Melioidosis: The 2014 Revised RDH Guideline

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Abstract

Since the start of the 2009/2010 wet season the numbers of confirmed melioidosis cases in the Top End of the Northern Territory have far exceeded historical averages, with the majority of the increase being in the urban Darwin region. The Darwin Prospective Melioidosis Study commenced on 1 October 1989 and over the years the approach to diagnosis and treatment of melioidosis has evolved, based on the cumulative experience of Royal Darwin Hospital (RDH) clinicians and the RDH and Menzies laboratory staff and that of colleagues elsewhere in Australia and overseas. In February 2014 the RDH Melioidosis Guideline was revised and is presented here. Antibiotic doses in patients with renal impairment and durations of the intravenous and oral phases of therapy based on clinical parameters have been refined and are now presented in Tables.

Epidemiology

Melioidosis results from infection with the soil and water bacterium *Burkholderia pseudomallei*.[1] Disease occurs in humans and many animals and mostly follows percutaneous inoculation, although inhalation of aerosolized bacteria is probable during severe weather events such as tropical storms and cyclones. Aspiration has also been documented with near drowning and instances of ingestion have occurred from mastitis-associated infected breast milk.[2, 3] Zoonotic transmission is exceedingly rare, as are person-to-person transmission and laboratory-acquired infection.

The known endemic distribution of *B. pseudomallei* has expanded beyond the traditional melioidosis-endemic regions of Southeast Asia and northern Australia, with recent case reports of melioidosis from the Americas, Madagascar, Mauritius, India and elsewhere in south Asia, China and Taiwan.[4]

The first reported case of melioidosis in the Northern Territory was in 1960.[5] Since October 1989 we have prospectively documented all cases of melioidosis in the Top End. Over the 20 years from 1 October 1989 until 30 September 2009 there were 540 culture-confirmed cases with 78 deaths (14%) in the Darwin Prospective Melioidosis Study (DPMS). With heavy rains in the wet seasons from 2009-2012 case numbers rose dramatically; 91 cases (11 fatal) in 2009-2010; 64 cases (9 fatal) in 2010-2011; and 97 cases (10 fatal) in 2011-2012. In addition following very heavy rains early in 2011 there were an unprecedented 6 cases in Central Australia which were considered acquired in Central Australia rather than in the Top End. Previously cases of melioidosis in central Australia were mostly in people who acquired infection in the Top End. *B. pseudomallei* has been recovered from various environmental locations in Central Australia.

With a much drier year in 2012-2013 there was a decrease in melioidosis in the Top End with 36 cases (2 fatal), but cases have risen again with the heavy rains since October 2013.

Over 80% of cases in the Top End occur during the wet season (1 November – 30 April).

Pathogenesis

Serological surveys suggest that most infections are asymptomatic, with rates of seropositivity by indirect haemagglutination assay (IHA) of over 50% in parts of northeast Thailand.[6] In contrast, in the Top End of the Northern Territory, IHA seropositivity (titre >1:20) in long term Darwin residents is <5% but in remote communities in Arnhem Land it can be as high as 20% (unpublished data).

The clinical presentations of melioidosis and outcomes are thought to be determined by a combination of route of infection, infecting dose of bacteria, putative *B. pseudomallei* strain differences in virulence and most importantly host risk factors for disease.

Diabetes is the most important risk factor for melioidosis, followed by **hazardous alcohol use, chronic renal disease, and chronic lung disease.**[7, 8] Over recent years in Darwin it has become clear that **malignancy and immunosuppression**, especially cancer chemotherapy and dexamethasone use with radiotherapy, are also important risk factors. Cardiac failure is also a likely independent risk factor for melioidosis.

Although animal studies support there being differential virulence between strains of *B. pseudomallei*, the specific virulence factors responsible for clinical disease and severe infection remain surprisingly poorly elucidated.[9]

The vast majority of melioidosis cases are from infection during the current or recent wet season, with an incubation period of 1-21 days (mean, 9 days) in those presenting with acute disease (85% of all cases). A more chronic course following infection (chronic melioidosis, defined as symptoms being present for >2 months) occurs in 11% of all cases.[10] Latent infection with subsequent activation is well recognised in melioidosis, with the longest documented period of latency being an extraordinary 62 years,[11] but in the DPMS this is considered very uncommon and accounts for under 4% of all cases.

