NT Health Guideline

Approval Date: 10/2/24

NT Melioidosis Guideline

Contents

Applicability

This guideline must be considered by:

- NT Health Hospitals all employees

Guideline statement

This guideline provides additional information to advise on diagnosis and management of melioidosis.

NORTHERN TERRITORY GOVERNMENT

Relationship to key associated documents

Related documents are listed below:

- Adult Sepsis Recognition and Management Acute Care Facilities NT Health Guideline
- Adult Community Acquired Pneumonia in the Top End TEHS Guideline
- Prevention of Opportunistic Infections in Patients Undergoing Immunosuppression TE, BR, EA Regions Guideline
- Trimethoprim Sulfamethoxazole Factsheet
- Melioidosis CDC Factsheet

Guideline details

Purpose

To advise on diagnosis and management of melioidosis.

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 non-fatal drowning, and ingestion of unchlorinated water supplies contaminated with *B.pseudomallei* probably accounts for the higher rates of melioidosis seen in children in South and Southeast Asia than in Australia[2]. Rare instances of ingestion have occurred from mastitis-associated infected breast milk[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. Melioidosis is now recognised widely across Asia, including Sri Lanka, India, Bangladesh, China and Taiwan, in some Indian Ocean and Pacific nations, Madagascar and Africa, South and Central America, the Caribbean and most recently the southern USA [4]. *B. pseudomallei* evolved in the environment of Australia. The historical spread globally and links with movement of humans, animals and plants over millennia and in recent centuries and decades require further elucidation, as does the distinction of this international dispersal from the unmasking of unrecognised endemicity seen in recent years as laboratory diagnostic capacity improves globally [4].

The first reported case of melioidosis in the Northern Territory was in 1960[5]. Since October 1989 all cases of melioidosis have been prospectively followed in the Top End. Over the 30 years from October 1st 1989 until September 30th 2019, there were 1148 culture-confirmed cases, with 133 deaths (12%) in the Darwin Prospective Melioidosis Study (DPMS). [6] 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 an unprecedented 6 cases occurred 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 rose again to 64 in 2013-2014 (5 fatal) and 70 in 2014-2015 (3 fatal). Numbers then dropped again with the dry years and in 2018-2019 there were 42 cases (1 fatal), in 2019-2020 45 cases (1 fatal) and in 2020-2021 30 cases (3 fatal). With the return of more rain in the last 2-3 years, linked to consecutive La Nina weather cycles, the case numbers in 2021-2022 rose to 74 (6 fatal), then 87 (6 fatal) in 2022-2023. With the return of El Nino and drier conditions, case numbers may well decrease in 2023-2024, however global warming has made this more unpredictable.

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

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 [7]. In contrast, in the Top End of the Northern Territory, IHA seropositivity (titre greater than 1:20) in long term Darwin residents is less than 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 mode 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 kidney disease, and chronic lung disease[8,9].** Over recent years in Darwin it has become clear that **immunosuppressive therapy**, most notably high dose corticosteroids, is an important risk factor. **Malignancy** has been considered a risk factor, but teasing out the role of specific chemotherapy regimens requires further studies, as does the risk of individual and classes of biological therapy monoclonal antibodies. 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 [9,10].

The vast majority of melioidosis cases are from infection during the current or recent wet season, with an incubation period of 1-21 days (median, 4 days) in those presenting with acute disease (88% of all cases). A more chronic course following infection (chronic melioidosis, defined as symptoms being present for longer than 2 months) occurs in 9% of all cases[11]. Chronic melioidosis usually presents as respiratory symptoms and radiology findings that mimic tuberculosis, or a chronic non-healing skin sore. Latent infection with subsequent activation is well recognised in melioidosis, with periods of latency described of several decades[12], but in the Darwin Prospective Melioidosis Study this is considered very uncommon and accounts for under 3% of all cases.

Clinical features

Around half of melioidosis cases present with pneumonia, which can be part of a fatal sepsis, a less severe unilateral infection indistinguishable from other community-acquired pneumonias or a chronic illness mimicking tuberculosis[13,14]. Other presentations range from skin lesions without systemic illness[15], to overwhelming sepsis with abscesses disseminated in multiple internal organs[11]. Genitourinary disease with prostatic abscesses is especially common in the Top End[16]. Bone, joint and neurological infections are all well documented[17]. Blood cultures are positive in over 50% of all patients.

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 based on 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), contrast 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.

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 or ASH Infectious Diseases team.** Melioidosis is a laboratory-notifiable disease in the NT.

