but *B. cepacia* selective

agar is a good substitute where this is not available. Negative culture does not rule out melioidosis since patients already on effective antimicrobial agents may be culture negative.[30]

Antimicrobial susceptibility testing of *B. pseudomallei* for trimethoprim-sulphamethoxazole (TMP-SMX) is inaccurate using the disc diffusion method and requires an alternative methodology such as the *E*-test,[34] but this may not be feasible in resource-restricted settings. A large study conducted in Thailand demonstrated that all *B. pseudomallei* isolates that did not grow right up to the disc were susceptible by *E*-test.[34] These could be classified as 'probably susceptible' in a resource-poor setting, although this should be verified wherever possible.

The polymerase chain reaction (PCR) has been evaluated for the diagnosis of melioidosis, but is not in routine use and its sensitivity is not better than culture.[35,36] Serodiagnosis in melioidosis-endemic areas has no value since background seropositivity in the healthy population is high. Serodiagnosis has greater utility in travellers who have no history of residence in a region where melioidosis is endemic and who have made one or a small number of discrete visits during which exposure could have occurred. Ideally, paired sera should be tested in parallel (acute and convalescent samples at least 2 weeks apart). Paired sera demonstrating a rising antibody titre to *B. pseudomallei* in an individual who does not normally reside in an endemic area supports the diagnosis of melioidosis in the presence of clinical features of disease. The exposure event may have occurred months or years prior to presentation and may not be remembered. In this case, a single high antibody titre at presentation is indicative of exposure. A small number of patients with culture-proven melioidosis do not mount a detectable antibody response, and a negative result does not rule out exposure or active infection. The most commonly used serodiagnostic test is the indirect haemagglutination assay (IHA). The assay is poorly standardized worldwide, and cut-offs ranging from an IHA titre of 1:10–1:40 have been used to indicate exposure and 1:40–1:160 to indicate active disease. Improved serodiagnostics for melioidosis represents an area of clinical need.

Antimicrobial therapy

Appropriate antimicrobial agents should be commenced immediately on suspicion of the diagnosis of melioidosis, since delayed or ineffective therapy is associated with a very high mortality rate.[37] Antimicrobial recommendations are given in Table 3. Treatment is divided into intravenous and oral phases. Initial parenteral therapy is given for 10–14

days or until clinical response is seen (whichever is the longer). Ceftazidime or a carbapenem antibiotic is the treatment of choice. Ceftazidime is used as first-line therapy in Thailand, with a switch to a carbapenem antibiotic in the event of treatment failure on ceftazidime. Parenteral treatment at the Royal Darwin Hospital, Australia (which sees the highest number of cases in Australia) consists of ceftazidime, or meropenem plus G-CSF if the patient has septic shock.[38] The use of G-CSF in patients with severe melioidosis in Thailand is not supported by published evidence.[39] The results of an ongoing randomized trial of ceftazidime versus meropenem for the treatment of melioidosis in Thailand will not be available for several years. The routine addition of TMP-SMX to ceftazidime or meropenem during the initial intensive therapy phase was discontinued in 2005.[40] TMP-SMX is usually used in Australia for patients with neurological or prostatic melioidosis in view of its excellent penetration, the evidence for which is based on expert opinion and case series.[41] Intravenous amoxicillin-clavulanic acid (AMC) is second-line empiric treatment.

The switch from parenteral to oral antimicrobial therapy is made once the patient shows clear evidence of clinical improvement, including an absence of fever for 48 h and negative repeat blood culture taken at around 1 week after the onset of therapy. Prolonged parenteral therapy may be required for patients with disseminated infection, involvement of the central nervous system, bone or joint, and patients with deep-seated abscesses that cannot be drained.

Oral therapy consists of TMP-SMX alone (Australia) or in combination with doxycycline (adults in Thailand). Results are pending of a randomized controlled trial, which has recently been completed in Thailand to determine whether TMP-SMX and TMP-SMX plus doxycycline are equivalent. AMC is an alternative for patients with

Table 3 Treatment recommendations for melioidosis.