Clinical features

Around half of melioidosis cases present with pneumonia, which can be part of a fatal septicaemia, a less severe unilateral infection indistinguishable from other community-acquired pneumonias or a chronic illness mimicking tuberculosis.[12, 13] Other presentations range from skin lesions without systemic illness,[14] to overwhelming sepsis with abscesses disseminated in multiple internal organs.[10] Genitourinary disease with prostatic abscesses is especially common in the Top End.[15] Bone, joint and neurological infections are all well documented.[16] Blood cultures are positive in over 50% of all patients. Patients with chronic melioidosis present with either pneumonia or non-healing skin sores.

Diagnosis

The likelihood of diagnosing melioidosis is maximized if the diagnosis is considered in at-risk subjects and appropriate clinical samples from a variety of sites are sent to the microbiology laboratory for microscopy and culture.

Culture is the mainstay of diagnosis. Diagnosis of melioidosis (i.e. active disease) is NOT made on the basis of a positive serology (IHA) result, although melioidosis serology should be ordered if melioidosis is suspected. Serologic testing alone is not a reliable method of diagnosis and culture confirmation should always be vigorously sought in patients with suspected melioidosis.

All patients with suspected melioidosis should have the following samples, if available, taken for culture:

- Blood cultures
- Sputum
- Urine
- Swab of an ulcer or skin lesion; placed into Ashdown's selective medium (purple bottle) to enhance recovery of the organism
- Abscess fluid or pus
- Throat swab; placed into Ashdown's selective medium
- Rectal swab; placed into Ashdown's selective medium.

Chest X-ray should be performed in all suspected cases. In any confirmed melioidosis case (i.e. culture positive), CT or ultrasound of abdomen and pelvis is required to detect any internal abscesses, irrespective of clinical presentation. In children and females who are not significantly systemically unwell, ultrasound is preferable to minimise radiation exposure. CT is the best imaging to detect prostatic abscesses. CT chest is not routine.

All confirmed cases of melioidosis and any suspected cases without confirmation despite appropriate diagnostic work up (as above) should be referred to the **RDH Infectious Diseases team.**

Treatment

All cases of melioidosis in the Top End are managed and followed up by the RDH Infectious Diseases team.

For **initial intensive therapy:**

- Ceftazidime (wards) 2 g (child: 50 mg/kg up to 2 g) IV, 6-hourly for at least 14 days

OR

- Meropenem (ICU) 1 g (child: 25 mg/kg up to 1 g) IV, 8-hourly for at least 14 days

See Appendix for dosing in renal impairment.

Regular monitoring of urea and electrolytes, creatinine, LFTs, FBE including eosinophil count and CRP are required. If renal impairment develops adjust dosing as per Appendix for dosing in renal impairment.

It is policy in RDH ICU for all patients in ICU/HDU with melioidosis septic shock to be given granulocyte colony-stimulating factor (G-CSF) 300ug IV daily, unless contraindicated and beginning as soon as the Microbiology Laboratory flags a probable *B. pseudomallei* infection. The main contraindication for commencing G-CSF is an acute coronary event, but abnormal liver function is not considered a contraindication for giving G-CSF in patients with melioidosis at RDH. G-CSF is continued for 10 days or for the duration of ICU/HDU stay depending on clinical response, unless a contraindication develops such as total blood white cell count >50,000 $X10^6$/L.

For neurological melioidosis meropenem is the initial IV therapy and the meropenem dose is doubled to 2 g (child: 50 mg/kg up to 2 g) IV, 8-hourly.

For neurological melioidosis, osteomyelitis and septic arthritis, genitourinary infection including prostatic abscesses, and skin and soft tissue infections, add trimethoprim+sulfamethoxazole from commencement of therapy in the eradication doses as below.

Prolonged IV therapy (4 to 8 weeks or longer) is necessary for complicated pneumonia, deep-seated infection including prostatic abscesses, neurological melioidosis, osteomyelitis and septic arthritis.[17,18]

See Table for duration of initial intensive IV therapy.