Treatment

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

For **initial intensive therapy**, use (see Table 2 below for dosing in renal impairment):

1. ceftazidime (ward) 2 g (child: 50 mg/kg up to 2 g) IV, 6-hourly for at least 14 days

OR

1. meropenem (ICU) 1 g (child: 25 mg/kg up to 1 g) IV, 8-hourly for at least 14 days
    a. De-escalation to ceftazidime to be considered when able

For adults with septic shock requiring intensive care support and with augmented renal clearance (creatinine clearance of more than 130mL/min/1.73m^2), use meropenem 2g IV, 8-hourly. Administer the 2g dose over 3 hours to improve attainment of PK/PD targets. Consider swapping to standard dose meropenem when the patient's critical illness resolves and the susceptibility results show that the isolate does not have a high minimum inhibitory concentration (MIC).

For patients with reduced renal function, we recommend meropenem dose adjusting according to dosing in Table 2.

At RDH we generally restrict use of meropenem for treating patients with melioidosis who are in ICU and for initial empirical CareFlight and ED therapy of patients with critical sepsis who are considered likely to need ICU therapy on admission. Patients being treated for melioidosis on the general hospital wards and those discharged from ICU are generally treated with ceftazidime.

Regular monitoring of urea and electrolytes, creatinine, LFTs, FBE including eosinophil count and CRP are required and adjust dosing if renal impairment develops (see Table 2 for dosing in renal impairment).

It is policy in RDH ICU for all adult patients in ICU/HDU with melioidosis septic shock to be considered for granulocyte colony-stimulating factor (G-CSF) - Filgrastim 300 microgram IV daily, unless contraindicated, beginning as soon as the Microbiology Laboratory flags a probable *B. pseudomallei* infection[18]. The main contraindication to commencing G-CSF is an acute coronary event; abnormal liver function is not considered a contraindication for giving G-CSF in patients with melioidosis[18]. Decision to commence G-CSF is a collaborative decision between the ICU and IFD specialists on ward service. 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 more than 50,000 $X10^6$/L.[19]

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. The dose should be administered over 3 hours to improve attainment of PK/PD targets. There is also a theoretical reduction in the risk of neurotoxicity compared to standard more rapid infusions of 2g (which result in high peak concentrations).

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. This does not alter the subsequent duration of the eradiction therapy as in Table 1.

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**[19,20]. Double-dose meropenem is also sometimes used in long bone **melioidosis osteomyelitis** when there is presumptive high bacterial burden of infection.

See Table 1 below for duration of initial intensive IV therapy, which has evolved from the modifications of the 2015 and 2020 Darwin Melioidosis Treatment Guidelines[19,20].

24 hour ceftazidime 6g infusors have been used for melioidosis in Hospital in the Home (HITH) since the mid-1990s. A prospective study[21], published in 2004, confirmed that this mode of therapy was safe and effective when administered in tropical Darwin. Patients receiving ceftazidime via 24 hour infusion are encouraged to remain inside in air conditioning at 25 degrees or less as much as possible to mitigate the theoretical patient exposure to pyridine as ceftazidime degrades in heat. For patients that are unable to remain inside in air conditioning for prolonged periods of time, the treating infectious diseases consultant may elect to treat the patient with 2 x 24 hour ceftazidime infusors which are changed every 12 hours, giving the same total daily dose.

Eradication therapy is required after the initial intensive therapy. The doses used in Darwin were previously changed to be consistent with those used in Thailand[22]. Use:

trimethoprim+sulfamethoxazole child 6+30 mg/kg up to 240+1200 mg; adult 40-60kg, 240+1200 mg; more than 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 1 overleaf for duration of eradication therapy after initial IV intensive therapy.

See Table 2 overleaf for antibiotic dosing adjustment for those with renal impairment.

Patients on trimethoprim+sulfamethoxazole prolonged oral therapy require monitoring for side effects, as some of these are serious. See Table 3 overleaf for trimethoprim+sulfamethoxazole side effects and monitoring parameters. Minimum one monthly blood tests and medical reviews are required.

Because of the high rates of trimethoprim+sulfamethoxazole adverse effects seen with the Darwin melioidosis regimen[23], commencing in the 2023-2024 melioidosis season we are using a graded introduction of trimethoprim+sulfamethoxazole, with the limited literature supporting that this may decrease the overall rate of trimethoprim+sulfamethoxazole adverse effects[24]. The graded introduction will vary by patient weight and renal function and will be used for all melioidosis patients, including those requiring ICU therapy. For patients with neurological melioidosis the full dose will be commenced immediately. This means that for those with melioidosis pneumonia and bacteremia without a focus, where trimethoprim+sulfamethoxazole has not been part of the initial intensive therapy, it will now need to be commenced during the intensive phase so that the full trimethoprim+sulfamethoxazole dose has been reached by completion of the intravenous therapy. The graded dose will take 1 - 2 weeks to reach full dose, depending on circumstances.

