Clinical review: Tuberculosis on the intensive care unit

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Abstract
Rates of tuberculosis (TB) are increasing in most west European nations. Patients with TB can be admitted to an ICU for a variety of reasons, including respiratory failure, multiorgan failure and decreased consciousness associated with central nervous system disease. TB is a treatable disease but the mortality for patients admitted with TB to an ICU remains high. Management challenges exist in establishing a prompt diagnosis and administering effective treatment on the ICU with potentially poor gastric absorption and high rates of organ dysfunction and drug toxicity. In this review reasons for ICU admission, methods of achieving a confident diagnosis through direct and inferred methods, anti-tuberculosis treatment (including steroid and other adjuvant therapies) and specific management problems with particular relevance to the intensivist are discussed. The role of therapeutic drug monitoring, judicious use of alternative regimes in the context of toxicity or organ dysfunction and when to suspect paradoxical tuberculosis reactions are also covered. Diagnostic and therapeutic algorithms are proposed to guide ICU doctors in the management of this sometimes complicated disease.

Introduction
Tuberculosis (TB) remains a significant public health problem worldwide, with an estimated 8.7 million cases and 1.4 million deaths from it in 2011 [1]. Immigration patterns, the HIV pandemic and iatrogenic immuno-suppression have made TB a more common disease in western European nations; TB rates in the UK have increased over the past 2 years [2], with a rate of 14.4 cases/100,000 population. Patients with suspected or actual tuberculosis may be on a high dependency unit (HDU)/ICU setting for a variety of reasons. Mortality for patients admitted with active TB and respiratory failure requiring mechanical ventilation is poor, with reported in-hospital mortalities of 33 to 67% [3-5]. It is a treatable disease and a proactive approach with timely intervention is required in the treatment of critically ill TB patients, as delays to starting therapy can be associated with worse survival [6]. TB patients on ICU present special challenges, including obtaining microbiological confirmation, providing effective anti-tuberculosis treatment (ATT) with poor absorption and high rates of organ dysfunction, and apparent deterioration of TB during appropriate treatment (paradoxical reactions). This review describes the reasons patients with TB may be on a HDU/ICU and aims to discuss management with particular relevance to the intensivist and the ICU environment.

Reasons and outcome for ICU admission in tuberculosis patients
TB usually affects the lungs but may present acutely in almost any organ system and mimic other infectious or non-infectious processes [7]. Most studies of TB patients on ICU involve patients with pulmonary TB [6,8]. Common reasons for admission are acute respiratory failure [3,4], and development of multi-organ failure (MOF) [9]; high rates of acute respiratory distress syndrome (ARDS) are seen [10], although post mortem studies suggest that confluent tuberculous bronchopneumonia may mimic ARDS [3]. Neurological deterioration due to tuberculosis meningitis (TBM) is a rarer but important reason for ICU admission. Presentations of TB are myriad and more unusual reasons for ICU admission exist (some of these are listed in Table 1).

Respiratory failure due to pulmonary tuberculosis
Advanced pulmonary TB can cause respiratory failure; the incidence of respiratory failure in hospitalised pulmonary TB patients is about 1.5% [3]. The majority of patients will have abnormal chest X-rays (CXRs) including cavitatory lesions and bilateral infiltrates [8] (Figure 1). Contributing factors such as bacterial pneumonia, chronic obstructive pulmonary disease and malignancy may be present in about 72% of cases [11].
Patients with TB requiring ICU care may have high rates of co-morbidities and ICU related complications. In one German study [8] 65.5% of patients had deranged liver function, 12.1% chronic pancreatitis, 8.6% chronic renal failure and 6.9% HIV co-infection. ICU related complications were also common, with nosocomial pneumonia in 67.2% patients, pneumothorax in 13.8%, ARDS in 12.1%, acute renal failure in 12.1% and MOF in 3.4%. Rates of co-existing extra-pulmonary TB can be up to 19 to 22% [6,8].

Delay in appropriate treatment due to lack of early recognition of TB may result in progressive multi-organ involvement and ICU admission [6] and an important opportunity between hospital admission and ICU presentation may exist. Given the high ARDS rates in ventilated patients with TB, standard mechanical ventilation strategies to reduce ARDS may be appropriate, including lower tidal volumes and a conservative fluid strategy [12].

Mortality is high for patients with active TB and respiratory failure; a Canadian study found a significantly higher in-hospital mortality of 69% for patients requiring mechanical ventilation for TB in comparison to ARDS of any cause (56%) and nontuberculous pneumonia (36%) requiring mechanical ventilation [13]. Risk factors for mortality include older age, nosocomial pneumonia, TB destroyed lung, MOF, a duration of symptoms of more than 4 weeks, and an APACHE-II score >20 [14,15].