Table. Darwin melioidosis treatment duration guideline

Antibiotic Duration-Determining Focus	Minimum intensive phase duration (weeks)[a]	Eradication phase duration (months)
Skin abscess	2	3
Bacteraemia with no focus	2	3
Pneumonia		
without lymphadenopathy[b] or ICU admission	2	3
with either lymphadenopathy[b] or ICU admission	4	3
Deep-seated collection and septic arthritis[c]	4[d]	3
Osteomyelitis	6	6
Central nervous system infection	8	6

a. Use clinical judgement to guide prolongation of intensive phase if improvement is slow or if blood cultures remain positive at 7 days
b. Defined as enlargement of any hilar or mediastinal lymph node to greater than 10mm diameter
c. Defined as abscess anywhere other than skin, lungs, bone, CNS
d. Intensive phase duration is timed from date of most recent drainage of collection (e.g. prostatic abscess) where culture of the drainage specimen grew *B. pseudomallei* or where no specimen was sent for culture; clock is not reset if drainage specimen is culture-negative

Eradication therapy is required after the initial intensive therapy. The doses used in Darwin have recently changed to be consistent with those used in Thailand,[19] use:

- Trimethoprim + sulfamethoxazole child 6+30 mg/kg up to 240+1200 mg; adult 40-60kg, 240+1200mg; >60kg, 320+1600 mg orally, 12-hourly for at least a further 3 months

PLUS

- Folic acid 5 mg (child: 0.1 mg/kg up to 5 mg) orally, daily for at least a further 3 months.

See Table for duration of eradication therapy after initial IV intensive therapy.

See Appendix for dosing in renal impairment.

Appendix. Darwin melioidosis adult treatment dosing in renal impairment (The Zulfikar Jabbar Guideline[20])

	Dose adjustment by CLcr (ml/min) [a]			Dose adjustment for dialysis [b]		
	31-50	**15-30**	**<15**	**HD**	**CAPD**	**CRRT**
Ceftazidime	Up to 60kg 1 g q8h Over 60kg 2 g q8h	Up to 60kg 1g q12h Over 60kg 2g q12h	Up to 60kg 1 g q24h Over 60kg 2 g q24h	as for eGFR <15, dose after dialysis	as for eGFR <15 (if intravenous route inconvenient, can administer intraperitoneally with dwell time of >6 hr and 25% extra dose)	2g q12h
Meropenem	1 g q12h	1 g q12h	1 g q24h	as for eGFR <15, dose after dialysis	as for eGFR <15	1 g q8h
TMP+SMX[c]	Up to 60kg 240+1200 mg q12h Over 60kg 320+1600 mg q12h	Up to 60kg 240+1200 mg q24h Over 60kg 320+1600 mg q24h	Up to 60kg 240+1200 mg q24h Over 60kg 320+1600 mg q24h	as for eGFR <15, dose after dialysis	as for eGFR <15	as for eGFR 15-30

[a] CLcr- Creatinine clearance is calculated by Cockroft-Gault method [140-age (years) x ideal body weight) x 0.85 (female) /0.814 x serum creatinine (micromol/L) x 72)]. Recommend to use ideal body weight for weight based dose calculation

[b] HD- haemodialysis; CAPD- chronic ambulatory peritoneal dialysis; CRRT- continuous renal replacement therapy

[c] TMP+SMX: trimethoprim+sulfamethoxazole. Folic acid 5mg daily is added for the duration of therapy

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Policy and fact sheet update January-June 2014

The Centre for Disease Control (CDC) fact sheets and guidelines are updated on a regular basis. Below are the fact sheets updated over January to June 2014. They can be found on the CDC website at http://health.nt.gov.au/Centre_for_Disease_Control/Publications/CDC_Factsheets/index.aspx

- **Cerebral palsy**
- **Fetal alcohol spectrum disorder**
- **Mosquito borne diseases**
- **Pertussis information for medical practitioners**
- **Hepatitis B**
- **Strongyloidiasis**
- **Measles information for general practitioners**
- **Trichomoniasis**
- **Yersiniosis**
- **Clinic 34 free confidential sexual health service**