MELIOIDOSIS — A RARE BUT SERIOUS TROPICAL DISEASE THAT COULD AFFECT TRAVELLERS

By Ian M. Heslop, MSc, MRPharmS

This article is a brief review of the recent literature about melioidosis aimed at providing pharmacists with some background knowledge of an interesting but serious condition

In north-east Thailand, the organism that causes melioidosis is present in two thirds of paddy fields

The monsoonal wet season breaks in the tropical areas of northern Australia between November and February and the rains may continue until April. The rainfall at other times of the year is relatively low and so the rains are welcome, but the wet season also brings an increase in the number of reported cases of some tropical diseases, such as melioidosis, Ross River fever and dengue fever. Melioidosis is a serious infectious disease, endemic to the tropical areas of northern Australia and South East Asia and is due to an infection by the organism *Burkholderia pseudomallei*. Although the infection is rare in other parts of the world, and even in some southern Australian states, health professionals and pharmacists in the United Kingdom should be aware of its existence. This is chiefly because of the increase in tourism to endemic areas, bringing people from the UK into greater contact with the disease, and the ability of the disease to spread to other areas.

Melioidosis is a severe disease, with a high mortality if septicemia occurs, and the organism can persist in the body for several years before emerging.

DISTRIBUTION

Melioidosis has only been studied in a small number of countries, mainly Australia, Thailand, Singapore and Malaysia but it is assumed to be widespread in tropical South East Asia including Myanmar (formerly Burma), Vietnam, Indonesia and the Philippines.[1] The incidence of melioidosis in other tropical areas is unclear, possibly due to a lack of recognition by clinicians and a lack of facilities capable of isolating and identifying *B pseudomallei*, especially in tropical rural areas. There is evidence that the disease might be endemic on the Indian subcontinent and in some Caribbean countries, and there have also been reports from South Africa and the Middle East. It is unclear whether the disease has recently spread to these areas or whether the increase in incidence is due to greater recognition and identification, but melioidosis is beginning to be recognised as an emerging problem.[1]

There have been occasional reports of cases of melioidosis in temperate countries, including an outbreak in France in the 1970s,[2] but most reported cases in temperate areas have been imported from the tropics.

Melioidosis was first reported in Australia in an outbreak in sheep in Winton, north Queensland in 1949[3] and the first human case was reported in Townsville, north Queensland in a 32-year-old diabetes patient who developed fatal septicemia in 1950.[4] Since then, melioidosis has been increasingly recognised as a common cause of sepsis in humans and animals and, until new therapies became available, melioidosis was the commonest cause of fatal community-acquired bacteraemic pneumonia in endemic areas such as northern Australia and north-east Thailand.[3]

THE DISEASE

Initially it was thought that melioidosis was a zoonotic disease with a reservoir in rodents.[5] But it is now recognised that *B pseudomallei* is a widely distributed environmental saprophytic organism present in the

Ian Heslop is the assistant director of pharmacy clinical services at The Townsville Hospital, Townsville, North Queensland, Australia. Correspondence to Ian Heslop, Pharmacy Department, The Townsville Hospital, 100 Angus Smith Drive, Douglas, Townsville Q4814 Australia (e-mail Ian_Heslop@health.qld.gov.au)

soils and water of northern Australia and South East Asia. In north-east Thailand the organism is present in two thirds of paddy fields[5] and 80 per cent of children have antibodies by the time they are four years old, although the significance of this is complicated by the recent identification of an avirulent, antigenically cross-reacting organism *B thailandensis*. Little is known about the climatic, physical, chemical and biological factors that affect the proliferation of the organism in the soil, but research is currently being undertaken to acquire greater understanding of the interactions between the organism, the environment and the human-animal hosts, and how the infection is acquired.[5]

Within endemic areas melioidosis is not evenly distributed but exists in "hot spots". This was initially reported during the Vietnam War. Possible reasons are that there is an uneven distribution of the organism in the soil, a difference in virulence of local strains and differences in practices, such as farming techniques, which could lead to increased exposure. It is assumed that most cases of animal or human melioidosis arise through exposure to contaminated soils or muddy water although only 6 per cent of cases have a clear history of inoculation.[5] The association between rainfall and melioidosis is recognised because melioidosis is rare in countries with low rainfall. However, in Thailand, 75 per cent of cases present during the wet season, and in Australia increases in incidence of the disease often coincide with particularly heavy wet seasons.[3,5] The reasons for this are not clear cut.

