Tuberculosis on the intensive care unit

ABSTRACT

Patients with tuberculosis admitted to the intensive care unit represent a small (1–3%) yet significant subset of the global tuberculosis burden. This article reviews current evidence supporting the diagnosis and management of patients with tuberculosis admitted to an intensive care unit from a combination of cohort studies and national and international tuberculosis guidelines. This review considers admission, diagnosis, mechanical ventilation, infection control, treatment and prognosis of patients with tuberculosis admitted to an intensive care unit. It highlights both diagnostic and management challenges and areas where ambiguity remains and further evidence is required.

The bacterial species *Mycobacterium tuberculosis* is the leading cause of tuberculosis globally. Transmission is invariably via inhalation of aerosol droplets. In the majority of patients infected it causes an asymptomatic latent infection and it progresses to active disease, predominantly respiratory disease, in only ~10%. However, *M. tuberculosis* elicits a complex immunological response, characteristically a type IV hypersensitivity reaction and granuloma formation, which can cause disease in almost every organ system.

In 2017, the World Health Organization reported that 6.3 million people developed tuberculosis, of which 1.6 million people died from the disease, making it both the 9th commonest cause of death and the leading cause of death from an infectious agent (World Health Organization, 2017). The incidence is greatest in south-east Asia, and India, Indonesia, China, the Philippines and Pakistan account for >50% of cases worldwide (World Health Organization, 2017). The UK has a low burden of disease, but parts of London report an incidence rate equivalent to rates in countries with high disease burdens (>50 per 100 000) (Public Health England, 2016). Within developed nations, tuberculosis is indicative of poverty and remains concentrated in areas with a large migrant population and high levels of social deprivation.

One aim of the World Health Organization 'End TB strategy' is to focus the provision of tuberculosis care into primary health-care systems. While this has been successful, a significant proportion of patients diagnosed with tuberculosis still require hospitalization and a subset (1–3%) of all tuberculosis patients require admission to an intensive care unit (Silva et al, 2010). Intensive care unit admission usually indicates a poor prognosis and is a substantial financial burden for health-care systems and society (Hagan and Nathani, 2013). Daily intensive care unit costs in the UK are ~£2000. The cost of treating a patient in the UK with complicated tuberculosis (multidrug resistant or in the context of HIV co-infection), a group in whom intensive care unit admission may be necessary, can be in the range of £50–70 000, greater than 10 times the cost of treating a patient with uncomplicated tuberculosis (NHS England Case for Change, 2011).

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Intensive care unit admission in patients with tuberculosis

Patients with tuberculosis may require admission to the intensive care unit for close monitoring or organ support. Acute respiratory failure requiring mechanical ventilation is the commonest indication for admission of the patient with tuberculosis to the intensive care unit, accounting for > 90% of all admissions (Silva et al, 2010) (*Table 1*). Admission may also be associated with acute renal failure (10%), neurological disorder (20%) and septic shock (20–34%). Multiple organ failure develops in 34–44% of admissions (Zahar et al, 2001; Lin et al, 2009), corresponding with a high incidence of concomitant pulmonary, extra-pulmonary and miliary (disseminated) tuberculosis (Zahar

Table 1. Presentation: reasons for admitting the patient with tuberculosis to the intensive care unit

Acute respiratory failure
Renal failure
Neurological disorder
Shock or septic shock
Multiple organ failure
Diabetic ketoacidosis
Delirium
Refractory status epilepticus
Severe electrolyte disturbances
Iatrogenic: anti-tuberculosis drug regimen induced, postoperative

et al, 2001). Other aspects of tuberculosis that may lead to an intensive care unit admission include spinal, cerebral, bone marrow, gastrointestinal, urogenital, pericardial or haematological disease. Meningeal tuberculosis has been seen in up to 20% of patients with tuberculosis admitted to the intensive care unit (Lanoix et al, 2014).

Up to 30% of patients with a diagnosis of tuberculosis admitted to an intensive care unit may have decompensated as a result of factors indirectly related to infection (Frame et al, 1987), including diabetic ketoacidosis, delirium secondary to alcohol withdrawal, refractory status epilepticus and severe electrolyte disturbances (Frame et al, 1987; Erbes et al, 2006; Balkema et al, 2014; Lanoix et al, 2014). In addition, patients may require intensive care unit support as a result of anti-tuberculosis drug-induced hepatotoxicity which in some cases can lead to fulminant hepatic failure and consideration for liver transplantation.

