

Melioidosis

Authors: Prof Bart Currie (MSHR); Dr Dan Ewald

Topic Reviewers: Robyn Dixson (RAN, Yirrkala Clinic); Michael Jenkins (RAN, Maningrida Clinic); Liz Stephenson (RAN, Nhulunbuy CDC); Dr Penny Roberts-Thomson (Nguuu Clinic); Dr Steven Skov

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Overview of melioidosis

Introduction

Melioidosis is an infection with the bacterium *Burkholderia pseudomallei*, previously known as *Pseudomonas pseudomallei* until the mid-1990s. It is an environmental organism found in soils and water across the Top End of Australia and in Asia.

'It is in the dirt and you can't kill it with a big stick' (memories of a doctor's introduction to melioidosis in the Torres Strait). *B. pseudomallei* is characteristically resistant to penicillin, ampicillin, first and second generation cephalosporins, gentamicin, tobramycin, and streptomycin.

Until new therapies recently became available it was the commonest cause of fatal community-acquired bacteremic pneumonia at Royal Darwin Hospital (and possibly also Katherine and Gove Hospitals). In 2000 (an unusually wet year) there were two cases in Central Australia.

Clinical picture

B. pseudomallei can cause infection in almost any part of the body. Most infection is thought to be acquired through percutaneous inoculation, although inhalation and ingestion are also possible.

Most cases occur in the wet tropics, during the wet season, though rarer temperate cases do occur and some people may become infected while visiting the wet tropics and develop the illness after returning to cooler/ dryer climates. The incubation period has been ascertained from the Top End study to be one to 21 days, with a mean incubation period of nine days.

Pneumonia is the commonest presentation of melioidosis. As well as severe septicaemic pneumonia, with mortality often over 50%, many patients present with milder forms of pneumonia, which respond well to appropriate antibiotics. Other presentations of melioidosis include skin abscesses or ulcers, abscesses in the internal organs (such as the prostate, spleen, kidney and liver), fulminant septicemia with multi-organ abscesses and unusual neurological illnesses, such as brainstem encephalitis and acute flaccid paraplegia.

People without symptoms or a known history of disease can also be found to be positive on serological testing, indicating asymptomatic infection. A small proportion of these people can 're-activate' from latent infection many years later in life, analogous to tuberculosis. However, re-activation represents probably less than 5% of Top End cases, with the vast majority of presentations following infection during the current wet season.

Diagnosis

Diabetes is the most important risk factor for melioidosis, with around 40% of cases in the NT being diabetic. In addition, excessive alcohol consumption, chronic renal disease, chronic lung disease and excessive kava drinking are risk factors for melioidosis. While the majority of patients with melioidosis have one or more of these risk factors, melioidosis can also occur in children and healthy adults. However, severe disease and death are extremely rare in people without (above mentioned) identified risk factors.

The likelihood of diagnosis is increased by using selective culture media (modified Ashdown's broth), frequent sampling (sputum, throat, rectal and ulcer swabs) and collection of blood cultures. Clinicians should liaise with laboratory staff to ensure selective media are available including for remote communities.

Treatment

Early diagnosis and appropriate antibiotic therapy decrease mortality. Once melioidosis is confirmed the usual treatment recommended is: **Initial intensive therapy for at least 14 days** with: intravenous high dose ceftazidime or meropenem plus high dose cotrimoxazole, in hospital.

A long period of **eradication therapy for at least three months** is needed to avoid relapse/recrudescence. This is usually done with oral monotherapy using high dose cotrimoxazole.

The duration of the intensive and eradication therapy may need to be prolonged in deep-seated infections, bone, joint and CNS infections.

In patients in ICU with melioidosis septic shock, a G-CSF protocol has been associated with decreased mortality.

Melioidosis in more detail

Epidemiology

Excellent summaries of what is known about the global distribution of melioidosis are provided by Dance (Dance, 1990; Dance, 1991; Dance, 2000b). The majority of cases of melioidosis currently being diagnosed are from South-East Asia, most notably Thailand (Punyagupta, 1989; Chaowagul, et al., 1989; Vuddhakul, et al., 1999), with an estimated 2000-3000 cases each year (Leelarasamee, 2000), Malaysia (Puthucheary, et al., 1981; Puthucheary, et al., 1992; Vadivelu, et al., 1997), Singapore (Chan, v, 1985; Tan, et al., 1990; Yap, et al., 1991; Yap, et al., 1995; Singapore Committee on Epidemic Diseases, 1995; Lim, et al., 1997) and northern Australia (see below).