Exposure to *B pseudomallei* does not always result in disease, and whether exposure results in disease probably depends on a balance between the bacterial strain's virulence, the immune status of the host (or presence of other recognised risk factors) and the size of the inoculum.

Melioidosis has a variety of presentations. Pneumonia and severe septicaemic pneumonia (with a mortality rate often above 50 per cent) are the commonest. Other presentations include skin abscesses or ulcers, abscesses in the internal organs, eg, the prostate, the spleen, the kidneys or the liver, septicaemia with multi-organ abscesses, and unusual neurological presentations such as brainstem encephalitis and acute flaccid paraplegia. Patients without symptoms or a known history of the disease can be found to be positive on serological testing, indicating asymptomatic infection. Like those infected by tuberculosis, a small proportion of these people can "reactivate" from latent infection many years later.

Staff at the Royal Darwin Hospital have been prospectively studying all cases of melioidosis in the tropical "top end" of the Northern Territory since 1989.[3] Over a nine-year period there have been 206 culture-confirmed cases of melioidosis with an average annual incidence over the study period of 16.5/100,000 (although the incidence rises in years with a heavy wet season, eg, 1997/98 when it rose to 34.5/100,000). The overall mortality to melioidosis was found to be 21 per cent; 74 per cent of cases were male and 50 per cent were indigenous Australians (although only 24 per cent of the population in the area is indigenous Australian).

DRR. NORTON

Burkholderia pseudomallei: ***the organism that causes melioidosis***

In the study 46 per cent of cases had a septicaemic presentation with 39 per cent mortality. A non-septicaemic presentation occurred in 50 per cent of cases with a 4 per cent mortality rate. Half of the non-septicaemic patients had pneumonia and the other presentations included skin or soft tissue abscesses, genitourinary infections, osteomyelitis, arthritis and peritonitis. A small number presented with neurological melioidosis with brainstem encephalitis or acute paraplegia, with 25 per cent mortality in this group. Of the male cases 18 per cent had prostatic abscesses; these have been shown to be responsible for a number of cases with persisting disease despite appropriate antibiotic therapy. Drainage led to rapid improvement.[3]

Mode of infection

How the organism infects the host is still unclear. Older literature examining cases of melioidosis in veterans of the Vietnam War suggests that inhalation was the commonest mode of infection. But Australian studies have shown pneumonia following presumptive inoculating skin injuries, suggesting spread through the bloodstream to the lung rather than inhalation or spread from the upper respiratory tract.[3] Ingestion has been suggested to be responsible for some animal cases. It appears that in northern Australia, the majority of infections are from percutaneous inoculation on exposure to wet season soils or contaminated water. The roles of inhalation and possibly ingestion still need clarification. In the "top end" study 25 per cent of patients reported situations of possible percutaneous exposure to soil or muddy water during the wet season.[3] Despite presumptive inoculation, the disease mostly occurred at distant sites, with no signs of disease at the site of inoculation. Less than 5 per cent of cases in the study were "reactivations", the majority of presentations following infection during the current wet season. In those cases where an incubation period could be identified from inoculation injury to onset of symptoms (25 cases), the incubation period was found to be one to 21 days with a mean incubation period of nine days. Epidemiological data suggest that after periods of intense rainfall, the incubation period can be shorter and the severity and mortality of melioidosis increased.