Co-infection with HIV occurs in 68.7% and 40% of intensive care unit admissions as a result of tuberculosis, in both high burden and low burden tuberculosis regions respectively (Zahar et al, 2001; Silva et al, 2010). This subset of patients falls outside of the remit of this review as it is generally the patient's HIV status which determines management.

Diagnosis of tuberculosis on the intensive care unit

While many patients will already have an established diagnosis of tuberculosis before their intensive care unit admission a high level of suspicion should be maintained in patients who have had close contact with tuberculosis-positive individuals, or in whom specific risk factors are present (*Table 2*). Patients with tuberculosis admitted to the intensive care unit do not always display the classical, clinical-radiological signs that suggest a differential of tuberculosis. Clinicians should remember that while pulmonary tuberculosis is one of the commonest ways in which tuberculosis presents, it may present in almost any organ system.

Table 2. High-risk individuals: factors predicting increased risk of having or contracting tuberculosis

Tuberculosis contacts	
Immunocompromised	
New entrants from high-incidence countries (>40/100 000 as per National Institute for Health and Care Excellence (2016) guidance)	
Underserved groups	Homeless
	Misuse substances
	Prisoners
	Vulnerable migrants
	Children in care services

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Diagnosis of pulmonary tuberculosis requires three consecutive sputum samples, collected at 8–24-hour intervals, preferably with at least one being an early morning sample, to be sent for microscopy, culture, Ziehl–Neelsen stain, polymerase chain reaction analysis and sensitivity testing (World Health Organization, 2013, 2017). Sputum samples from a mechanically ventilated patient will require an endotracheal aspirate, a non-directed bronchial lavage or a bronchoalveolar lavage. However, bronchoalveolar lavage has been associated with complications in mechanically ventilated patients, especially with acute respiratory distress syndrome, that include pneumothorax, hypoxaemia and haemorrhage. In the absence of a randomized controlled trial comparing bronchoalveolar lavage with less invasive alternatives, it remains unclear if bronchoalveolar lavage is clinically justified in mechanically ventilated critically ill patients.

Appropriate extra-pulmonary specimens should be obtained to determine the extent of extra-pulmonary tuberculosis. These may include lymph node tissue, CSF, joint aspirates, other tissue biopsies, ascitic or pericardial fluid, urine, blood and stool.

Pulmonary tuberculosis

Pulmonary tuberculosis on the intensive care unit commonly presents as acute respiratory failure. Background symptoms may include a productive cough, night sweats, fever, weight loss, anorexia, a history of previous tuberculosis and an abnormal chest X-ray. An atypical chest X-ray, particularly the presence of consolidation, may cause misdiagnosis of pulmonary tuberculosis. In a retrospective analysis of 89 patients diagnosed with pulmonary tuberculosis on the intensive care unit, only six had typical radiological features: patchy, poorly defined consolidation with or without cavitation, fibrosis, calcification, lung destruction or miliary lesions. When compared as part of a matched case-control analysis with 89 patients without pulmonary tuberculosis admitted to the same intensive care unit, no significant differences in radiographic patterns were identified between the groups (Wu et al, 2009).

CNS tuberculosis

Meningeal tuberculosis is the commonest CNS presentation (accounting for up to 20% of patients with tuberculosis on the intensive care unit) and CSF analysis is the mainstay of diagnosis. A predominant lymphocytosis, raised protein level (0.5–3.0 g/litre) and CSF:plasma glucose <50% is typical and usually sufficient evidence to commence treatment if tuberculosis is part of the

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differential diagnosis. Treatment initiation should not be delayed for culture confirmation, since a delay is strongly associated with death (Thwaites et al, 2009). Tuberculosis may be successfully cultured from CSF, provided sufficient volumes of CSF (>6 ml) are obtained, although repeated lumbar punctures may be necessary. Common findings on imaging (computed tomography and magnetic resonance imaging) include hydrocephalus, basal enhancement and infarctions (Schnabel et al, 2015). A contrast-enhanced computed tomography is recommended in all patients as part of the work-up and can help with diagnosis or guide treatment decisions regarding hydrocephalus.

