CONTINUING MEDICAL EDUCATION

Melioidosis: A Potentially Life Threatening Infection

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Summary

Melioidosis is caused by the gram-negative bacillus, *Burkholderia pseudomallei*. It is endemic in tropical Australia and in Southeast Asian countries. The overall mortality from this infection remains extremely high despite recent advancement in its treatment. This review discuss about clinical manifestations, diagnosis and management of melioidosis.

Key Words: Melioidosis, Review, Diagnosis, Management

Introduction

Melioidosis is caused by the gram-negative bacillus, *Burkholderia pseudomallei*, a common soil and fresh water saprophyte in tropical and subtropical regions. It is endemic in tropical Australia[1] and in Southeast Asian countries, particularly Malaysia[2-3], Thailand[4] and Singapore[5]. However, only few doctors in these endemic areas are fully aware of this infection. Hence, the management of this infection is often not appropriate and suboptimal. A recent study in Pahang has shown the incidence of this infection in Pahang[3] is comparable with that in northern Thailand[4]. The overall mortality from this infection remains extremely high despite recent advancement in its treatment. In the Pahang study, only 32% of patients were given an appropriate antibiotic empirically and about half of the culture-confirmed cases were not treated with appropriate intravenous antibiotic chemotherapy and most cases were not given eradication therapy. This review is to present to doctors working in endemic areas about the diagnosis and proper management of melioidosis.

Epidemiology

The incidence of melioidosis varies between countries and also in different parts of the same country. For example in Thailand, it is most commonly seen in the north-eastern region with an incidence of 4.4 per 100,000 population per year[4]. In Northern Australia, the incidence is higher (16.5 per 100,000 populations per year)[1] than that in Thailand[4]. The incidence in Pahang and Singapore is 6.1 per 100, 000 population per year[3] and 1.7 per 100,000 population per year[5], respectively. However, the true incidence may be higher than that reported as most of these studies included culture-confirmed cases only. Furthermore, some patients with mild infection from the rural areas may not present to the hospital. More and more melioidosis cases are being reported from previously unreported parts of the world especially southern China[6], Taiwan[7], India[8], Laos[9] and Vietnam[10] but the true endemicity in these areas is not established. Also isolated cases have been reported in the temperate countries among travellers returning from endemic areas[11-13].

Melioidosis is a disease involving all age groups but commonly occurs in people between the ages of 40 to 60 years[3] and is related to farming. It is less common in the paediatric age group. In the Australia study[1], only 4% of patients were younger than 15 years whereas in Malaysia, 7.6%[14] and in Thailand, 10-17%[15] of

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patients were in this age group. It is more common in males than females with the male to female ratio being 1.5:1 to 4.5:1[1-5]. This may be due to more males being exposed in soil related occupations. Farming has been shown to be strongly associated with incidences of melioidosis[4]. For instance in Thailand, 81% of melioidosis patients were rice-farmers and their family members[4]. Currently, the postulated mode of transmission is direct entry of the organism into the blood stream via very minor wounds or skin abrasions. Therefore, a definite history of injury is uncommon (5.2%)[4]. The second commonest mode of infection is inhalation of contaminated dust. Strong wind increases contaminated dusts in air resulting in an increased number of melioidosis cases during the raining season[1,3,4]. Other common modes of infection reported are drowning[4], motor vehicle accident[3], via breast milk[16], perinatal transmission[17] and human-to-human transmission[18].

Melioidosis occurs commonly (53-85%) in adults with underlying diseases that predispose them to infection. In contrast, less than 20% of the paediatric patients have underlying diseases and almost all cases of localised disease in this age group have no predisposing factors[14,15,19,20]. In adults, diabetes mellitus is the commonest underlying disease (20-74% of cases)[1-5]. Alcoholism and the consumption of kava (an extract of the root of the plant consumed by the Aboriginal people in Australia in place of alcohol) seem to be a major factor associated with melioidosis in Australia. However, such habitual risk factors are less common in Southeast Asia. Other underlying diseases thought to be associated with melioidosis are chronic renal failure, renal calculi, chronic lung disease (especially cystic fibrosis in Australia), human immunodeficiency virus (HIV) infection, intravenous drug abuse, malignancy, systemic lupus erythematosus and corticosteroid therapy. Table I summarises the epidemiology and mortality of melioidosis in some of the endemic countries.