Initial parenteral therapy
Ceftazidime 50 mg/kg/dose (up to 2 g) every 6–8 h, or meropenem 25 mg/kg/dose (up to 1 g) every 8 h
Duration of therapy a minimum of 10–14 days, and longer (≥4 weeks) for deep-seated infection
Oral eradication therapy
TMP/SMX 8/40 mg/kg/dose orally BD*
>60 kg, 2 × 160/800 mg (960 mg) tablets BD
40–60 kg, 3 × 80/400 mg (480 mg) tablets BD
<40 kg, 1 × 160/800 mg (960 mg) or 2 × 80/400 mg (480 mg) tablets BD
With or without doxycycline 2.5 mg/kg/dose (up to 100 mg) orally BD
Duration at least 3–6 months, with actual duration guided by clinical response to therapy

Note: Doses are based on normal renal function.
*Twice daily.

intolerance to TMP-SMX and is first-line therapy for children and pregnant women in Thailand, but is associated with an increased risk of relapse compared with TMP-SMX-based therapies.[42] Pharmacodynamic and pharmacokinetic modelling indicate that the recommended AMC dose should be 20/5 mg/kg every 8 h.[43] Twice daily doses or formulations containing AMC ratios >4 to 1 are not recommended.[44] Chloramphenicol is no longer recommended for the treatment of melioidosis.[45] Its use in current clinical practice is extremely rare and reserved for neurological infection if ceftazidime, carbapenems or trimethoprim–sulphamethoxazole cannot be used.[46] In resource-poor settings where parenteral therapy is often difficult to provide or sustain, patients may be treated with oral antimicrobial drugs. Under such circumstances, the regimen prescribed will be dictated by drug availability and cost, and chloramphenicol may form a component of treatment.

The recommended duration of oral treatment is 3–6 months.[2] For patients with hepatosplenic abscesses, duration of therapy should be guided by time to resolution on serial abdominal imaging. It is not known whether a shorter course of therapy may be adequate for patients with mild and localized disease, such as a single subcutaneous abscess. Monitoring of drug adherence is crucial, as this is probably the most important factor in determining recurrence.

Management and outcome

Investigation of patients with suspected or confirmed melioidosis will depend on available resources, with only some of the tests detailed here being available in many regions of the world where melioidosis is endemic.

Diabetes mellitus should be excluded. Serial laboratory tests are required to detect acute renal failure, abnormal liver function tests, anaemia and coagulation abnormalities, all of which are common during severe melioidosis. Serum C-reactive protein does not always give an accurate reflection of disease severity.[47] All patients should have a chest radiograph. The common radiographic patterns of acute pneumonia are localized patchy alveolar infiltrate, bilateral diffuse patchy alveolar infiltration or multiple nodular lesions consistent with haematogenous spread. Upper lobe infection in a patient with a subacute or chronic presentation can be difficult to distinguish from pulmonary tuberculosis on the basis of clinical features and radiological changes. The development of empyema and/or lung abscess is well recognized, and repeated chest radiographs are indicated for patients with proven respiratory involvement. Arterial blood gases should be

taken in patients with lung involvement or sepsis. Abdominal ultrasound, CT scan or other imaging should be performed to exclude the presence of abscesses in the liver and spleen, and to investigate clinical evidence of prostatic involvement.

Collections of pus should be drained wherever feasible. Fever clearance is often slow (median fever clearance time of around 9 days), and without evidence of clinical deterioration is not normally sufficient to indicate a change in therapy. Sputum and draining abscess cultures may remain culture positive for *B. pseudomallei* for several weeks in a patient who is otherwise responding to treatment. Follow-up blood culture should be performed weekly during parenteral therapy, as a positive *B. pseudomallei* culture is indicative of ongoing sepsis as well as a strong predictor of death. Routine cultures of other sample types should not be performed since there is no clinical benefit derived from doing so. Patients who are failing treatment (examples of which include worsening of an existing site of infection, new dissemination of infection or late-onset organ dysfunction) should undergo repeat culture of all available samples to detect the emergence of secondary antimicrobial resistance, prior to switching to an alternative antimicrobial regimen.

While patients with severe melioidosis often require intensive care management, many people who develop melioidosis will do so in a geographical region where such resources are not available. The disparity in healthcare resources is reflected in the overall mortality from melioidosis of ~40% in Thailand and 15% in Australia.[48] APACHE II score is an independent predictor of death from melioidosis. Time to blood culture positivity, the number of bacteria/ml in blood or urine, and a positive sputum culture all have prognostic significance.[49] Patients with pus culture positive for *B. pseudomallei* are more likely to survive, probably because such patients have contained infection.

Recurrent melioidosis

This is the second most serious complication of melioidosis (after death), occurs in 5–25% of cases, is associated with further mortality (24% in Thailand), and should be considered in all febrile patients with a history of melioidosis.[42] Definitive evidence of recurrence is the isolation of *B. pseudomallei* from a patient who has completed a course of antimicrobial treatment for melioidosis and has documented evidence of recovery. Some patients with clinical features of recurrence may be culture negative.