The two locations where melioidosis is arguably the most important single bacterial pathogen for humans are some north-eastern provinces in Thailand and the Top End of the Northern Territory of Australia. Melioidosis is the commonest cause of fatal community-acquired bacteraemic pneumonia at Royal Darwin Hospital (Currie, 1993a). Average annual incidence of melioidosis in the Top End between 1989 and 1998 was 16.5/100

000, with a rate of 34.5/100 000 for the year spanning the 1997-98 monsoon, which was particularly wet (Currie, et al., 2000c).

Re-activation of latent infection, analogous to tuberculosis, is well recognised and led to concerns of disease in soldiers returned from Vietnam, with estimates from serology studies of around 225 000 potential cases, termed the 'Vietnamese time bomb' (Spotnitz, 1966; Clayton, et al., 1973). However while occasional cases of re-activation of *B. pseudomallei* still occur in Vietnam veterans (Mackowiak & Smith, 1978; Chodimella, et al., 1997) it is rare in comparison to the numbers exposed.

Although the endemic area for melioidosis has generally been stated to be between the latitudes 20°S and 20°N (Dance, 1991; Leelarasamee & Bovornkitti, 1989), Winton in outback western Queensland the location of the first description of melioidosis from Australia, is below this latitude and just inside the tropics at 22°S. However, by far the majority of human cases still occur above 20°S, with disease recognised across northern Australia.

There is considerable variation across northern Australia, with less disease in the Kimberley in the far north west (Inglis, et al., 2000a) than in the adjacent Top End of the Northern Territory. Even within the Top End there are variations, with melioidosis clearly more common in some Aboriginal communities than others (unpublished data).

In addition to newly recognised foci of melioidosis in Australia and globally, there has been a steady increase in the number of cases of melioidosis diagnosed in the Northern Territory, beyond the increase in population (Currie, et al., 2000c). In the 19 years after the first reported case in the Northern Territory from 1960 (Crotty, et al., 1963), there were 36 further cases diagnosed (average two cases per year), with 10 in the five years from 1975-79 (Rode & Webling, 1981). From 1984-90 there were 54 confirmed cases (average nine cases per year) (Woods, et al., 1992). In the 10 years from October 1989 there were 252 culture-confirmed cases (average 25 cases per year) (Currie, et al., 2000d). Recent years have seen over 40 cases diagnosed each year (Currie, et al., 2000c).

While increased awareness of melioidosis amongst clinicians and the public and improved laboratory diagnosis clearly account for some of the increased numbers, it is considered unlikely that large numbers of cases were being missed in the Northern Territory from 1980 onwards. Dance has discussed possible reasons for a genuine increase in melioidosis incidence (Dance, 2000b). These include an increased number of individuals with risk factors for melioidosis, such as diabetes, alcohol excess and renal disease, all of which are emerging problems in the Indigenous population of northern Australia. In addition it is possible that there has been an increase of *B. pseudomallei* in the environment.

Environmental aspects

The understanding of *B. pseudomallei* as a widely distributed environmental saprophyte has recently been summarised by Dance (Dance, 2000a). Although originally considered a zoonotic infection (Stanton & Fletcher, 1932), zoonotic infection is in fact very rare, with only three possible cases described from Australia (Low Choy, et al., 2000). It is now clear that both animals and humans acquire infection from organisms present in soil and surface water. Furthermore, molecular typing has shown that animals and humans can be infected by the same environmental clone of *B. pseudomallei* (Currie, et al., 1994; Haase, et al., 1995b).

Many factors are likely to influence the presence and distribution of *B. pseudomallei* in the environment. These include temperature, rainfall and humidity, sunlight and UV irradiation, pH of soil and water and other chemical factors such as soil composition, vegetation and use of fertilisers (Dance, 2000a).

An extensive and meticulous epidemiological investigation into a dry season cluster of melioidosis cases in a remote Kimberley (north-west Western Australia) coastal community suggested contamination of the local water supply and chlorination failure were responsible for transmission of *B. pseudomallei* (Inglis, et al., 1998; Inglis, et al., 1999). Five cases (three fatal) occurred over a six-week period (Inglis, et al., 1999). Further studies showed contamination of a water storage tank and of spray formed in a pH-raising aerator unit. Typing of the isolates by pulsed-field gel electrophoresis confirmed clonality of the human and environmental isolates (Inglis, et al., 2000a).