Clinical Manifestation

Asymptomatic seroconversion is common in endemic countries as evidenced by positive serology in up to 50% of healthy adults in these countries[21-23]. As in the case of *Mycobacterium tuberculosis, B. pseudomallei* may remain dormant in macrophages for many years following infection before causing disease when the host's immune system deteriorates. This is evident in American soldiers who developed melioidosis many years after returning from Vietnam[24]. Currently, there is no data on the outcome of these asymptomatic patients with positive serology or whether treatment is necessary.

There are several classifications of the clinical manifestation of melioidosis. It may present as acute or chronic infection (defined as more than two months of symptoms). The acute form of the disease commonly presents with septicaemia and is associated with very high mortality. On the other hand, the chronic form commonly presents as long-standing suppurative focal abscesses with fever and wasting and is associated with a good prognosis[25]. In endemic areas, 88-90% of cases present with the acute form of melioidosis[26-27]. It can also be classified as localised or disseminated infection. The latter is seen in 15-30% of cases[2,3]. The widely accepted classification is the presence or absence of bacteraemia as this is an important predictor of the ultimate outcome. The reported incidence of bacteraemia is 46-92% in most of the endemic areas[1-4]. The highest incidence of bacteraemia of 92% reported in the literature is from Malaysia[3]. This is probably related to late presentation as the patients normally seek traditional treatment before presenting to the hospitals. A higher frequency of diabetes mellitus in this study[3] may be another contributing factor as individuals with diabetes are at higher risk for bacteraemic melioidosis[28]. In Northern Thailand, 20% of community acquired septicaemia is due to melioidosis and this infection contributes to 39% of the mortality due to septicaemia[29].

Fever is the commonest presentation and is present in almost all patients[2,3]. The duration of fever may vary from a few days to months. Melioidosis is one of the causes of pyrexia of unknown origin in endemic areas. Symptoms and signs depend on the site or organ involved. Patients presenting with shock have a poor prognosis and have mortality in excess of 80% even in a good centre[1].

White blood cell counts on admission commonly (55.6% of cases) show leucocytosis but may be normal or low (3.7% of cases)[3]. Other evidence of sepsis such as thrombocytopenia, disseminated intravascular coagulopathy, renal impairment, abnormal liver function, metabolic and respiratory acidosis are common presentations in severe infections.

Pulmonary Melioidosis

Pneumonia is the commonest clinical manifestation and is present in half of the cases[1-3]. Patients may present with acute fulminant pneumonia with septicaemia which commonly requires mechanical ventilation and

intensive care. This manifestation is associated with a mortality exceeding 80%[1]. On the contrary, a more indolent presentation is associated with a better outcome[24]. Cough is commonly productive of purulent sputum and associated with fever. Haemoptysis is rare in acute disease but may be present in up to 31% of patients with the chronic form of the disease[24,30]. The chest radiograph in acute disease commonly shows either a localised patch or bilateral diffuse patchy alveolar infiltration or multiple nodular lesions which may coalesce, cavitate (cavities are usually thin-walled and rarely contain air-fluid level) and form abscesses. In the chronic form of the disease, the chest radiograph findings may be difficult to distinguish from that of pulmonary tuberculosis which typically involves the upper lobes with patchy alveolar infiltrates and cavitations[24,30-33]. Sparing of the apical region and lack of calcification suggest the likelihood of melioidosis rather than pulmonary tuberculosis[30]. Pleural involvement occurs in 9-33% of cases and thoracic empyema is occasionally seen[2,24,30-33]. Pyopericardium and hilar lymphadenopathy are rare. There was a case report on bronchiolitis obliterans organising pneumonia associated with pulmonary melioidosis that responded well to steroid therapy[34].

Skin and Subcutaneous Involvement

Skin and subcutaneous involvement is the second commonest presentation[2,7,29]. Blisters, superficial erythematous pustules, clusters of violaceous skin abscesses, cellulites and subcutaneous abscesses are commonly seen[1-4,29]. Skin biopsy or aspiration of the pustules or vesicles may yield the organism. Lymphadenitis or lymph node abscess is commonly seen in children. The cervical lymph nodes are most commonly involved mimicking tuberculous lymphadenitis[14,15,19,20].