Recurrence may represent relapse (failure to eradicate the infecting strain), or re-infection following exposure to a new bacterial strain. In

Northeast Thailand, a quarter of recurrent melioidosis is due to re-infection.[50] Choice and duration of oral antimicrobial therapy and patient compliance are the most important determinants of relapse, followed by blood culture positivity and multifocal distribution.[42] Distinguishing between relapse and re-infection is important since this has implications for antimicrobial therapy.[51] If all recurrent infections are assumed to be relapses, the attending physician may switch to less effective second-line treatment (e.g. AMC) based on the assumption that recurrence represents failure of first-line treatment with TMP-SMX-based regimens.

Making the distinction between relapse and re-infection requires genotyping of the bacterial isolate causing the first and subsequent episode to determine if they are the same or different. If they are the same clone, the probability of this happening by chance during re-infection is extremely low and such cases are assumed to represent relapse. Genotyping is often unavailable in areas where melioidosis is endemic, and a clinical scoring system has been devised based on readily available parameters to determine the most probable cause for recurrence.[51]

Prevention

There is no licensed vaccine, and none in clinical trials. Prevention depends on avoidance of contact with *B. pseudomallei*. Rice farming involves extensive contact with soil and water, but the use of full-length boots and gloves is not popular in a tropical climate. Increased mechanization would reduce contact time with soil. Research that defines the relative role of different routes of infection is needed to underpin preventive programmes.

Concluding comments

Prevention and reduction in mortality of affected individuals are the two key priorities for melioidosis research. Studies are needed that provide an accurate geographical risk map, and that define the relative role of different routes of infection. The death rate from melioidosis is higher in many parts of Asia than in Australia, a function of access to intensive care. Rapid administration of antimicrobial drugs, early recognition of sepsis and adequate fluid resuscitation may be feasible goals in some resource-restricted settings, and would be predicted to reduce mortality from melioidosis (and other causes of severe bacterial sepsis). Studies are required to define safe and affordable interventions that improve outcome where intensive care facilities are unavailable,

such as protocols to optimize fluid management and glycemic control in a general ward setting.

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References

1 Currie BJ, Dance DA, Cheng AC. The global distribution of Burkholderia pseudomallei and melioidosis: an update. *Trans R Soc Trop Med Hyg* 2008;**102**(Suppl. 1):S1–4.
2 Cheng AC, Currie BJ. Melioidosis: epidemiology, pathophysiology, and management. *Clin Microbiol Rev* 2005;**18**:383–416.
3 Suputtamongkol Y, Hall AJ, Dance DA *et al*. The epidemiology of melioidosis in Ubon Ratchatani, northeast Thailand. *Int J Epidemiol* 1994;**23**:1082–90.
4 Currie BJ, Fisher DA, Howard DM *et al*. The epidemiology of melioidosis in Australia and Papua New Guinea. *Acta Trop* 2000;**74**:121–7.
5 Merianos A, Patel M, Lane JM *et al*. The 1990–1991 outbreak of melioidosis in the Northern Territory of Australia: epidemiology and environmental studies. *Southeast Asian J Trop Med Public Health* 1993;**24**:425–35.
6 Howe C, Sampath A, Spotnitz M. The pseudomallei group: a review. *J Infect Dis* 1971;**124**:598–606.
7 Limmathurotsakul D, Chaowagul W, Day NP *et al*. Patterns of organ involvement in recurrent melioidosis. *Am J Trop Med Hyg* 2009;**81**:335–7.
8 Inglis TJ, Garrow SC, Henderson M *et al*. Burkholderia pseudomallei traced to water treatment plant in Australia. *Emerg Infect Dis* 2000;**6**:56–9.
9 Currie BJ, Mayo M, Anstey NM *et al*. A cluster of melioidosis cases from an endemic region is clonal and is linked to the water supply using molecular typing of Burkholderia pseudomallei isolates. *Am J Trop Med Hyg* 2001;**65**:177–9.
10 Chantratita N, Wuthiekanun V, Limmathurotsakul D *et al*. Genetic diversity and microevolution of Burkholderia pseudomallei in the environment. *PLoS Negl Trop Dis* 2008;**2**:e182.
11 Inglis TJ, Foster NF, Gal D *et al*. Preliminary report on the northern Australian melioidosis environmental surveillance project. *Epidemiol Infect* 2004;**132**:813–20.
12 White NJ. Melioidosis. *Lancet* 2003;**361**:1715–22.
13 McCormick JB, Sexton DJ, McMurray JG *et al*. Human-to-human transmission of Pseudomonas pseudomallei. *Ann Intern Med* 1975;**83**:512–3.
14 Holland DJ, Wesley A, Drinkovic D *et al*. Cystic fibrosis and Burkholderia pseudomallei Infection: an emerging problem? *Clin Infect Dis* 2002;**35**:e138–40.
15 Kunakorn M, Jayanetra P, Tanphaichitra D. Man-to-man transmission of melioidosis. *Lancet* 1991;**337**:1290–1.
16 Ashdown LR. Nosocomial infection due to Pseudomonas pseudomallei: two cases and an epidemiologic study. *Rev Infect Dis* 1979;**1**:891–4.
17 Limmathurotsakul D, Wongratanacheewin S, Teerawattanasook N *et al*. Increasing incidence of human melioidosis in Northeast Thailand. *Am J Trop Med Hyg* 2010;**82**:1113–7.
18 How SH, Ng TH, Jamalludin AR *et al*. Pahang melioidosis registry. *Med J Malaysia* 2009;**64**:27–30.
19 Heng BH, Goh KT, Yap EH *et al*. Epidemiological surveillance of melioidosis in Singapore. *Ann Acad Med Singapore* 1998;**27**:478–84.
20 Currie BJ, Jacups SP, Cheng AC *et al*. Melioidosis epidemiology and risk factors from a prospective whole-population study in northern Australia. *Trop Med Int Health* 2004;**9**:1167–74.