A similar situation has been documented from the Northern Territory. Nine cases of melioidosis with four deaths occurred over a 28-month period in members of a small remote Aboriginal community in the Top End (Currie, et al., 2000e). Typing by pulsed-field gel electrophoresis showed isolates of *B. pseudomallei* from six of the cases to be clonal and also identical to an isolate from the unchlorinated community water supply. It was considered possible that the clonal bacteria persisted and were propagated in biofilm in the unchlorinated water supply system. *B. pseudomallei* has also been isolated from rural bore water in the Darwin region (Currie, et al., 2000c). These case clusters and the 1980s Queensland piggeries outbreak – which was terminated by adequate chlorination of the water supply (Ketterer, et al., 1986) – have public health implications for quality of water standards and prevention of melioidosis in endemic locations such as northern Australia.

Mode of infection

Recent reviews support the predominant role of percutaneous inoculation of *B. pseudomallei* (Leelarasamee & Bovornkitti, 1989; Dance, 1990; Currie, et al., 2000c). In the Northern Territory presentations with pneumonia following presumptive inoculating skin injuries have been documented (Currie, et al., 2000c), suggesting haematogenous spread to the lung rather than inhalation or spread from the upper respiratory tract. This is analogous to post-primary tuberculosis, with disease from haematogenous spread localising in the upper lung zones, where highest alveolar oxygen tension exists (Citron & Girling, 1987). Furthermore, septicaemic melioidosis pneumonia cases are often more systemically ill than suggested by initial chest X-ray, supporting the concept of spread to, rather than from, the lung (Currie, et al., 2000c).

Despite the presumptive percutaneous inoculation in cases of melioidosis with a well defined cutaneous exposure event, subsequent disease mostly occurred at distant sites without evidence of active melioidosis at the inoculation site (Currie, et al., 2000c).

Epidemiological studies in patients with genitourinary melioidosis in the Northern Territory have to date not shown any evidence of sexual transmission of *B. pseudomallei* (unpublished data).

It has been noted that, despite the large bacterial load in severely ill patients with septicaemic pulmonary melioidosis, person-to-person transmission is extremely unusual (Kunakorn, et al., 1991; Dance, 2000a).

This supports the primary importance of host risk factors for development of melioidosis.

Asymptomatic infection, incubation, acute and chronic disease and latent infection

Serology studies suggest that most infection with *B. pseudomallei* is asymptomatic (Nigg, 1963; Strauss, et al., 1969a, Ashdown & Guard, 1984; Kanaphun, et al., 1993), with severe clinical disease occurring mostly in those with risk factors such as diabetes, renal disease and alcoholism (Guard, et al., 1984; Leelarasamee & Bovornkitti, 1989; Suputtamongkol, et al., 1994a). Studies in north Queensland also suggested that for those with risk factors such as diabetes and alcoholism there is an increased prevalence of asymptomatic infection (seropositivity) as well as of clinical disease (Ashdown & Guard, 1984). Although this association may reflect confounding factors such as increased exposure, a case control study from Thailand demonstrated a significant interaction between diabetes and occupational exposure for melioidosis cases (Suputtamongkol, et al., 1999). This is consistent with an increased susceptibility to infection in diabetics exposed to *B. pseudomallei*.

Seropositivity in the Top End varies from under 5% to 13% (Currie, et al., 2000c). To date there is no definitive evidence for development of immunity to melioidosis with natural exposure to *B. pseudomallei*. Re-infection with a different strain of *B. pseudomallei* following successful treatment of melioidosis has been documented (Desmarchelier, et al., 1993; Haase, et al., 1995a).