Risk factors

Melioidosis can occur in children and fit adults, but the majority of patients also have one or more risk factors, and severe disease and death are rare in patients without identified risk factors. In the "top end" study, of the confirmed cases, 36 per cent suffered from diabetes, 37 per cent were heavy alcohol consumers, 24 per cent had chronic lung disease, 11 per cent chronic renal failure and 28 per cent had other risk factors, including malignancy or corticosteroid usage. Within the group 9 per cent were heavy drinkers of kava (an extract of the plant *Piper methysticum* which is drunk in some Aboriginal communities as an alternative to alcohol).[3] The incidence of diabetes and renal impairment is also higher in indigenous Australians which, with other factors, may partly explain the greater than expected incidence of melioidosis described in the study in this population.

Diagnosis

In tropical countries, melioidosis remains an important public health problem, particular-

ly with regard to diagnosis and treatment. Clinical presentations vary considerably from fatal septicaemia to chronic localised infection and sub-clinical infection is not uncommon in people residing in endemic areas, eg, north-east Thailand. If inappropriately handled, the mortality rate of acute septicaemic cases rises to 70–80 per cent.[6] Even when diagnosis is made early and therapy initiated, the mortality rate is still high. Septicaemia caused by *B pseudomallei* is difficult to differentiate from other organisms, and bacterial isolation and identification is still the standard method of diagnosis, although a number of immunological and molecular approaches have been or are being developed. Isolation and identification has the advantage of being simple and relatively cheap but requires experienced personnel to interpret results. It also takes three to four days to obtain results, which may hamper successful treatment since a high percentage of patients admitted with acute septicaemia die in the first 24–48 hours.[6]

TREATMENT

B pseudomallei is resistant *in vitro* to penicillin, amino-penicillins, first and second-generation cephalosporins, most aminoglycosides, macrolides and rifampicin.[7] However it is susceptible *in vitro* to some third generation cephalosporins (ceftazidime but also cefotaxime and ceftriaxone), carbapenems, chloramphenicol, tetracyclines, co-trimoxazole and some fluoroquinolones.[7] It is also susceptible to beta-lactam/beta-lactamase inhibitor combinations such as co-amoxiclav. The carbapenems show the greatest activity in terms of minimum inhibitory concentrations and are active against bacterial strains that have a reduced susceptibility to ceftazidime or co-amoxiclav.[7]

In Thailand, the standard therapy for confirmed cases of acute severe melioidosis was a combination of intravenous antibiotics, chloramphenicol (100mg/kg per day), doxycycline (4mg/kg per day) and co-trimoxazole (60mg/kg per day), but this had a high failure rate especially in septicaemic melioidosis.[7] Ceftazidime is now the first-line drug of choice after several trials comparing the use of ceftazidime with the above "conventional regimen" showed that ceftazidime reduced mortality rates by 50 per cent.[7] Ceftazidime has also been compared with co-amoxiclav and, although the mortality rates are similar, co-amoxiclav had a higher rate of treatment failure.[7]

In severe melioidosis, intravenous therapy should be given for at least 10 days and continued until there is definite evidence of clinical improvement. This can take several weeks if visceral abscesses are present, and fever persisting for more than a week does not necessarily imply treatment failure. Supportive therapy should be instituted as necessary and surgical drainage of abscesses performed.[7]

Relapses are common in melioidosis and the morbidity and mortality of relapsed disease is similar to that seen in primary cases; treatment of severe disease should follow the same principles. The median time for relapse is 21 weeks and prolonged oral therapy should be offered following successful IV treatment to minimise the risk of relapse. There are few studies of oral maintenance therapy, co-amoxiclav (750mg eight-hourly) has been shown to be effective, often given with supplementary amoxicillin (500mg eight-hourly). But the only comparative clinical trial suggested it was less effective than the oral conventional four-drug regimen (chloramphenicol 40mg/kg per day, doxycycline 4mg/kg per day and co-trimoxazole 50mg/kg per day). But the four-drug regimen is toxic, side effects are common and compliance is poor.[7] Ciprofloxacin (500mg twice daily) is potentially useful, but is associated with a high incidence of relapse and treatment failure.[7] Other simple non-toxic regimens are required. Doxycycline alone (4mg/kg per day) has been used but again was associated with a high rate of relapse.