Other common CNS manifestations include cerebral tuberculomas and spinal disease, which may occur as part of miliary tuberculosis. Tissue biopsy and culture, rather than CSF culture, is the mainstay of diagnosis of cerebral tuberculomas and spinal disease. If there is concomitant extra-neural disease, tissue biopsy should ideally be obtained from these safer extra-neural biopsy sites, e.g. lymph node biopsy, gastric aspirate or bone marrow aspirate.

Magnetic resonance imaging is the imaging modality of choice for suspected cerebral tuberculomas and spinal disease. The technical limitations of magnetic resonance imaging include difficulty differentiating tuberculomas from other causes of ring-enhancing lesions and differentiating spinal tuberculosis from other infective causes of osteomyelitis or neoplasia (Thwaites et al, 2009). Magnetic resonance imaging scanning in critically ill patients can also be logistically problematic. Problems with isolation of the patient can include disconnection alarms on infusions or a ventilator going unnoticed and in the event of deterioration dismounting from the magnetic resonance imaging machine can cause unwanted delay.

Miliary (disseminated) tuberculosis

Disseminated disease has been seen in up to 30% of patients with tuberculosis admitted to the intensive care unit and disseminated disease appears to predispose individuals to acute respiratory distress syndrome, perhaps to a greater degree than isolated pulmonary tuberculosis (Silva et al, 2010; Lee et al, 2011). As with pulmonary tuberculosis, the utility of the chest X-ray in diagnosing military tuberculosis is limited and the typical miliary pattern (innumerable, small (<5 mm) pulmonary nodules scattered throughout the chest) is often not seen. Pulmonary involvement is better identified on high-resolution computed tomography or by sputum culture. Diagnosis of extra-pulmonary disease is aided by computed tomography, positron emission tomography–computed tomography and magnetic resonance imaging, in addition to histological analysis and culture of tissue biopsies and blood. Choroid tubercles seen on fundoscopy also suggest disseminated tuberculosis. Less common presentations include critical bowel obstruction or perforation of a viscus, renal tract pathology manifesting with flank pain, frequency, dysuria, haematuria and acute kidney injury, and pericardial tuberculosis.

Mechanical ventilation in patients with tuberculosis

The incidence of acute respiratory failure in patients with tuberculosis on the intensive care unit corresponds with the high requirement for endotracheal intubation and mechanical ventilation identified (> 50%) (Balkema et al, 2014; Lanoix et al, 2014). Mechanical ventilation has independently been associated with an increased risk of mortality (Balkema et al, 2014; Lanoix et al, 2014). Ventilator-associated pneumonia is the most common nosocomial infection and accounts for 30% of mortality on the intensive care unit in this patient group (Balkema et al, 2014; Lanoix et al, 2014).

Non-invasive ventilation avoids some of the complications associated with mechanical ventilation. No data exists on the use of non-invasive ventilation in the management of patients with acute respiratory failure secondary to tuberculosis and perhaps this is the result of infection control concerns and the increased risk of aerosolisation with non-invasive ventilation methods. Indeed isolation of patients with pulmonary tuberculosis is important while they are infective (up to 2 weeks from starting treatment), ideally in a negative pressure side room (National Institute for Health and Care Excellence, 2016).

Tuberculosis infection control on the intensive care unit

Tuberculosis is spread by the airborne route and the infectiousness of a patient with tuberculosis is directly related to the number of droplet nuclei carrying *M. tuberculosis* expelled into the air. These particles can remain suspended in the air for several hours, allowing person to person spread. Infectiousness of a patient declines after treatment has been started but the rate of decline does vary between patients. There is a requirement to protect other patients and health-care workers from the risk of infection, and expert help should be sought locally from the infection control team.

National guidelines on the management of tuberculosis provide a framework for infection control measures within the hospital environment, which can be broadly applied to the intensive care unit (National Institute for Health and Care Excellence, 2016). Ideally patients with infectious tuberculosis should be managed in a negative pressure side room. Health-care workers and visitors should wear FFP3 masks when aerosol-generating procedures are being performed and/or when caring for a patient with suspected or confirmed multidrug resistant tuberculosis (National Institute for Health and Care Excellence, 2016). De-

Table 3. Treatment: a checklist for the management of anti-tuberculosis regimen-associated hepatotoxicity and nephrotoxicity

