INVITED ARTICLE

Melioidosis in Critical Care: A Review

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Abstract

Key Points: (1) Diabetes, hazardous alcohol use, and/or significant heart disease are more likely to develop a critical illness with melioidosis. (2) Pneumonia is the most common presentation. Those with pneumonia or bacteremia are most likely to require intensive care unit admissions. (3) Culture is the mainstay for the diagnosis. However, it is noted that *Burkholderia pseudomallei* is often wrongly identified as *Pseudomonas* or other *Burkholderia* species by commonly available commercial techniques. (4) Therapy consists of an intensive phase with intravenous antibiotics to prevent mortality followed by an eradication phase with oral antibiotics to prevent relapse. (5) Meropenem is the drug of choice for those with septic shock or neurological involvement. For patients with nonpulmonary organ focal sites of infection (neurologic, prostatic, bone, joint, cutaneous, and soft tissue melioidosis), the addition of trimethoprim-sulfamethoxazole (TMP-SMX) to ceftazidime/carbapenem during intensive therapy is recommended. TMP-SMX is the drug of choice for oral antibiotic therapy during the eradication phase. (6) Adequate source control is essential for successful treatment and to prevent relapse. (7) The use of granulocyte-colony stimulating factor (G-CSF) those with septic shock is controversial.

Keywords: Bacteremia, Intensive care, Melioidosis, Pneumonia.

Indian Journal of Critical Care Medicine (2021): 10.5005/jp-journals-10071-23837

Background

Melioidosis is caused by the gram-negative oxidase positive, intracellular bacterium, *Burkholderia pseudomallei*, an environmental saprophyte found in soil and freshwater surface. This was first described in 1912 by Whitmore and Krishnaswami as "glanders like illness" in Burma (now Myanmar) among those with morphine addiction.[1] The disease is now endemic not only in India but also in other parts of Southeast Asia, China, and Australia.[2] The incidence of melioidosis in India is highest after the rains during the monsoon period, particularly in those with risk factors, such as diabetes mellitus, chronic lung disease, chronic renal disease, or immune dysfunction. The clinical spectrum can range from isolated cutaneous lesions or abscesses, pneumonia to fulminant septicemia.[3] Melioidosis is a challenging disease due to diagnostic difficulties and a protracted treatment course.

Epidemiology

B. pseudomallei has a unique capacity to survive even in hostile environmental conditions including temperature extremes, acidic milieu, and antiseptic solutions.[3] Melioidosis has a high prevalence in Southeast Asia, China, and Australia. The majority of cases are reported from Thailand, Malaysia, Singapore, and Northern Australia where cases peak during the rainy season. Sporadic cases have also been reported from the Middle East, Africa, Caribbean, and Central and South America.[4] Diabetes mellitus, alcohol binge, and chronic kidney disease have been identified as strong risk factors for the disease.

The average incubation period is about 9 days and may range from 1 to 21 days.[6] Predominant mode of transmission is percutaneous inoculation after exposure to wet soil or water surfaces. Inhalational mode of acquisition is associated with a shorter incubation period and a higher risk of septic shock and death.

The disease can also be acquired by ingestion particularly unchlorinated potable water. Rare cases of zoonotic transmission, nosocomial spread, and vertical transmission have also been reported.[3] Melioidosis is more common in adults than children with a reported median age of 49 years.[7]

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How to cite this article: Sridharan S, B Princess I, Ramakrishnan N. Melioidosis in Critical Care: A Review. Indian J Crit Care Med 2021; 25(Suppl 2):S161–S165.