For example, in those over 60kg with normal renal function, the new recommendation is a graded dose over 8 days; 40/200mg (half a SS tablet) BD for 2 days, 80/400mg (1 SS tablet) BD for 2 days, 160/800mg (1 DS tablet) BD for 2 days, 240/1200mg (1.5 DS tablets) BD for 2 days, then full dose 320/1600mg (2 DS tablets) BD to commence the defined period of eradication therapy (see below and Table 1 for eradication periods). For those 60kg or under and for those with impaired renal function, the IFD team will determine the graded dosing schedule.

Eg 60kg or more with normal renal function	- 2 days 40/200mg (half SS tablet) BD - 2 days 80/400mg (1 SS tablet) BD - 2 days 160/800mg (1 DS tablet) BD - 2 days 240/1200mg (1.5 DS tablet) BD - Then full dose 320/1600mg (2 DS tablets) for defined eradication period

Note, more rapid introduction of trimethoprim+sulfamethoxazole may be considered for unwell patients with deep seated infection.

All patients who undergo intensive therapy and eradication therapy for melioidosis require counselling regarding monitoring for side effects of medication. Consumer factsheets, including the Trimethoprim Sulfamethoxazole Factsheet should be given as educational aids, and interpreters and Aboriginal health care practitioners are to be used where necessary.

Prophylaxis for melioidosis with trimethoprim+sulfamethoxazole is recommended in selected circumstances (such as dialysis patients during the wet season and selected immunosuppression scenarios. See Prevention of Opportunistic Infections in Patients Undergoing Immunosuppression TE, BR, EA Regions Guideline). See Table 2 footnote for dosing.

Virtually all primary clinical isolates of *B. pseudomallei* have the same standard antimicrobial susceptibility profile. The standard therapy used in these guidelines reflects this. Acquired resistance to each of the antimicrobials used has been documented but is very uncommon. Nevertheless, antimicrobial susceptibility testing is routinely performed on all *B. pseudomallei* isolates should recrudescent disease occur while the patient is on therapy, or should the patient be admitted with recurrent melioidosis (relapse or new infection as determined by bacterial genotyping) after therapy has been completed. Acquired resistance has occurred in the context of high bacterial burden and requirement for prolonged therapy, such as seen sometimes with bronchiectasis and cystic fibrosis and with extensive melioidosis osteomyelitis or multiple and/or large internal splenic abscesses.

Table 1: The 2024 Darwin Melioidosis Treatment Duration Guideline

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

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 or vasculature

d. Intensive phase duration is timed from date of most recent drainage of collection (eg prostatic abscess) where culture of the drainage specimen or resected material grew *B. pseudomallei* or where no specimen was sent for culture; clock is not reset if drainage specimen is culture-negative

e. Except in CNS melioidosis, trimethoprim+sulfamethoxazole is introduced as graded dosing (see text). Cessation of intravenous therapy and commencement of the timed eradication phase is set only once the full planned dose of trimethoprim+sulfamethoxazole is reached.

f. Life-long suppressive antibiotic therapy may be required following vascular prosthetic surgery

Table 2: Darwin Melioidosis Adult Treatment Dosing in Renal Impairment (The Zulfikar Jabbar Guideline[25])

	Dose adjustment by CrCl (ml/min) [a]			Dose adjustment for dialysis [b]		
	31-50	15-30	less than 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 CrCl less than 15, dose after dialysis on dialysis days	as for CrCl less than 15 (if intravenous route inconvenient, administer intraperitoneally with dwell time of longer than 6 hr and 25% extra dose)	2g q8h
Meropenem	1 g q12h	1 g q12h	1 g q24h	as for CrCl less than 15, dose after dialysis on dialysis days	as for CrCl less than 15	1 g q8h
TMP+SMX [cde]	Up to 60kg 240+1200 mg q12h Over 60kg 320+1600 mg q12h	Up to 60kg 120+600 mg q12h Over 60kg 160+800 mg q12h	Up to 60kg 120+600 mg q12h Over 60kg 160+800 mg q12h	as for CrCl less than 15, dose after dialysis on dialysis days	as for CrCl less than 15	as for CrCl 15-30

[a]CrCl: 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)]. See TG Adult Creatinine clearance calculator.

For obese patients, consider using adjusted body weight for calculation—contact AMS pharmacist or IFD.

[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

[d]**For prophylaxis**, use TMP+SMX at around one quarter of the total daily treatment dose. If over 60kg this is:

For CrCl over 30mL/min, use double strength (DS) (160+800 mg) 1 tablet daily

For CrCl 15-30mL/min, use single strength (SS) (80+400 mg) 1 tablet daily OR DS (160+800 mg) 1 tablet 3 times a week

For CrCl less than 15mL/min (non-dialysis) - use SS (80+400 mg) 1 tablet 3 times a week

For dialysis patients, use DS (160+800 mg) 1 tablet 3 times a week post dialysis.