Hepatoxicity	Check liver function tests before starting		
	Check alanine transaminase at day 14, 28 and if suspect liver injury		
	Alanine transaminase ≥3x upper limit of normal: consider other drugs		
	Alanine transaminase ≥5x upper limit of normal: stop isoniazid, rifampicin and pyrazinamide		
Nephrotoxicity	Check urea and electrolytes, estimated glomerular filtration rate, creatinine before starting		
	If creatinine clearance <30 ml/min:	Isoniazid	300 mg daily
		Rifampicin	<50 kg: 450 mg daily ≥50 kg: 600 mg daily
		Pyrazinamide	25–30 mg/kg 3x/week
		Ethambutol	15–25 mg/kg 3x/week

escalation of isolation can be considered after 2 weeks of treatment, taking into account individual patient factors and local policy. Contact tracing and testing of other people (staff, patients and public) may be necessary if insufficient isolation was implemented at any point.

Tuberculosis treatment on the intensive care unit

There is no evidence to suggest that treatment of patients with tuberculosis on the intensive care unit should differ from standard World Health Organization (2010) guidelines, consisting of quadruple therapy, with isoniazid, rifampicin, pyrazinamide and ethambutol. This is dependent on enteral absorption – if impaired, rifampicin and isoniazid may be administered parenterally. Additional parenteral options include quinolones (moxifloxacin), an aminoglycoside (e.g. amikacin) and linezolid. Therapeutic drug monitoring is advised, because of the variable pharmacokinetics and pharmacodynamics. Additionally, some drugs (rifampicin) may adhere to the nasogastric tube and be preferentially administered intravenously while the patient is on the intensive care unit. Management of drug-resistant tuberculosis, rates of which are low (<15%) among patients admitted to the intensive care unit, is complex and requires the involvement of infectious diseases clinicians (Erbes et al, 2006; Lee et al, 2011).

Toxicity and drug interactions should be carefully monitored for. Specifically, interactions with rifampicin are widespread, because of its inhibition of cytochrome PY450. Rifampicin will interact with the following drugs which are commonly used on intensive care units: morphine, fentanyl, midazolam, phenytoin, corticosteroids and antifungals.

Role of corticosteroids

Adjunctive treatment with corticosteroids in patients with meningeal tuberculosis significantly improves survival (Thwaites et al, 2009). The dose of dexamethasone prescribed is based on the severity of meningitis, as determined by the Glasgow coma score. A reducing dose of 0.3–0.4 mg/kg/d, initially given intravenously and then orally, for 6–8 weeks is recommended (Thwaites et al, 2009). Possible mechanisms include a reduction in meningeal inflammation (including paradoxical reactions), a reduction in brainstem encephalopathy and a reduction in the frequency of adverse events which subsequently require a change in anti-tuberculosis chemotherapy (Thwaites et al, 2009). Corticosteroids are also recommended as an adjunct for pericardial tuberculosis, decreasing re-accumulation of pericardial effusions and the risk of long-term pericardial fibrosis (Mayosi et al, 2002). Using corticosteroids to treat individuals admitted to the intensive care unit with acute respiratory distress syndrome secondary to miliary tuberculosis has been associated with a significant decrease in mortality (Deng et al, 2012).

Drug interactions affecting the tuberculosis patient on the intensive care unit

Patients on the intensive care unit routinely present the intensivist with unique clinical therapeutic challenges, with regards to both pharmacodynamics and pharmacokinetics. The same can be said for patients with tuberculosis on the intensive care unit, who present with organ failure and receive a hepatotoxic and nephrotoxic anti-tuberculosis regimen (*Table 3*).

Hepatotoxicity

Isoniazid, rifampicin and pyrazinamide are hepatotoxic and it is for this reason that liver function tests must be performed before starting anti-tuberculosis treatment (Saukkonen et al, 2006). Alanine aminotransferase levels should also be checked at times of peak incidence of drug-induced liver injury (at day 14 and day 28 of therapy) (Saukkonen et al, 2006). Alternative drugs should be considered in patients with unstable liver disease and an alanine aminotransferase level more than three times the upper limit of normal (Saukkonen et al, 2006). Generally, the greater the level of liver derangement, the fewer