Source of support: Nil

Conflict of interest: None

Risk Factors for Disease (Table 1)

Diabetes, hazardous alcohol use, preexisting renal disease, thalassemia, and occupational exposure are traditional risk factors for the disease. In a case-control study from Thailand, it was observed that diabetes was a significant risk factor for the development of bacteremic disease.[5] Other risk factors include chronic lung disease (where this pathogen can colonize and cause disease similar to *B. cepacia)*[4], malignancy, and immuno suppressive therapy (mainly steroid use).[5]

Risk Factors for Admission to Intensive Care Unit

In a review of 24-year experience from the Royal Darwin Hospital intensive care unit (ICU) the median length of stay was 7 days with a mean acute physiology and chronic health evaluation II score of 23 (standardized mortality ratio—0.5) and

Table 1: Risk factors for melioidosis

• Diabetes
• Alcohol excess (binging)
• Renal disease
• Chronic lung disease
• Thalassemia
• Malignancy
• Immunosuppressive therapy

median sequential organ failure assessment scores on days 1, 3, and 5 of 8, 8, and 7, respectively. Diabetes, hazardous alcohol use, and/or significant heart disease were more likely to develop a critical illness with melioidosis.[2]

Clinical Spectrum

Infection with *B. pseudomallei* can be latent and can subsequently reactivate to active disease. Reactivation from a latent focus can be as long as 62 years from the time of exposure. Active disease can be acute (described as symptoms lasting less than 2 months before diagnosis) or chronic (symptoms longer than 2 months). While *B. pseudomallei* infections can be symptomatic or asymptomatic, most symptomatic cases present with acute infection.[6] Septicemic patients are acutely unwell and present with high fever with little or no cough while the nonsepticemic patients with pneumonia have a productive cough as the predominant symptom.

In the Darwin study, pneumonia was identified as the principal presentation of melioidosis (278 (51%) of 540 patients) followed by genitourinary infection (76 patients (14%)). However, in the same study, neurological melioidosis was noted only in 14 patients (3%). Almost half of the cases were bacteremic (298 patients (55%)). One hundred and sixteen (21%) patients developed septic shock out of which fifty-eight patients died[7] (Table 2).

In a review published by Stephens et al., it was noted that those presenting with pneumonia (75%) or bacteremia (87%) were likely to need ICU admissions.[2] Cutaneous disease is more common in children (60% of children vs 13% adult cases) whereas pneumonia and bacteremia are more common in adults (54 and 59% vs 16 and 20% in children).[8] Brainstem encephalitis is a classical neurological feature of this disease. The involvement of cranial nerves (mainly facial nerve) and accompanying peripheral motor weakness are other characteristic findings of this disease.[7] Lymphadenitis, thyroid abscesses, adrenal abscesses, mycotic aneurysms, mediastinal masses, and pericardial collections are a few of the rare foci of this infection, often described in case reports.[5]

Diagnosis

Melioidosis should be considered in any febrile traveler with or without the classical risk factors, returning from an endemic region presenting with septic shock. Positive cultures are the mainstay of diagnosis. Hence, it is imperative to send blood cultures and other appropriate cultures (such as pus from abscess or CSF, etc.) in all suspected cases.

Though *B. pseudomallei* readily grows in the standard blood culture media, it is often misidentified as *Pseudomonas* or other *Burkholderia* species by some commonly available commercial techniques (Fig. 1).[9] Ashdown selective media further enhances recovery if a delay in transport of the sample is likely. With the advent of newer techniques, such as matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF), and other automated systems, misidentification errors have been greatly minimized.[10] Identification of *B. pseudomallei* can also be made by simple screening and combining with commercially available API 20NE or 20E biochemical kit. The screening system may include bipolar staining on Gram stain, positive oxidase reaction, typical growth characteristics (wrinkled colonies with metallic sheen) (Fig. 1),[9] and resistance to certain antibiotics such as intrinsic resistance to colistin.[11]

Table 2: Clinical presentations and outcomes of 540 melioidosis cases over 20 years in the Northern Territory of Australia[7]