Miliary tuberculosis
Miliary TB is a form of TB where there is haematological dissemination from focal infection into the blood, leading to seeding of multiple organs with TB bacilli. A minority of patients may present with symptoms of less than four weeks duration. An underlying predisposing condition such as diabetes or steroid use will be present in about a third of patients [16] and immunosuppression due to HIV or iatrogenic reasons may also contribute [17]. The CXR may be initially normal for the first few weeks of the disease. Mortality is about 25% overall [16] but assumed near 100% if untreated. Patients with miliary TB may be more likely to develop ARDS than patients with isolated pulmonary TB and MOF may account for most of the mortality of patients with miliary TB on ICU [10]. A retrospective study by Silva and colleagues [4], which included high rates of extrapulmonary TB (about 63%) and HIV seropositivity, described MOF in over 80% of patients.

Disseminated TB can rarely lead to a septic shock with MOF presentation, sometimes described as Landouzy septicaemia after the original report [18]. This is usually described in association with HIV infection [19], and recently associated with monoclonal antibodies used in the treatment of rheumatological disease [17], but can also occur in patients with no obvious risk factors [20]. Disseminated TB may also cause adrenal insufficiency [21], which should be considered in the context of refractory hypotension or hyponatraemia.

Tuberculosis meningitis and other central nervous system tuberculosis
Tuberculosis of the central nervous system (CNS) occurs in approximately 1% of TB cases, and includes TBM and cerebral tuberculomas. It carries a high mortality and is probably fatal if untreated. It is the reason for about 6 to
18% [4,6] of TB related ICU admissions. In a French case series of TBM admitted to ICU [22], nearly all patients were admitted due to a falling conscious level, 75% required mechanical ventilation and 33% underwent a neurosurgical procedure; 1 year mortality was 65%. Clinical symptoms range from an acute illness mimicking bacterial meningitis to a non-specific illness of fever and headache, with a smaller proportion having cranial nerve palsies [22]. The mean duration of symptoms ranges from 12 to 29 days in most series and approximately one-third will have symptoms lasting less than a week [7]. The majority of the literature on CNS TB comes from the paediatric age group. Cerebral tuberculomas can present as seizures (focal and generalised), as well as with focal neurological signs; occasionally a tuberculous brain abscess can form that may require neurosurgical intervention as well as ATT [23].

As well as a high mortality, TBM poses two additional particular challenges for the intensivist relevant to neurocritical care - hydrocephalus and hyponatraemia. Hydrocephalus is common and develops radiologically in about 77% [24] of cases. It is usually due to communicating hydrocephalus associated with tuberculous exudates in the basal cisterns, but may be non-communicating in a smaller (17 to 25%) proportion of cases - for example, due to obstruction at the outlet foramen of the fourth ventricle or the cerebral aqueduct by oedema or a tuberculoma [25]. Hydrocephalus may increase the intracranial pressure, leading to reduced cerebral perfusion and ischaemia, and in more advanced cases cause brain herniation. Non-communicating hydrocephalus usually requires a neurological procedure such as a shunt procedure or an endoscopic third ventriculostomy [26]. Cases of communicating hydrocephalus should also be discussed with a neurosurgical centre. There may be a role for external ventricular drainage in patients with a low Glasgow coma score and TBM [27]. Hyponatraemia is common in TBM patients and is independently associated with a worse outcome [26]. It is multifactorial, and the syndrome of inappropriate anti-diuretic hormone and cerebral salt wasting probably both play a role [28]. The best approach to TBM-associated hyponatraemia is uncertain, and hypertonic saline, fluid restriction, fludrocortisone and demeclocycline may all have a role depending on the fluid state of the patient [26]. Other aspects of neurocritical care may be relevant for TBM. These additional interventions may include intra-cranial pressure monitoring [25], a higher transfusion threshold [29], and control of fever [30].

**Diagnosis of tuberculosis**

Culture confirmation of tuberculosis should be obtained where possible [31]; the World Health Organisation (WHO) recommends all patients suspected to have pulmonary TB submit at least two sputum specimens for microscopic examination [32]. Culture not only confirms the diagnosis but also provides drug susceptibility testing. In the UK, 8.4% of isolates were resistant to any first line drug, and 1.6% of isolates were multi-drug resistant TB (MDR TB) [2]; rates of MDR TB are much higher in some countries.