KEY POINTS

- Acute respiratory failure requiring mechanical ventilation is the indication for admission to the intensive care unit in over 90% of cases.
- The gold standard for tuberculosis diagnosis is specimen culture which can be impeded in the mechanically ventilated patient.
- Mechanical ventilation is independently associated with increased mortality.
- Quadruple therapy is the mainstay of treatment, but is subject to alteration if enteral absorption is impaired or if concomitant prescribing with opioids and benzodiazepines.
- Factors predicting poor prognosis include multiple organ failure, sepsis, adult respiratory distress syndrome, high sequential organ failure assessment (SOFA) score, delayed treatment and the need for organ support.

hepatotoxic drugs should be considered. Close monitoring of biochemistry is a routine component of care within the intensive care unit. This may explain the relatively low incidence of hepatotoxicity in patients admitted to the intensive care unit with tuberculosis, as acute changes in liver biochemistry are promptly managed by adjustments to anti-tuberculosis dosing regimens. This may also explain the observation of a higher alanine aminotransferase threshold level, of five times the upper limit of normal, required for discontinuation of isoniazid and rifampicin on the intensive care unit (Zahar et al, 2001).

Nephrotoxicity

Pyrazinamide and ethambutol undergo significant renal excretion and renal function must be checked before starting treatment. In individuals with renal failure, provided dose adjustments for pyrazinamide and ethambutol are made, the standard anti-tuberculosis regimen is still recommended (Milburn et al, 2010). Dose adjustments are indicated in individuals with a creatinine clearance <30 ml/min. These patients should receive both a reduced dose of pyrazinamide (25–30 mg/kg) and ethambutol (15–25 mg/kg) and a reduced dosing interval of three times weekly (Milburn et al, 2010). Formal guidance on the management of patients with tuberculosis on the intensive care unit with requiring continuous renal replacement is yet to be outlined. Nephrotoxicity in patients with tuberculosis on the intensive care unit is also yet to be reported in the literature.

Prognosis of the patient with tuberculosis on the intensive care unit

When compared with all patients with tuberculosis, patients with tuberculosis who require admission to the intensive care unit have a higher mortality (above 50%, with an overall range of 20–70%) (Lin et al, 2009; Silva et al, 2010; Balkema et al, 2014; Lanoix et al, 2014) (*Table 4*). Mortality from acute respiratory failure secondary to tuberculosis pneumonia is significantly higher than acute respiratory failure as a result of non-tuberculosis pneumonia and more similar to mortality from acute respiratory distress syndrome (Lin et al, 2009).

Table 4. Prognosis: ten factors predicting mortality

Acute respiratory distress syndrome
Multiple organ failure
Sepsis
Ventilator-associated pneumonia
Other infections
Mechanical ventilation
Vasoactive drugs
Renal replacement therapy
High sequential organ failure assessment (SOFA) scores
Treatment delay (>30 days)

Factors predicting worse outcomes within the intensive care unit include the development of acute respiratory distress syndrome, multiple organ failure, sepsis, ventilator-associated pneumonia and concomitant infections, the requirement for mechanical ventilation, vasoactive drugs and renal replacement therapy, high SOFA scores and a treatment delay of more than 30 days (Erbes et al, 2006; Valade et al, 2012; Balkema et al, 2014; Lanoix et al, 2014). Other factors identified as predictors of poor outcome include early admission to the intensive care unit, low CD4 counts in HIV+ individuals, miliary tuberculosis, high Acute Physiology and Chronic Health Evaluation (APACHE II) scores, pancreatitis, lymphopaenia, hypoproteinaemia and low Glasgow coma scores (Erbes et al, 2006; Valade et al, 2012; Balkema et al, 2014; Lanoix et al, 2014). By contrast, the first prospective analysis of tuberculosis within the intensive care unit only identified a low CD4 count and high APACHE II score as predictors of mortality (Balkema et al, 2014).

Conclusions

This review has considered current evidence on the diagnosis and management of patients with tuberculosis requiring admission to the intensive care unit. Most of the evidence to date is from retrospective cohorts and case series – more prospective research needs to be conducted in this area. Intensive care unit patients are ultimately a heterogeneous patient population and the complexity of tuberculosis pathogenesis exacerbates this. As such management of patients with tuberculosis on the intensive care unit invariably requires complex shared management with infectious diseases, in addition to possible input from nephrologists, hepatologists and pharmacists. This review provides a starting framework for the intensivist in making a diagnosis and managing a patient with tuberculosis on the intensive care unit. **BJHM**

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