	Total		*Bacteremic*		*Nonbacteremic*	
	Number	*Deaths (mortality)*	*Number*	*Deaths (mortality)*	*Number*	*Deaths (mortality)*
Septic shock	116 (21%)	58 (50%)	103	48 (47%)	13	10 (77%)
Pneumonia	88	43 (49%)	78	35 (45%)	10[a]	8 (80%)
No evident focus	13	8 (62%)	12	7 (58%)	1[b]	1 (100%)
Genitourinary	10	5 (50%)	9	4 (44%)	1[c]	1 (100%)
Osteomyelitis/septic arthritis	4	2 (50%)	4	2 (50%)	0	0 (0%)
Soft tissue abscess	1	0 (0%)	0	0	1	0 (0%)
Nonseptic shock	424 (79%)	19 (4%)	195	13 (7%)	229	6 (3%)
Pneumonia	190	12 (6%)	89	9 (10%)	101	3 (3%)
Skin infection	68	0 (0%)	1	0 (0%)	67	0 (0%)
Genitourinary	66	2 (3%)	41	2 (5%)	25	0 (0%)
No evident focus	52	2 (4%)	47	2 (4%)	5	0 (0%)
Soft tissue abscess(es)	18	0 (0%)	4	0 (0%)	14	0 (0%)
Osteomyelitis/septic arthritis	16	0 (0%)	10	0 (0%)	6	0 (0%)
Neurological	14	3 (21%)	3	0 (0%)	11	3 (27%)
Total	540	77 (14%)	298 (55%)	61 (20%)	242 (45%)	16 (7%)

[a]Seven blood cultures not done, three blood cultures negative;
[b]Culture +ve for *B. Pseudomallei* only from rectal swab, although fatal septic shock;
[c]Blood culture not done. DOI: 10.137/journal.pntd.0000900.t002

Fig. 1: Colony morphology on MacConkey agar (dry wrinkled colonies with metallic sheen)[9] *(isolated from a patient with joint swelling and sepsis with rapid progression to a fatal outcome*)

Patients presenting with acute pneumonia secondary to melioidosis may have lobar or multilobar consolidation, necrotizing lesions, or pleural effusion on chest radiography. Findings in chronic melioidosis include cavitation, nodular or streaky infiltrates with fibrosis.[12] In a study by Currie et al., it was observed that 28% of primary pneumonia patients had involvement of more than one lobe of the lung. Mortality was higher in such patients than in those with single-lobe disease (32 vs 14%). CT scan of the abdomen may reveal abscesses in the prostate, spleen (frequently multifocal), liver, and kidneys. Although CT brain of patients with encephalomyelitis due to melioidosis may be normal, MRI brain or spinal cord may reveal increased signal intensity on T2-weighted scans.[13]

Therapy

Melioidosis is a challenge in terms of therapy due to misidentification of the pathogen, delay in diagnosis due to nonsuspicion of the disease outside endemic regions and protracted course of the disease that requires prolonged antibiotics.

Antibiotics (Table 3)

Intensive Therapy

Noncritically ill patients without CNS involvement

The intensive phase of therapy, consisting of either ceftazidime, meropenem, or imipenem is given for 10 to 14 days. An open randomized trial conducted in Thailand in 1989, comparing the use of ceftazidime (120/mg/kg/day) versus "conventional" therapy consisting of doxycycline, chloramphenicol, trimethoprim-sulfamethoxazole (TMP-SMX) for treatment of severe melioidosis concluded that mortality was halved when ceftazidime was used.[14] Similar results were obtained in another study from Thailand when ceftazidime was combined with TMP-SMX for severe melioidosis.[15] As TMP-SMX has excellent tissue penetration it is recommended to use any one of the three (meropenem/imipenem/ceftazidime) with TMP-SMX (up to 320/1600 mg q12h) in the setting of neurologic, cutaneous, bone, joint, and prostatic disease.