The incubation period for melioidosis has been ascertained in the Darwin prospective melioidosis study, which commenced in October 1989. Of the 206 *B. pseudomallei* culture confirmed cases of melioidosis up to September 1998, 52 (25%) had likely inoculating events (Currie, et al., 2000c). These were specifically recalled situations where usually percutaneous exposure to soil or muddy water occurred during the monsoon. In the 25 cases where a clear incubation period could be determined between the inoculating injury and the onset of symptoms, the incubation period was one to 21 days (mean nine days). This is consistent with a reported series of nosocomial melioidosis cases from Thailand, where incubation period was three to 16 days (mean 9.5 days) (Sookpranee, et al., 1989a). Rapid onset of melioidosis (even within 24 hours of inoculation) has been seen in presumed aspiration following near drowning (Achana, et al., 1985; Lee, et al., 1985), as well as in a small number of patients with heavy environmental exposure in the Darwin series. It is likely that inoculating dose, mode of infection, host risk factors and differential virulence of infecting *B. pseudomallei* isolates all influence the incubation period (Howe, et al., 1971; Bovornkitti, et al., 1985).

The Darwin study has also characterised presentations as acute or chronic disease. Acute disease is most common and was defined as symptoms being present for less than two months on presentation. Chronic disease was defined as illness with symptoms for longer than two months duration on presentation. Of 252 cases of culture-confirmed melioidosis in the 10 years until September 1999, 222 (88%) presented with acute illness and 30 (12%) with chronic illness, with no fatalities in the latter group (Currie, et al., 2000a).

Intracellular survival of *B. pseudomallei* in human and animal hosts is likely to explain the ability for latency, with possible parallels to

environmental 'latency' with the recently described ability of *B. pseudomallei* to survive inside free-living amoebae (Inglis, et al., 2000b). It has long been recognised that, analogous to tuberculosis, *B. pseudomallei* has the potential for re-activation. Hence the concern of the 'Vietnamese time bomb' in returned soldiers (see above). Latent periods from exposure to *B. pseudomallei* in an endemic region to onset of melioidosis in a non-endemic region have been documented as long as 26 years (Mays & Ricketts, 1975) and 29 years (Chodimella, et al., 1997) from the USA and 19 years (Newland, 1969) and 24 years (Kingston, 1971) from Australia. However documented cases of re-activated *B. pseudomallei* are very uncommon. The small numbers of such cases in the USA in comparison to the estimated 225 000 seropositive soldiers who returned from Vietnam (Spotnitz, 1966; Clayton, et al., 1973), suggest re-activation of *B. pseudomallei* is an infrequent event.

The vast predominance of cases of melioidosis occurs in the monsoonal wet seasons of the various endemic regions. Seventy-five per cent of cases in north-east Thailand were in June to November (Suputtamongkol, et al., 1994a) and 85% of cases in the Northern Territory were in November to April (Currie, et al., 2000a). These data support the concept that, in addition to most infections with *B. pseudomallei* being asymptomatic, most cases of melioidosis in endemic areas are recent infections presenting with acute illness, predominantly in the wet season (Ashdown & Guard, 1984; Guard, et al., 1984; Chaowagul, et al., 1989; Dance, 1991; Currie, et al., 2000c).

The Darwin study data suggested that only 3% of cases of melioidosis are from re-activation of *B. pseudomallei* from a latent focus (Currie, et al., 2000a).

In summary, from the Darwin prospective study 85% of cases of melioidosis occurred in the wet season (November to April), with 88% presenting with acute illness and 12% having chronic illness (sick for more than two months). Incubation period was one to 21 (mean nine) days amongst the 97% of cases considered due to recent infection with *B. pseudomallei*. Only 3% of cases overall were considered to be re-activation from a latent focus. It remains unknown what proportion of asymptomatic seropositive people have latent infection with the potential for re-activation.

Risk factors for melioidosis

The most important risk factors for melioidosis are diabetes, alcohol excess and renal disease (Leelarasamee & Bovornkitti, 1989). The importance of diabetes as the most commonly associated risk factor for melioidosis has been well documented in the major melioidosis endemic countries (Puthuchear, et al., 1981; Guard, et al., 1984; Chaowagul, et al., 1989; Suputtamongkol, et al., 1994a; Puthuchear, et al., 1992; SCED, 1995; Suputtamongkol, et al., 1999; Currie, et al., 2000d).