Intra-abdominal Abscesses

Liver and/or spleen abscesses are present in 4-17% of adult melioidosis[1-4]. Liver abscesses are frequently (82%) multiple and less likely to cause right upper quadrant pain and tenderness as compared to other pyogenic abscesses[35]. Liver abscess is associated with splenic abscess in 56% of cases which are commonly multiple as well. Serology is not useful in differentiating liver abscesses due to melioidosis from other pyogenic abscesses in endemic areas but the presence of multiple nodular opacities on the chest radiograph strongly suggests melioidoisis[35]. In Northern Thailand, the majority of liver and splenic abscesses are due to melioidosis[35-36]. Other rare intraabdominal lesions are empyema of the gall bladder, pancreatic abscess and adrenal abscess[1-2].

Urogenital Tract Infection

About 18% of adult males with melioidosis in Australia had prostatic abscess and the patients commonly presented with fever, abdominal pain, dysuria, diarrhoea and acute urinary retention requiring catheterisation[1]. However, prostatic abscess is not commonly seen in Thailand and Malaysia probably due to underdiagnosis as not all melioidoisis patients undergo abdomen and pelvic CT scan examination. Digital rectal examination is useful to detect prostatic involvement but it cannot differentiate between prostatic abscess and acute prostatitis due to other causes. Other urogenital complications of melioidosis are pyelonephritis, perinephric abscess and scrotal abscess[1-3,29].

Neurological Melioidosis

Melioidosis involving the central nervous system is less common, 4% in the Australian series[1]. However, it can involve the whole central nervous system causing macroscopic or microscopic brain abscesses, meningo-encephalitis, brain stem encephalitis and transverse myelitis. Headache is another common symptom together with fever. Other presentations include unilateral limb weakness, cerebellar signs, brainstem palsies (commonly VI, VII and bulbar palsy) or flaccid paraplegia[37]. Cerebrospinal fluid examination commonly shows high protein with predominantly mononuclear cells. The glucose level in the cerebrospinal fluid may be normal or slightly decreased. Initial brain CT may be normal or show non-specific changes. Magnetic resonance imaging is the investigation of choice and shows abnormality in all cases. The common finding is multiple diffuse high signal lesions reflecting the clinical findings. Nearly half of the patients may require mechanical ventilation with a mortality rate of 25%[37].

Musculoskeletal Melioidosis

Septic arthritis most commonly affects the knee (50%) followed by the ankle (13%), wrist (10%) and elbow (10%)[38] joints. Osteomyelitis is less common[1-4].

Other Organs that are Rarely Involved

It may be difficult to know the site of infection in some patients as they succumb to the disease (37-65%) within 48 hours of admission before investigation could be performed[2,3,29]. Other rare presentations of melioidosis are mycotic aneurysm[1,39], pericardial effusion[1-2], psoas abscess[1] and infected thyroid cyst[29].

Melioidosis in Children

As in adults, melioidosis in children may present as an acute septicemia with foci of infection in the lungs (the most frequently involved organ), liver, spleen or other organs. Progression into shock is rapid and mortality rate is also high[14-15,19-20]. Localised infection is common in childhood, especially involving the head and neck region. Unilateral suppurative parotitis has been reported to account for 40% of localised melioidosis in Thailand[15,40] and patients commonly present with fever and cheek pain. Physical examination commonly shows unilateral parotid swelling with abscess formation that may cause facial nerve paralysis, periorbital cellulitis and conjunctivitis. Purulent discharges at the opening of Stensen's duct and the ear (if spontaneous rupture of the abscess into the auditory canal occurs) may be seen. It can rarely cause dissemination or septicaemia[39]. Pharyngocervical melioidosis is also common and the child commonly presents with fever and sore throat with or without cervical lymphadenopathy. It mimics upper respiratory tract infection caused by other bacteria and as such diagnosis is difficult without culture confirmation from throat or pus swab[41]. Fortunately, the prognosis for localised infection is generally good[42].

Mortality

Mortality due to melioidosis is extremely high especially in the bacteraemic form. A study by Puthucheary *et al* [2] many years ago showed the mortality was 65% in patients with bacteraemic melioidosis. The higher mortality in this study was probably due to undertreatment as only 24% of the patients received appropriate empirical antibiotic therapy. A more recent study in Australia[1] (1989 to 1999) reported a lower mortality of 37% with bacteraemic melioidosis. This was probably due to the wider use of ceftazidime or carbapenams and better intensive care. However, this lower mortality rate has not been recorded in all endemic areas as the most recent study in Malaysia from 2000 to 2003 revealed a mortality of 54% in bacteraemic melioidosis[3]. This was probably due to the lack of awareness among doctors in Malaysia regarding the appropriate treatment of melioidosis as only 52% of culture-confirmed cases in that study received an appropriate antibiotic. In Singapore (1997 to 2001), the mortality was 53% and was higher among those with pneumonia (73%)[33].