Table 3: The 2020 revised Darwin melioidosis treatment guidelines[18]

Antibiotic duration determining focus	*Minimum intensive phase duration (in weeks)*[a]	*Eradication phase (in months)*[f]
Skin abscess	2	3
Bacteremia with no focus	2	3
Unilateral unilobar pneumonia without lymphadenopathy,[b] ICU admission, and with negative blood cultures	2	3
Multilobar unilateral or bilateral pneumonia without lymphadenopathy,[b] ICU admission, and with negative blood cultures OR Unilateral unilobar pneumonia without lymphadenopathy,[b] ICU admission, but with positive blood cultures	3	3
Pneumonia with either lymphadenopathy[b] or ICU admission OR Multilobar unilateral or bilateral pneumonia with positive blood cultures	4	3
Deep-seated collection[c]	4[d]	3
Osteomyelitis	6	6
Central nervous system infection	8	6
Arterial infection[e]	8[d]	6[g]

[a]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 10 mm diameter;
[c]Defined as abscess anywhere other than skin, lung, bone, CNS or vasculature. Septic arthritis is considered a deep-seated collection;
[d]Intensive phase duration is timed from the date of the most recent drainage or resection 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 specimen is culture-negative;
[e]Most commonly presenting as mycotic aneurysm;
[f]If concurrent oral therapy is not indicated in the intensive phase, oral eradication therapy to commence at the start of the final week of planned intensive intravenous therapy, with the timing of eradication duration commencing from the day after last intravenous therapy;
[g]Life-long suppressive antibiotic therapy may be required following vascular prosthetic surgery

Patients with central nervous system (CNS) disease

The Darwin treatment guidelines recommend meropenem (2 gm intravenous 8th hourly) combined with TMP-SMX with a prolonged intensive phase for a minimum of 8 weeks as the treatment of choice for those with neurological involvement.

Critically ill patients in ICU (**Fig. 2**)

Carbapenems have a lower Minimum Inhibitory Concentration (MIC) to *B. pseudomallei*, a faster time-kill profile, and postantibiotic effect as compared to ceftazidime. In the trial done by Simpson et al, from Thailand, although high-dose imipenem offered no survival benefits as compared to ceftazidime, it has been shown that it was at least as effective as ceftazidime for severe melioidosis, with fewer treatment failures in those given imipenem.[16] Unlike imipenem, meropenem is safer in those with renal dysfunction or CNS disease and has a more favorable dosing schedule. These are key factors in critically ill patients who require faster control of the bacterial load.[17] Based on multiple observational studies from Australia, which concluded that meropenem produced a better outcome than ceftazidime, meropenem is now considered the drug of choice of melioidosis septic shock.[2,5,17,18]

Eradication Therapy

The initial phase is followed by a subsequent eradication phase for a period of 3 to 6 months to prevent relapses.[18] Based on the landmark randomized trial from Thailand (MERTH study), it is recommended that TMP-SMX be given alone as compared to the previous recommendation of combining this medication with doxycycline.[19] Doxycycline may be considered as an alternative when TMP-SMX cannot be used due to intolerance or any other contraindication. Amoxicillin-clavulanate is the preferred agent for pregnant women and children.

Additional Management Components

Patients with Septic Shock (**Fig. 2**)

- Supportive care for patients with melioidosis septic shock is the same for septic shock due to any other cause which