The rates of diabetes in Thai studies of melioidosis cases were 23% (Punyagupta, 1989), 32% (Chaowagul, et al., 1989) and more recently 60% (Suputtamongkol, et al., 1999), compared to a rate of 37% in the Darwin prospective study (Currie, et al., 2000d). Studies in the Northern Territory and Thailand showed adjusted risk ratios of diabetes in cases of melioidosis versus controls of 12.9 (95%CI 5.1-37.2) (Merianos, et al., 1993) and 5.9 (95% CI 4.0-8.9) (Suputtamongkol, et al., 1999), respectively. The Thai study also showed a statistically significant predisposition to bacteraemic disease versus non-bacteraemic disease in diabetics with melioidosis (OR 1.32; 95%CI, 1.05-1.66) (Suputtamongkol, et

al., 1999). Furthermore, logistic regression demonstrated a significant interaction between diabetes and occupational exposure (Suputtamongkol, et al., 1999), consistent with Ashdown and Guard's earlier serology studies suggesting diabetics to be at increased risk for infection with *B. pseudomallei* as well as for developing melioidosis (Ashdown & Guard, 1984).

The importance of alcohol excess as a risk factor for melioidosis was recognised in the Northern Territory (Rode & Webling, 1981) and in north Queensland (Guard, et al., 1984), but is not as evident in studies from Thailand (Chaowagul, et al., 1989, Suputtamongkol, et al., 1994a). Alcoholism appears to be even less common as a risk factor in Malaysia (Puthuchear, et al., 1992) and Singapore (SCED, 1995). This may well reflect the differences in alcohol consumption by the various populations, but further comparative studies will be informative. In Thailand 12% of melioidosis cases had a history of heavy alcohol consumption (Suputtamongkol, et al., 1999), compared to 39% in the Darwin study (Currie, et al., 2000d).

Chronic renal disease is also a recognised risk factor for melioidosis in the endemic region (Chaowagul, et al., 1989; Suputtamongkol, et al., 1994a; Puthuchear, et al., 1992; SCED, 1995; Suputtamongkol, et al., 1999; Currie, et al., 2000d). Renal disease was present in 27% and 20% of patients in the Thai studies (Chaowagul, et al., 1989; Suputtamongkol, et al., 1999), compared with 10% in the Northern Territory study (Currie, et al., 2000d).

Other risk factors identified for melioidosis include chronic lung disease (present in 27% of cases in the Northern Territory study) (Currie, et al., 2000d), thalassemia (in 7% of Thai patients with an OR of 10.2; 95%CI, 3.5-30.8) (Suputtamongkol, et al., 1999) and probably various malignancies, steroid therapy and tuberculosis, although their roles as independent risk factors are yet to be confirmed (Suputtamongkol, et al., 1999).

The association of melioidosis with the consumption of kava has recently been recognised in Australia (Currie, et al., 2000c). Kava is an extract of the root of the plant *Piper methysticum* and was introduced to remote Aboriginal communities by missionaries as an alternative to alcohol. Kava consumption was noted in 8% of melioidosis cases in the Northern Territory study and whether kava is an independent risk factor for melioidosis and other infectious diseases is currently being assessed (Currie, et al., 2000d).

Overall, risk factors are less commonly present in children compared to adults (Dance, et al., 1989a; Lumbiganon & Viengnondha, 1995; Edmond, et al., 1998). Although fulminant melioidosis can occur in healthy individuals, severe disease and fatalities are uncommon in those without defined risk factors.

In the Northern Territory study, 51/252 cases (20%) had no identified risk factor and there was only one fatality in this group (Currie, et al., 2000d). This was an elderly male, and recent multivariate analysis has shown age over 50 to be an independent risk factor for fatal melioidosis (Currie B & Jacups S, in preparation).

In summary, diabetes is the most important risk factor for melioidosis, with alcohol excess, chronic renal disease and chronic lung disease also important. Severe disease and death are unusual in the absence of risk factors.

Table 1: Clinical presentations of melioidosis over 10 years in the Top End from; Currie, et al., 2000d

		Number	Died	Mortality rate
Bacteraemic				
Pneumonia	- Septic shock	37	31	84%
	- Other	29	0	0%
Genitourinary	- Septic shock	5	4	80%
	- Other	18	0	0%
Osteomyelitis/septic arthritis	- Septic shock	1	1	100%
	- Other	3	0	0%
Other	- Septic shock	7	7	100%
	- Other	17	0	0%
Non-bacteraemic				
Pneumonia		61	4	7%
Genitourinary		14	0	0%
Skin abscess		32	0	0%
Soft tissue abscess (es)		10	0	0%
Neurological		10	2	20%
Osteomyelitis/septic arthritis		5	0	0%
Other		3	0	0%
Total		252	49	19%

Clinical features

As noted already, there is an enormous spectrum of disease with *B. pseudomallei* infection. The majority of those infected are asymptomatic, but it remains unknown what proportion of asymptomatic seropositive people have latent infection with the potential for re-activation. Re-activation appears to be a rare event in endemic regions (Currie, et al., 2000a), but presumably accounts for those cases with latency of up to 29 years (Chodimella, et al., 1997).