21 Faa AG, Holt PJ. Melioidosis in the Torres Strait islands of far North Queensland. *Commun Dis Intell* 2002;**26**:279–83.
22 Warner JM, Pelowa DB, Currie BJ *et al*. Melioidosis in a rural community of Western Province, Papua New Guinea. *Trans R Soc Trop Med Hyg* 2007;**101**:809–13.
23 Chen YS, Lin HH, Mu JJ *et al*. Distribution of melioidosis cases and viable Burkholderia pseudomallei in soil: evidence for emerging melioidosis in Taiwan. *J Clin Microbiol* 2010;**48**:1432–4.
24 Chierakul W, Winothai W, Wattanawaitunechai C *et al*. Melioidosis in 6 tsunami survivors in southern Thailand. *Clin Infect Dis* 2005;**41**:982–90.
25 Su HP, Yang HW, Chen YL *et al*. Prevalence of melioidosis in the Er-Ren River Basin, Taiwan: implications for transmission. *J Clin Microbiol* 2007;**45**:2599–603.
26 Chierakul W, Rajanuwong A, Wuthiekanun V *et al*. The changing pattern of bloodstream infections associated with the rise in HIV prevalence in northeastern Thailand. *Trans R Soc Trop Med Hyg* 2004;**98**:678–86.
27 Wuthiekanun V, Chierakul W, Langa S *et al*. Development of antibodies to Burkholderia pseudomallei during childhood in melioidosis-endemic northeast Thailand. *Am J Trop Med Hyg* 2006;**74**:1074–5.
28 Ngauy V, Lemeshev Y, Sadkowski L *et al*. Cutaneous melioidosis in a man who was taken as a prisoner of war by the Japanese during World War II. *J Clin Microbiol* 2005;**43**:970–2.
29 Currie BJ, Fisher DA, Anstey NM *et al*. Melioidosis: acute and chronic disease, relapse and re-activation. *Trans R Soc Trop Med Hyg* 2000;**94**:301–4.
30 Limmathurotsakul D, Jamsen K, Arayawichanont A *et al*. Defining the true sensitivity of culture for the diagnosis of melioidosis using bayesian latent class models. *PLoS One* 2010;**5**.
31 Kanaphun P, Thirawattanasuk N, Suputtamongkol Y *et al*. Serology and carriage of Pseudomonas pseudomallei: a prospective study in 1000 hospitalized children in northeast Thailand. *J Infect Dis* 1993;**167**:230–3.
32 Gibney KB, Cheng AC, Currie BJ. Cutaneous melioidosis in the tropical top end of Australia: a prospective study and review of the literature. *Clin Infect Dis* 2008;**47**:603–9.
33 Peacock SJ, Chieng G, Cheng AC *et al*. Comparison of Ashdown's medium, Burkholderia cepacia medium, and Burkholderia pseudomallei selective agar for clinical isolation of Burkholderia pseudomallei. *J Clin Microbiol* 2005;**43**:5359–61.
34 Wuthiekanun V, Cheng AC, Chierakul W *et al*. Trimethoprim/sulfamethoxazole resistance in clinical isolates of Burkholderia pseudomallei. *J Antimicrob Chemother* 2005;**55**:1029–31.
35 Chantratita N, Wuthiekanun V, Limmathurotsakul D *et al*. Prospective clinical evaluation of the accuracy of 16S rRNA real-time PCR assay for the diagnosis of melioidosis. *Am J Trop Med Hyg* 2007;**77**:814–7.
36 Meumann EM, Novak RT, Gal D *et al*. Clinical evaluation of a type III secretion system real-time PCR assay for diagnosing melioidosis. *J Clin Microbiol* 2006;**44**:3028–30.
37 Chaowagul W, Simpson AJ, Suputtamongkol Y *et al*. Empirical cephalosporin treatment of melioidosis. *Clin Infect Dis* 1999;**28**:1328.
38 Stephens DP, Fisher DA, Currie BJ. An audit of the use of granulocyte colony-stimulating factor in septic shock. *Intern Med J* 2002;**32**:143–8.
39 Cheng AC, Limmathurotsakul D, Chierakul W *et al*. A randomized controlled trial of granulocyte colony-stimulating factor for the treatment of severe sepsis due to melioidosis in Thailand. *Clin Infect Dis* 2007;**45**:308–14.
40 Chierakul W, Anunnatsiri S, Short JM *et al*. Two randomized controlled trials of ceftazidime alone versus ceftazidime in combination with trimethoprim-sulfamethoxazole for the treatment of severe melioidosis. *Clin Infect Dis* 2005;**41**:1105–13.
41 Morse LP, Moller CC, Harvey E *et al*. Prostatic abscess due to Burkholderia pseudomallei: 81 cases from a 19-year prospective melioidosis study. *J Urol* 2009;**182**:542–7; discussion 47.
42 Limmathurotsakul D, Chaowagul W, Chierakul W *et al*. Risk factors for recurrent melioidosis in northeast Thailand. *Clin Infect Dis* 2006;**43**:979–86.
43 Chierakul W, Wangboonskul J, Singtoroj T *et al*. Pharmacokinetic and pharmacodynamic assessment of co-amoxiclav in the treatment of melioidosis. *J Antimicrob Chemother* 2006;**58**:1215–20.
44 Cheng AC, Chierakul W, Chaowagul W *et al*. Consensus guidelines for dosing of amoxicillin-clavulanate in melioidosis. *Am J Trop Med Hyg* 2008;**78**:208–9.