[e]Except in CNS melioidosis, trimethoprim+sulfamethoxazole is introduced as graded dosing (see text). Cessation of intravenous therapy and commencement of the timed eradication phase is set only once the full planned dose of trimethoprim+sulfamethoxazole is reached.

Table 3: Trimethoprim-Sulfamethoxazole (TMP+SMX) Side Effects and Monitoring Parameters

Predominant TMP+SMX Side Effects	Prevalence according to AMH[a] (%)	Prevalence in Tropical Northern Territory[b] (%)	Monitoring Parameters/ Comments	When to Consider Cessation or Change of TMP+SMX Oral Therapy[d]
Acute Kidney Injury (AKI)	Unknown	10.8	UECs. A rise of > 20% in creatinine is considered to be AKI	Renal adjustments as per Table 2. Change of antibiotic considered if AKI significant.
Rash	>1	7	Physical assessment[e] and encourage patient reporting	Consider cessation and change of antibiotic. In cases of mild rash with no other features of Severe Cutaneous Adverse Drug Reaction (SCAR), graduated desensitisation may be considered.
Bone Marrow Suppression	>1	6.4	WBCs, platelets, Hb[c] Platelets < 150 x 10^9/L Neutrophils < 1 x 10^9/L Haemoglobin < 100 g/L Ensure folic acid supplementation	Consider change of antibiotic. Mild cases use clinical judgement to dose reduce.
Nausea and/or Vomiting	>1	3.4	UECs, electrolytes, patient reporting	Excessive nausea and vomiting will reduce the absorption and effectiveness. Consider change of antibiotic or dose reduce.
Stevens-Johnson Syndrome (SJS), a type of SCAR	Unknown	Unknown	Flu-like symptoms followed by a painful blistering and desquamating rash[e] of skin and mucous membranes	Must cease antibiotic
Drug rash with Eosinophilia and Systemic Symptoms (DRESS), a type of SCAR	Unknown	1	Physical assessment for fever, lymphadenopathy, facial oedema, rash[e]. Blood markers such as atypical lymphocytes, eosinophils, LFTs, UECs	Must cease antibiotic
Liver Function Derangement	<0.1	1	LFTs Severe liver injury markers: ≥5x upper limit of normal (ULN) ALT or AST, or ≥3x ULN for ALT	Consider dose reduction or change of antibiotic. TMP+SMX is contraindicated in marked hepatic dysfunction.

Predominant TMP+SMX Side Effects	Prevalence according to AMH[a] (%)	Prevalence in Tropical Northern Territory[b] (%)	Monitoring Parameters/ Comments	When to Consider Cessation or Change of TMP+SMX Oral Therapy[d]
			with ≥2x ULN for bilirubin or ≥2x ULN for ALP	
Eosinophilia without DRESS	0.1-1.0	0.5	WBCs Eosinophilia >0.7 x 10^9/L	Consider change of antibiotic. Mild cases use clinical judgement to dose reduce
Headache	0.1-1.0	0.5	Encourage patient reporting	Consider change of antibiotic if persistent
Hyperkalaemia	>1	0.5	UECs	Consider dose reduction or antibiotic change

[a] From the Australian Medicines Handbook Adverse Effects[26]. To indicate the broad discrepancies between national and local prevalence.

[b] A retrospective cohort study reviewed side effects from oral eradication therapy in patients presenting with first episode culture-confirmed melioidosis in the tropical north of Australia's Northern Territory between October 2012 and January 2017[23].

[c] The trimethoprim component may cause megaloblastic changes (e.g., macrocytic anaemia, thrombocytopenia, leukopenia) by reducing folate available for haematopoiesis.

[d] Initial oral eradication therapy with trimethoprim-sulfamethoxazole may cause adverse effects that necessitate a dose reduction or change. Changes to a patient's eradication therapy requires an Infectious Disease Specialist review and approval.

[e] Early Severe Cutaneous Drug Reaction (SCAR) erythema and inflammation can be difficult to appreciate in pigmented skin and requires careful assessment.

The discharge summary of a patient discharged on prolonged TMP+SMX should direct clinicians to be aware of and to monitor patients for the above potential side effects.

Document History

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National Safety and Quality Health Service standards

National Safety and Quality Health Service standards							
Clinical Governance	Partnering with Consumers	Preventing and Controlling Healthcare Associated Infection	Medication Safety	Comprehensive Care	Communicating for Safety	Blood Management	Recognising & Responding to Acute Deterioration
☐	☐	☒	☒	☐	☐	☐	☒

Appendices

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