Table 1 shows the clinical presentations of the 252 cases in the 10 year prospective study from the Top End of the Northern Territory (Currie, et al., 2000c). As noted above, 88% presented with acute illness and 12% with chronic illness (symptomatic for >2 months) (Currie, et al., 2000a). In the Top End, 46% of cases were bacteraemic and overall mortality was 19% (Currie, et al., 2000d).

Pneumonia is the commonest clinical presentation of melioidosis in all studies (Howe, et al., 1971; Guard, et al., 1984; Punyagupta, 1989; Chaowagul, et al., 1989; Leelarasamee & Bovornkitti, 1989; Dance, 1990; Puthuchear, et al., 1992; SCED, 1995; Simpson, et al., 1999), accounting for half of the Northern Territory cases (Currie, et al., 2000c). The diversity of presentations other than pneumonia was demonstrated in the Thailand series of 686 cases presented at the National Workshop on Melioidosis in November 1985 (Punyagupta, 1989). Of those without

bacteraemia in the Top End study, 24% presented with skin ulcers or abscesses – well recognised presentations of melioidosis, as are septic arthritis and osteomyelitis (Punyagupta, 1989; Leelarasamee & Bovornkitti, 1989; Subhadrabandhu, et al., 1995; Popoff, et al., 1997). Also well recognised, whatever the clinical presentation, are abscesses in internal organs, especially spleen, kidney, prostate and liver (Punyagupta, 1989; Leelarasamee & Bovornkitti, 1989).

Antibiotic therapy

B. pseudomallei is characteristically resistant to penicillin, ampicillin, first and second generation cephalosporins, gentamicin, tobramycin, and streptomycin (Eickhoff, et al., 1970; Leelarasamee & Bovornkitti, 1989; Chaowagul, 2000). It has been shown to be susceptible to various newer beta-lactam antibiotics, especially ceftazidime, imipenem, piperacillin, amoxicillin/clavulanate, ceftriaxone and cefotaxime (Chau, et al., 1986; Cheong, et al., 1987; Ashdown, 1988; McEniry, et al., 1988; Dance, et al., 1989b; Yamamoto, et al., 1990; Smith, et al., 1994).

Emergence of resistance in *B. pseudomallei* during therapy has been well documented (Dance, et al., 1988; Dance, et al., 1989b; Godfrey, et al., 1991; Dance, et al., 1991; Toohey, et al., 1994; Smith, et al., 1994; Jenney, et al., 2001).

The carbapenems – imipenem and meropenem – have the lowest minimum inhibitory concentrations against *B. pseudomallei* (Ashdown, 1988; McEniry, et al., 1988; Dance, et al., 1989b; Yamamoto, et al., 1990; Smith, et al., 1994; Smith, et al., 1996). Furthermore, in vitro time-kill studies to measure the rate of bacterial killing showed the carbapenems to perform better against *B. pseudomallei* than ceftazidime (Smith, et al., 1994), including for various resistant isolates (Smith, et al., 1996). It was suggested that this might reflect enhanced penetration through the cell wall or preferential binding to different penicillin binding proteins. A surprising finding of the time-kill studies was that, unlike for imipenem, meropenem and piperacillin, bactericidal activity of ceftazidime was not confirmed (Smith, et al., 1994; Sookpranee, et al., 1991). Another theoretical advantage of carbapenems is the demonstration of a post-antibiotic effect against *B. pseudomallei* which is not present for ceftazidime (Walsh, et al., 1995a).

Most recently, 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 fewer treatment failures in those given imipenem (Simpson, et al., 1999).

Another trial in Thailand suggested cefoperazone/ sulbactam plus cotrimoxazole may be a useful alternative for the initial **intensive therapy**, although numbers in the study were inadequate for a conclusive result (Thamprajamchit, et al., 1998). A study in mice has suggested useful efficacy for cefpirome, especially when used in combination with cotrimoxazole (Ulett, et al., 1999).