The overall mortality in Australia (19%)[1] was lower than that of other regions probably because of a lower incidence of bacteraemic melioidosis (46%) in the Australia series. In Pahang[3], the overall mortality rate was 54% (92% bacteraemic form) compared to 44% in Thailand (60% bacteraemic form)[4]. Other possible factors associated with high mortality include a shorter duration of fever, lower platelet count, higher blood urea and presence of pneumonia, multi-organ involvement and septicaemia of unknown source[3].

Relapse and Recurrence

A study by Chaowagal *et al*[43] found that 23% of their patients had culture proven relapse with a yearly relapse rate of 15%. The mortality rate associated with relapse was 27% and patients with septicaemia, disseminated infection, short course of maintenance therapy and intensive therapy with antibiotics other than ceftazidime had higher risk of relapse. In the Australian study[26], 13% of patients had bacteriologically confirmed relapses with 11% mortality. Half of the relapses were due to poor adherence to the eradication therapy and another 37% of the relapses were related to doxycycline monotherapy.

Laboratory Diagnosis

Isolation of *B. pseudomallei* is best achieved using Ashdown medium that contains aminoglycoside to which this organism is resistant. Blood agar and chocolate media can be used for sterile specimens. More than 90% of the isolates are sensitive to ceftazidime, cefoperazone-sulbactam, doxycycline, chloramphenicol, amoxycillin clavulanate and imipenem[3,5,44]. Resistance to trimethoprim-sulfamethoxazole has been reported to be more than 50% by the disc diffusion method as compared to less than 10% by either the E-test, Microscan or agar dilution method[45]. Specimens for culture should be obtained from blood, urine and other sources which include joint fluid, sputum, cerebrospinal fluid, pus and tissue depending on suspected organ involvement. In patients who are unable to produce sputum, throat swab has been shown to have 100% specificity with 38% and 47% sensitivity in adult and paediatric patients, respectively[46-47]. Throat swab has the advantage of allowing early presumptive identification of the organism within 48 hours as compared to 3-4 days from blood culture. It is useful in paediatric patients and in patients who are too ill to produce sputum.

Serology has been studied extensively but a high background of positive serology in the general population limits its usefulness in an endemic area. A study in north-eastern Thailand has shown the indirect haemagglutination test (IHA) to have a sensitivity of 95% but a specificity of 59% by using a cut-off level of 1:20 dilution[29]. In that study, some of the non-

melioidosis septicaemic patients had positive titres of more than 1:1280. However, acute seroconversion in a clinically septic patient strongly suggests melioidoisis. Serology is useful to monitor disease activities and relapse[24]. Antigen detection using specific monoclonal antibody and specific nucleic acid amplification by polymerase chain reaction are newer methods that may give an earlier diagnosis but these tests are not yet commercially available[48-49].

In suspected or confirmed cases, chest radiograph should be taken as 50% of cases have lung involvement. Ultrasound examination should be done to locate intra-abdominal abscesses even in the absence of positive physical signs[3]. Abdominal and pelvic CT scan may be more sensitive in detecting microabscesses and prostatic abscess. Trans-rectal ultrasound can be used to detect prostatic abscess which is commonly multiple and larger than other bacterial prostatic abscesses[50]. Figure 1 summarises the list of investigations recommended in patients suspected to have melioidosis.

Management

The general management of melioidosis is the same as for any infection. Severe and life-threatening melioidosis should be managed in the intensive care unit. Large abscesses should be drained especially when patients are not responding well to antibiotic therapy. Fever may persist for a week or more despite appropriate antibiotic therapy. Patients with persistent fever lasting more than a week require further examination and investigations to look for occult abscesses. Control of blood sugar is important in diabetic patients.