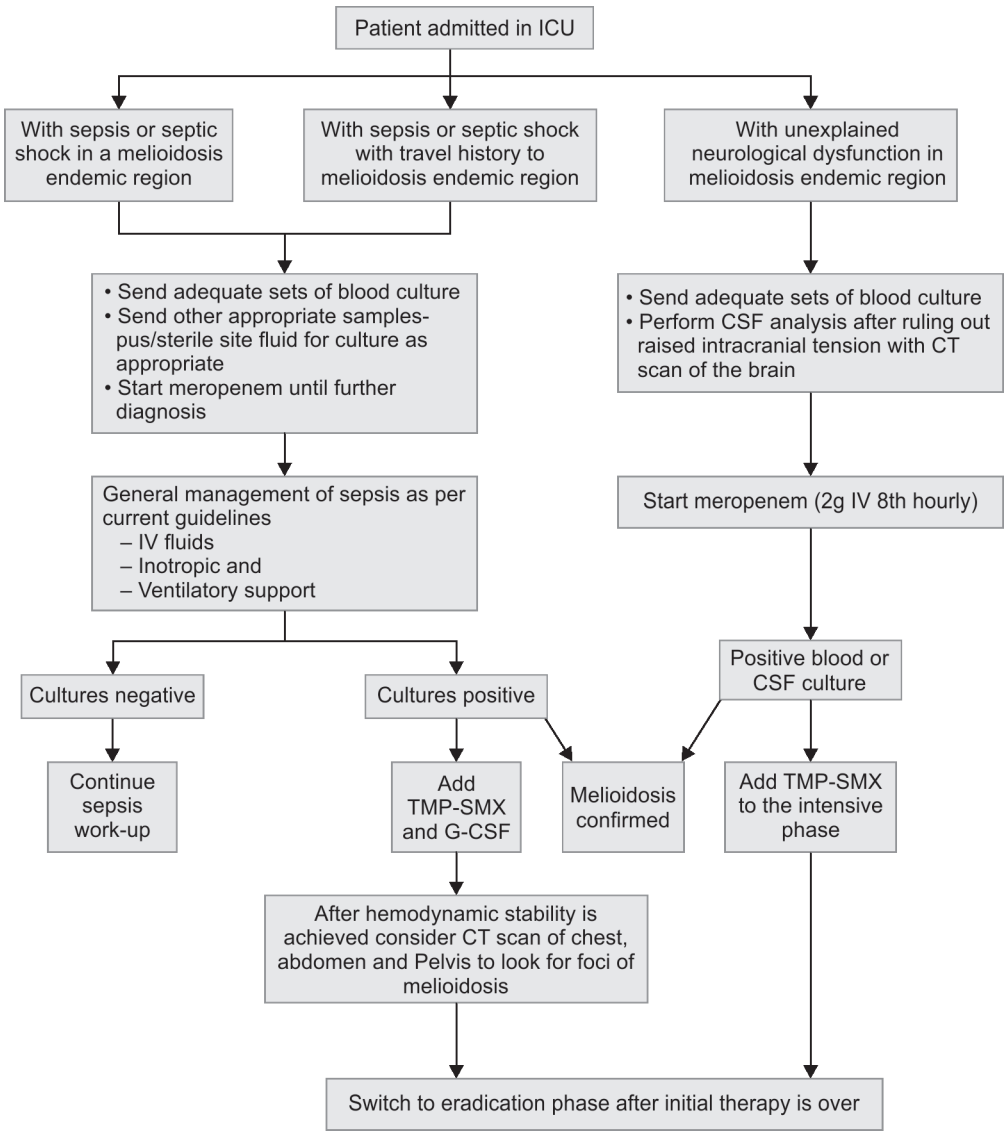

Fig. 2: Suggested algorithm for approach to patients with suspected melioidosis septic shock

includes IV fluid therapy, hemodynamic, and ventilatory support.

- *Role of G-CSF*: There are contrasting reports from studies done in Australia and Thailand on the role of G-CSF in patients with melioidosis septic shock. While observational data from Australia showed a significant survival benefit with the use of G-CSF, a randomized trial from Thailand concluded that there was no mortality benefit.[19–21] G-CSF is given as 300 mcg IV daily for at least 10 days, although the cost may be prohibitive in resource-limited areas.

Abscess Drainage

Adequate source control by either drainage or aspiration of abscesses plays a vital role in preventing treatment failures especially in septic joints and prostatic collection.

Prognosis

Recurrent melioidosis has become uncommon and the shift from relapsed infection to reinfection is mainly attributed to improved antibiotic therapy and the prolongation of the intensive phase.[2] However, relapses are common in those with severe melioidosis, multifocal disease, bacteremic melioidosis, and poor compliance. The prognosis for those with the chronic and nonbacteremic disease who received adequate therapy was excellent, with mortality rate being as low as 0 and 4% respectively, as noted in the 20-year Darwin prospective study.[7] However, mortality was as high as 50% in those who presented with acute fulminant melioidosis and 37% in those with bacteremia.[7]

Orcids

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