The duration of initial **intensive therapy** should be at least 10 days (Chaowagul, 2000). The Northern Territory guidelines state at least 14 days, with longer required if critically ill, or for extensive pulmonary disease, deep-seated collections or organ abscesses, osteomyelitis, septic arthritis and neurological melioidosis (Currie, et al., 2000d; Group, 2000/2001).

Ceftazidime infusions through a peripherally inserted central catheter (PICC line) using an elastomeric infusion device (Baxter, Sydney) have

enabled early discharge for hospital-in-the-home therapy (Currie, et al., 2000d). The absence of any postantibiotic effect with ceftazidime gives such a continuous infusion a theoretical advantage over intermittent dosing (Walsh, et al., 1995a).

Subsequent eradication therapy for melioidosis

Following initial **intensive therapy**, using ceftazidime or imipenem or meropenem, possibly in combination with cotrimoxazole, 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 recurrent melioidosis has confirmed that by far the majority are true relapses from failed eradication, rather than new infection (Desmarchelier, et al., 1993; Chaowagul, et al., 1993; Haase, et al., 1995a; Mohandas, et al., 1995; Currie, et al., 2000a).

There are a number of reasons for failure of **eradication therapy**.

1. The most important factor responsible for most recrudescence or relapse of melioidosis is poor compliance with eradication therapy (Chaowagul, et al., 1993; Rajchanuvong, et al., 1995; Currie, et al., 2000a; Jenney, et al., 2001). The reasons for poor compliance are complex and multifactorial, but availability and cost of medications and access to follow-up assessment are critical, as is the ability to recognise medication side effects and arrange alternative therapy where appropriate. We aim for regular follow-up of cases during the eradication phase, with free antibiotics and action plans for defaulters, analogous to tuberculosis programs (Currie, et al., 2000d).
2. Relapses have been found to be 4.7 times (95%CI: 1.6-14.1) more common in patients with severe disease compared with those with localised melioidosis (Chaowagul, et al., 1993).
3. Use of ceftazidime in the initial **intensive therapy** was also associated with a halving of relapse (Chaowagul, et al., 1993).
4. Duration of **eradication therapy** is also critical, with relapses following oral therapy of eight weeks or less more likely than if eradication is given for longer than 12 weeks (Suputtamongkol, et al., 1991, Chaowagul, et al., 1993). Hence the recommendations that **eradication therapy** should be for 12-20 weeks (Rajchanuvong, et al., 1995, Chaowagul, 2000) or 'at least 3 months' (Group., 2000/2001, Currie, et al., 2000d).
5. The choice of agents for the **eradication therapy** is important. Both amoxicillin/clavulanate (Rajchanuvong, et al., 1995) and oral quinolones (ciprofloxacin or ofloxacin) (Chaowagul, et al., 1997) have been found to be less effective in preventing relapse than 'conventional' eradication with chloramphenicol (given usually only for the first four to eight weeks), cotrimoxazole and doxycycline.

Reports on in vitro susceptibility of *B. pseudomallei* for quinolones generally show resistance or intermediate results (Chau, et al., 1986; Ashdown, 1988). Disc diffusion techniques can give false-sensitive results, hence the cautions against use of quinolones (Ashdown & Currie, 1992). However, quinolones are still being used in some circumstances, possibly with the consideration of the noted excellent postantibiotic effect of ciprofloxacin (Walsh, et al., 1995a) and their ability for intracellular activity and potential activity in the presence of biofilm (Vorachit, et

al., 2000). At present quinolones are not recommended as first-line agents for eradication of *B. pseudomallei*, although there is currently a study comparing azithromycin plus ciprofloxacin against doxycycline plus cotrimoxazole (Chaowagul, 2000).

The most important recent trial of **eradication therapy** was a comparison of doxycycline alone (the most commonly used eradication regimen in the Northern Territory until 1998) versus 'conventional' chloramphenicol (first four weeks only), cotrimoxazole and doxycycline combination (Chaowagul, et al., 1999a). Relapses were significantly commoner in the doxycycline-alone group, resulting in a recommendation that doxycycline not be used alone as first-line eradication therapy (Chaowagul, et al., 1999a). Similar failures of doxycycline alone as **eradication therapy** were being noted in the Northern Territory (Currie, et al., 2000a), with some *B. pseudomallei* relapse isolates showing acquired doxycycline resistance (Jenney, et al., 2001).