45 Chaowagul W, Chierakul W, Simpson AJ *et al*. Open-label randomized trial of oral trimethoprim-sulfamethoxazole, doxycycline, and chloramphenicol compared with trimethoprim-sulfamethoxazole and doxycycline for maintenance therapy of melioidosis. *Antimicrob Agents Chemother* 2005;**49**:4020–5.
46 Limmathurotsakul D, Chaowagul W, Wongsrikaew P *et al*. Variable presentation of neurological melioidosis in Northeast Thailand. *Am J Trop Med Hyg* 2007;**77**:118–20.
47 Cheng AC, Obrien M, Jacups SP *et al*. C-reactive protein in the diagnosis of melioidosis. *Am J Trop Med Hyg* 2004;**70**:580–2.
48 Cheng AC, Jacups SP, Ward L *et al*. Melioidosis and Aboriginal seasons in northern Australia. *Trans R Soc Trop Med Hyg* 2008;**102**(Suppl. 1):S26–9.
49 Walsh AL, Smith MD, Wuthiekanun V *et al*. Prognostic significance of quantitative bacteremia in septicemic melioidosis. *Clin Infect Dis* 1995;**21**:1498–500.
50 Maharjan B, Chantratita N, Vesaratchavest M *et al*. Recurrent melioidosis in patients in northeast Thailand is frequently due to reinfection rather than relapse. *J Clin Microbiol* 2005;**43**:6032–4.
51 Limmathurotsakul D, Chaowagul W, Chantratita N *et al*. A simple scoring system to differentiate between relapse and re-infection in patients with recurrent melioidosis. *PLoS Negl Trop Dis* 2008;**2**:e327.