New liquid culture techniques should give a culture result in 2 to 4 weeks [31]. An initial targeted sample for auramine or Ziehl-Neelsen stain is important as this would help confirm TB in the appropriate clinical situation. There is little evidence specific to diagnosis in an ICU setting. TB can present acutely and a high index of suspicion should be had in the majority of ill patients with an abnormal CXR, particularly if risk factors for TB are present. An incidental finding of acid fast bacilli (AFB) in sputum in a patient not suspected to have TB may be due to non-tuberculous mycobacteria (NTM) and correlation with other diagnostic data such as radiology and immune status is advised; 35% of AFB seen in sputum was due to NTM in one study [33]. NTM may cause pulmonary disease especially in the immunosuppressed or may not be significant. Conversely, an AFB-positive specimen in a patient with a suggestive history, clinical features and radiology should be assumed to be TB unless proved otherwise; TB PCR may have a role if there is doubt.

In patients who are expectorating, serial sputum sampling probably provides a yield similar to bronchoscopy [34]. Microbiological sampling in the non-expectorating patient may be carried out via bronchoscopy if the patient is intubated. Transbronchial biopsy may provide histology to enable rapid diagnosis and may increase the diagnostic yield [35]; this can carry a risk of complications in the mechanically ventilated patient (mainly bleeding and pneumothorax [36]) but in selected patients the risk/benefit ratio may be favourable, particularly in patients with diffuse lung shadowing or miliary disease. Specialised procedures such as bronchoscopy through a non-invasive ventilation mask may facilitate sampling in a hypoxic non-intubated patient and this is carried out in our institution. Where facilities exist, induced sputum may have a role in some patients and has been shown to have similar or better sensitivities to bronchoscopy (73 and 87% sensitivity, respectively) in smear-negative patients [37]). No data on the utility of respiratory secretions obtained at suction for diagnosis of TB on ICU/HDU exist but transtracheal aspirates have shown a high sensitivity (88%) in smear-negative patients [38]. If there are signs and symptoms reinforced by appropriate investigations consistent with a TB diagnosis, treatment should be started without waiting for culture results, and continued even if subsequent culture results are negative [31].
Non-pulmonary samples
Extrapulmonary TB is common in ICU patients with pulmonary TB and in the context of advanced immunosuppression associated with HIV [39]; in the latter, visualised AFB may be due to NTM. Whilst culture is central to confirmation of the mycobacterium, PCR for TB may have a role in this patient population to help establish a diagnosis [40]. Most forms of extrapulmonary TB have a lower bacterial load than pulmonary disease and histology/cytology such as pleural biopsies and lymph node aspiration play a more prominent role in diagnosis. A lymphocytic pleural effusion, caseating granulomas or granulomas with Langhan’s giant cells are suggestive of TB [31], although other conditions may also cause these histological changes; lymphoma is a main alternative diagnosis. A lymphocytic pleural effusion, caseating lymph node aspiration play a more prominent role in the diagnosis. 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Interferon gamma release assays/nucleic acid amplification tests
The past decade has seen the development of interferon gamma release assays (IGRAs) in the diagnosis of latent TB. IGRAs work on the principle of measuring the cytokine interferon gamma released from T cells in response to synthetic antigens that are also found in MTB and have an approximate 90% sensitivity and 99% specificity for diagnosis of latent TB [48]. These antigens are absent from Mycobacterium bovis and most NTM so are not affected by prior Bacillus Calmette-Guérin vaccination or most NTM exposure.

IGRAs cannot distinguish between latent and active TB and therefore may be positive in an individual who has latent TB but another cause for ICU admission. It is recommended that IGRAs should not be used as a routine diagnostic tool in active TB, although there may be a role in using IGRA with other complementary tests when TB is suspected, especially if samples are difficult to obtain [49]. A negative test does not exclude active TB. ICU admission has also been associated with a false negative IGRA [50] and so the role of IGRA in intensive care patients is less clear. There is ongoing research into next generation IGRAs and T-cell-based diagnostic platforms that may overcome some of the current limitations of IGRAs [51].