Since changing to **eradication therapy** with cotrimoxazole alone in the Northern Territory, relapses have been almost exclusively in non-compliant patients (Currie, et al., 2000d), consistent with the hypothesis that it is cotrimoxazole which is the critical component in the 'conventional' combination therapy. Current trials in Thailand will hopefully ascertain whether it is still beneficial to have combination therapy for the eradication phase of melioidosis treatment, or whether cotrimoxazole alone is adequate.

In summary, **initial intensive therapy** should be with ceftazidime or imipenem or meropenem, possibly with cotrimoxazole added, for a minimum of 14 days –longer (four to eight weeks or more) if critically ill, extensive pulmonary infection, deep-seated collections or organ abscesses, osteomyelitis, septic arthritis or neurological melioidosis. **Subsequent eradication therapy** should be for a minimum of three months, with high dose cotrimoxazole or conventional combination therapy.

In patients with septic shock, preliminary data suggest addition of G-CSF in addition to state of the art intensive care management may increase survival.

Protocol issues requiring special consideration

Who to treat/cover for melioidosis when you only have clinical suspicion of the diagnosis?

The risk factors of melioidosis are common (diabetes, alcohol abuse, renal failure, steroid treatment, chronic lung disease), and presentation to a remote health centre with fever and/or signs of pneumonia is relatively common. There is therefore a potentially large group of people being seen in remote settings (in the Top End) who should be suspected of having melioidosis.

Early treatment is important for survival, so waiting for failure of standard penicillin treatment regimens may lead to poor outcomes. However, experience from the Royal Darwin Hospital (RDH) suggests that a policy of treating moderate or severe pneumonia in a person with one or more risk factors for melioidosis with ceftriaxone 2 g (high dose) and evacuating to hospital seems to work well. This protocol has been in place for 10 years.

Decreased melioidosis mortality has paralleled increased awareness of melioidosis amongst urban and rural health staff in the Top End. Additionally, there has been a more recent policy of using ceftazidime or meropenem in initial antibiotic treatment regimens in patients admitted to

RDH critically ill with pneumonia, especially in the wet season and in those with risk factors. Most cases of melioidosis are in fact not critically unwell and it is appropriate to await definitive diagnosis by culture before beginning specific *B. pseudomallei* therapy. This therefore relies on a high level of clinical suspicion amongst health staff (especially for diabetics in the wet season) and on the collection of appropriate samples for culture. Hence the note on this in the CARPA STM protocol.

Common examples are those with a subacute/chronic pneumonia, who may be unwell but not critically ill for a few weeks, unrecognised until appropriate cultures (usually sputum) grow *B. pseudomallei*, or chronic unhealing skin sore(s)/abscess(es)/ ulcer(s) which have not responded to benzathine penicillin or flucloxacillin, and then culture *B. pseudomallei* when appropriate swabs are taken. Occasional cases of acute/subacute/chronic septic arthritis or osteomyelitis, or rarely cellulitis, are due to *B. pseudomallei*, making these conditions also worth considering as possible melioidosis, especially in diabetics, those with chronic renal impairment and alcohol excess.

Finally, an important syndrome has been increasingly recognised, especially by medical staff in East Arnhem. This is prostatic/genitourinary melioidosis in males who are heavy kava and/or alcohol drinkers presenting with a few days of fever, non-specific abdominal pain, often some diarrhoea and urinary difficulties (may not be painful, however) culminating in urinary retention. Drainage of prostatic abscess(es) is almost always required.

Serology has a limited role in diagnosis as both specificity (for active infection) and sensitivity (especially in acutely sick patients) are poor. A positive IHA (titre over 1/40) does need appropriate clinical assessment for active melioidosis and appropriate microbiology performed. It is now very rare for true cases of melioidosis in the Top End to be culture negative, provided the correct samples are taken. Therefore patients are not treated for melioidosis because of only a positive serology result. In confirmed cases serology titres may slowly decrease with treatment, but this is not universal.

Melioidosis needs to be considered in settings of; diabetic foot infection, osteomyelitis and septic arthritis.

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