Two trials are under way in Thailand. The first is examining the use of azithromycin and ciprofloxacin versus doxycycline and co-trimoxazole, and the second is examining the use of doxycycline and co-trimoxazole versus the conventional four-drug regimen of doxycycline, co-trimoxazole and chloramphenicol. Co-trimoxazole has been used alone in Australia.

In northern Australia empirical treatment protocols for community-acquired pneumonia are devised to cover melioidosis in patients with risk factors, as well as other important pathogens. Once melioidosis is confirmed the usual recommended treatment is 14 days' intensive therapy with intravenous high dose ceftazidime (2g IV every six to eight hours) with co-trimoxazole (320/1,600mg 12-hourly IV or oral) or doxycycline (100mg 12-hourly) followed by eradication therapy for at least three months with high dose co-trimoxazole. The duration of intensive and eradication therapy may need to be prolonged if deep seated infections in bones, joints or the central nervous system are present.

Currently no licensed vaccine exists for melioidosis although research is currently being undertaken to identify antigens produced by *B pseudomallei* with the purpose of developing a vaccine for high risk populations.[8]

Public education about melioidosis is also important, people should avoid contact with wet season soils or muddy water. Wearing footwear and gloves when gardening or working outdoors are important to prevent exposure. These measures are especially important to patients with diabetes or other recognised risk factors.

ANIMAL MELIOIDOSIS IN AUSTRALIA

As mentioned above, melioidosis was first reported in Australia in sheep in 1949. The disease is considered endemic in northern regions of Australia but there have also been reports of animal outbreaks in south-west Western Australia and southern Queensland. Infection occurs in many animal species and, as with human cases, also possesses latency and a wide range of manifestations.

Some species only develop melioidosis if immunocompromised, but sheep and goats are particularly susceptible, resulting in the requirement for pasteurisation of commercial goats' milk in tropical areas. Asymptomatic organ abscesses have also been found in pigs, but bovine melioidosis appears to be rare. Other species have also been affected, including camels and alpaca which have been moved to northern tropical areas. Melioidosis also occurs in wildlife, with reports in birds, crocodiles and kangaroos. There have been three possible zoonotic cases in Australia.9

Animal melioidosis can have considerable economic impact and is an area of significant public health concern.

The Journal *welcomes contributions about other rare diseases from which travellers may be at risk*

REFERENCES

1. Dance DAB. Melioidosis as an emerging global problem. Acta Tropica 2000;74:115–9.
2. Mollaret HH. 'L'affaire du Jardine des plantes' ou comment la melioidose fit son apparition en France. Med Mal Infect 1988;18:643–54.
3. Currie BJ, Fisher DA, Howard DM, Burrow JNC, Selvanayagam S, Snelling PL et al. The epidemiology of melioidosis in Australia and Papua New Guinea. Acta Tropica 2000;74:121–7.
4. Rimington RA. Melioidosis in north Queensland. Med J Aust 1962;I:50–3.
5. Dance DAB. Ecology of Burkholderia pseudomallei and the interactions between environmental Burkholderia spp. and human-animal hosts. Acta Trop 2000;74:159–68.
6. Sirisinha S, Anuntagool N, Dharakul T, Ekpo P, Wongratanacheewin S, Naigowit P et al. Recent developments in laboratory diagnosis of melioidosis. Acta Tropica 2000; 74:235-245.
7. Chaowagul W. Recent advances in treatment of severe melioidosis. Acta Tropica 2000;74:133–7.
8. Brett PJ, Woods DE. Pathogenesis of and immunity to melioidosis. Acta Tropica 2000;74:201–10.
9. Choy JL, Mayo M, Janmaat A, Currie BJ. Animal melioidosis in Australia. Acta Tropica 2000;74:153–8.