Definitive antibiotic treatment of melioidosis can be divided into an intensive and an eradication phase. The conventional regimen for the intensive phase was intravenous (IV) chloramphenicol, tetracycline and co-trimoxazole. These drugs are bacteriostatic and toxic. High dose ceftazidime has replaced this conventional regimen after two randomised controlled trials showed treatment with ceftazidime resulted in a 50% reduction in mortality of severe melioidosis[51,52]. Simpson *et al*[53] compared treatment with ceftazidime and imipenam and found no difference in mortality but treatment with the former was associated with a higher failure rate. There was one randomised study comparing intravenous co-amoxiclav to ceftazidime and found no difference in mortality but less failure rate in the ceftazidime group[54]. Two studies comparing cefoperazole-sulbactam with co-trimoxazole and ceftazidime with co-trimoxazole, respectively found similar efficacy, mortality rate and bacteria clearance rate[55-56]. Both studies used a lower dose of cefoperazole-sulbactam. In a non-randomised retrospective study, meropenam treatment was associated with a lower mortality than ceftazidime in severe sepsis patients, defined as patients requiring intensive care, clinical failure or intolerant to ceftazidime (25% versus 76%)[57]. However, this study listed a few confounding factors especially the use of granulocyte colony-stimulating factor (G-CSF) which might have contributed to the reduction in mortality[58].

After at least two weeks of intensive therapy with intravenous drug and clinical improvement, oral therapy should be commenced to prevent relapses. The conventional regimen for oral maintenance therapy was the combination of chloramphenicol, doxycycline and co-trimoxazole. Several studies have used various single drug regimens (co-amoxiclav or doxycline alone) or a combination of ciprofloxacin and azithromycin compared to the conventional regimen and the latter combination has been shown to be more effective in preventing relapses[59]. Recently, a randomized open labelled study found the combination of doxycycline and co-trimoxazole is as effective as the conventional regimen and is associated with fewer side effects[60]. In this study, treatment of less than 12 weeks was associated with a shorter time to relapse or death. The Australian experience for the past ten years found a very low failure rate of less than 1.6% with co-trimoxazole alone but whether adding doxycycline is beneficial or not requires further evaluation[1]. There have been no randomized trials of treatment of melioidosis in children due to the low incidence of this infection in the paediatric population. From the currently available data, we propose the treatment of melioidosis as shown in Figure 2.

Figure 1: Recommended investigations for suspected and confirmed melioidosis

In suspected or confirmed cases, the following investigations are necessary:

1. Blood culture and sensitivity
2. Urine culture and sensitivity
3. Melioidosis serology (Immunofluorescent antibody test/IFAT)
   (Titer of 1:80 is suggestive of melioidosis; if the titer is less than 1:80, repeat the test 2 weeks later)
4. Throat swab culture
5. Ultrasound examination of abdomen to detect abscesses in the liver, spleen, kidney, adrenals and prostate.
6. Chest X-ray.

Other useful investigations:

1. Culture and sensitivity of pus, cerebrospinal fluid, joint fluid, sputum, etc depending on the clinical suspicion of organ(s) involved.
2. Gram staining of clinical specimens (commonly shows one to five organisms per low-power field, short Gram-negative bacilli with a granular or safety-pin appearance.)
3. CT abdomen and pelvis or trans-rectal ultrasound of prostate if prostatic abscess is suspected.
4. PCR of joint fluid, urine, pus, etc

Figure 2: Recommended antibiotic treatment for melioidosis

A. Treatment in adults

Intensive therapy

Life threatening melioidosis (presence of respiratory failure requiring mechanical ventilation, impaired consciousness, acute renal failure requiring dialysis, DIVC or multi-organ failure.)

- IV meropenem (25mg/kg/dose; usual dose for adult: 750 mg to 1 gm TDS) with trimethoprim (8 mg/kg/day) and sulfamethoxazole (40 mg/kg/day) (usual dose 2880 mg per day) for at least two weeks. May substitute meropenam with imipenam (50mg/kg/day). Consider IV G-CSF 300 μg daily for ten days in patients with septicaemic shock.

Severe melioidosis (Presence of organ dysfunction, hypotension or disseminated infection)

- IV ceftazidime (100 mg/kg a day; usual dose for adult, 2 gm TDS) with trimethoprim (8 mg/kg/day) and sulfamethoxazole (40 mg/kg/day) for at least 2 weeks. May substitute ceftazidime with cefoperazone-sulbactam 1 gm TDS. Consider IV G-CSF 300 μg daily for ten days in patients with septicaemic shock.

Mild to moderate melioidosis

- IV amoxycillin-clavulanate (160mg/kg/day in six divided doses daily) for at least 2 weeks.

Eradication therapy

- Oral co-trimoxazole (trimethoprim 8mg/kg/day and sulfamethoxazole 40mg/kg/day) and doxycycline (4mg/kg/day in two divided doses per day) (Usual dose 960mg co-trimoxazole BD and doxycycline 100mg BD) are the standard oral combination regimen and should be administered for a total of 20 weeks. Amoxycillin/clavulanate (45mg/kg/day) combined with amoxycilin (30mg/kg/day), in four divided doses daily, is an alternative and can be used in pregnant women (for the same duration).

B. Treatment in Children

In children with **severe melioidosis**, IV ceftazidime 40mg/kg/dose eight hourly should be given for two weeks. IV meropenem 25mg/kg/dose may be considered in life threatening cases.

Maintenance therapy: Co-trimoxazole (trimethoprim 8mg/kg/day and sulfamethoxazole 40mg/kg/day) and doxycycline (4mg/kg/day in two divided doses) are the standard oral combination regimen and should be administered for a total of 20 weeks. Amoxycillin/clavulanate 15mg/kg/dose 8 hourly should be used instead of doxycycline in children below 8 years.

Localized melioidosis should be treated with incision and drainage with co-trimoxazole (Trimethoprim 8mg/kg/day and sulfamethoxazole 40mg/kg/day) and doxycycline (4mg/kg/day in two divided doses) for 6-eight weeks. Replace doxycycline with amoxicillin/clavulanate in children below 8 years.

Table I: Epidemiology and mortality of melioidosis in endemic countries

	Australia[1]	Thailand[4]	Pahang, Malaysia[3] (Adults only)	Singapore[5]
No of cases	252	423	135	372
Incidence*	16.5	4.4	6.1	1.7
Median age (year)	49	45	51	55
Male: female ratio	3:1	1.4:1	3.6:1	4.5:1
Paediatric patients (%)	4	-	7.6 [14]	2.4
Bacteraemia (%)	46	60	92	39
Mortality rate (%):				
Overall	19	44	54	40
Bacteraemic cases	37	-	54	55
Underlying disease (% of cases)				
At least one	80	53	85	77
Diabetes mellitus	37	20	74	57
Renal disease	10	13	6	6
Alcoholism	39	-	1	-
Chronic lung disease	27	<1	3	10
Kava consumption	8	-	-	-

* Per 100000 populations per year

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MCQs on Melioidosis: A Potentially Life Threatening Infection

1 The following statements are true regarding epidemiology of melioidosis:
a. It is common in tropical countries.
b. It is more common in males than females.
c. It is more common in children than adults.
d. A history of physical injury is common among patients with melioidosis.
e. Alcoholism is the commonest predisposing factor in most of the endemic countries.

2 The following statements on the clinical manifestation of melioidosis are true:
a. Liver abscess is the commonest presentation.
b. Liver abscess is usually single.
c. Haemoptysis is common in patients with acute fulminant pneumonia.
d. Unilateral suppurative parotitis is the commonest form of localised melioidosis in adults.
e. Blood cultures are positive in 40% or more of cases.

3 The following factors have been associated with an increased risk of relapse in melioidosis:
a. Patients treated with ceftazidime during intensive therapy.
b. Patients with localised infection.
c. Patients treated with 8 weeks of maintenance therapy.
d. Diabetes mellitus.
e. Doxycycline monotherapy.

4 The following factors are associated with a higher mortality in melioidosis:
a. Bacteremia.
b. Presence of pneumonia.
c. A longer duration of fever.
d. Disseminated infection.
e. A low platelet count.

5 The following statements on intensive treatment of melioidosis are true:
a. High dose ceftazidime has been shown to reduce the mortality of severe melioidosis by half as compared to conventional treatment.
b. Treatment with co-amoxiclav is associated with higher mortality compared to treatment with ceftazidime severe melioidosis.
c. Intravenous antibiotics can be changed to oral antibiotics if fever settles within 48 hours.
d. Intravenous granulocyte colony-stimulating factor can be used in patients with septicaemic shock.
e. Persistence of fever for a week or more despite appropriate antibiotic therapy always indicates treatment failure.