Nucleic acid amplification tests (NAATs) tend not to be routinely used, and the sensitivity and specificity can be highly variable compared with culture results [40]. A negative result does not exclude TB and a positive result does not give drug sensitivities. One exception is the Xpert MTB/RIF probe, which has shown a 98.2% and 72.5% sensitivity for diagnosing TB in smear-positive and smear-negative patients, respectively [52]. The probe also identifies mutations associated with rifampicin (R) resistance and may have a role where MDR TB is suspected; for this reason WHO suggests this test as a follow on test for patients with smear-negative samples. British recommendations for NAATs currently restrict their role to the case where rapid confirmation of a TB diagnosis in a smear-positive patient would alter management (for instance, if an NTM was suspected). There are few recommendations on the role of NAATs on non-respiratory samples. Data from meta-analysis gives a 56% sensitivity and 98% specificity for CSF, which is similar to microscopy [26]. There may be a role for NAAT on CSF when ATT treatment has been started without a confirmed diagnosis, as mycobacterial DNA may remain detectable for a month after the start of treatment [26].
Radiology
Upper lobe disease on a CXR was shown to increase the odds ratio of TB by 14.6 [53]. There are fewer data specific to ICU patients; small nodular or cavitary patterns on a CXR as well as a duration of illness of more than 2 weeks may be predictive of TB in some studies [54], although other studies fail to identify radiological changes specific for TB on an ICU [55]. In HIV co-infected patients, radiological appearances can vary and cavitation becomes less common as immunosuppression advances. An American study described a normal or near normal CXR in 19% of pulmonary TB patients with a CD4 count less than 200 cells/μl [56]. Computed tomography (CT) scanning may have a role in identifying active TB and allowing differentiation from old fibrotic lesions, with centrilobular nodules and a ‘tree in bud’ pattern often seen in active disease. Mediastinal lymphadenopathy and cavitation may also raise the suspicion of TB (Figure 2), and miliary shadowing may be present on CT even with a normal chest X-ray [57]. CT chest may help in gathering diagnostic information in an intubated patient where TB is suspected but not confirmed, and also allow targeting of bronchoscopy.

A proposed diagnostic algorithm for respiratory failure is presented in Figure 3.

Anti tuberculosis treatment and adjuvant therapies (including paradoxical reactions)
The standard treatment for non-MDR TB involves combination therapy of more than three drugs; R and isoniazid (H) provide a crucial backbone to ATT regimes, allowing shorter courses of 6 to 9 months (1 year for CNS TB) to be efficacious due to their bacteriocidal action. R and H are associated with the potential serious side effects of hepatotoxicity. Two other first line ATT, pyrazinamide (Z) and ethambutol (E), are renally excreted and E may be associated with optic nerve toxicity. Other drugs used to treat TB include fluoroquinolones (for example, moxifloxacin), aminoglycosides (for example, streptomycin or amikacin) and a range of other second line anti-TB drugs such as cycloserine or prothionamide. Not all ATT is available parenterally; parenteral preparations are available for R, H, fluoroquinolones and aminoglycosides. The management of HIV co-infection is complicated and detailed discussion is beyond the scope of this article; guidelines exist for management outside of the HDU/ICU [40]. Principles of HIV/TB co-infection management include awareness of the immune reconstitution inflammatory syndrome (IRIS), and when highly active antiretroviral therapy (HAART) should be started; this depends on the CD4 count but is recommended as soon as is practical in the very immunosuppressed (CD4 count <100 cells/μl) [40].

High rates of hepatic and renal dysfunction in ICU patients with TB provide specific challenges. Patients on the ICU may have uncertain enteral absorption [58]. Subtherapeutic levels of ATT have been associated with a slow clinical response, treatment failure and drug resistance [59]. The incidence of subtherapeutic levels of anti-TB drugs in ICU patients is not known but it is reasonable to have a low threshold for therapeutic drug monitoring in TB patients on the ICU. Our practice is to prefer parenteral therapy in severely ill patients for the initial 72 hours.

Additional bacterial infection can complicate TB-related ICU admissions [8] and a low threshold for additional anti-bactericidal therapy should be present.

Hepatotoxicity
Hepatotoxicity may be associated with older age, malnutrition, alcoholism, HIV or viral hepatitis co-infection [60]. In miliary TB it is important to ensure that the cause of the deranged liver function is not due to TB itself (by imaging or consideration of liver biopsy), as the management of deranged liver function in this context would be management of the TB. International guidelines differ slightly but suggest stopping TB medication if transaminases are more than three to five times the upper limit of normal or there is a bilirubin rise [60,61]. If it is crucial to continue ATT in the short term (for instance in TBM where treatment interruptions are an independent risk factor for death [26]), a combination of
relatively non-hepatotoxic drugs, such as an aminoglycoside, E and a fluoroquinolone, could be given [60]. Ethionamide and prothionamide may be an alternative to E as they penetrate the meninges well and do not have the concern of optic nerve toxicity [62]. As R and H are important for TB treatment, they are usually sequentially reintroduced once liver function tests improve with close monitoring, and standardised re-challenge protocols are provided [60,61]. In cases of severe or prolonged hepatotoxicity who have had R and H re-introduced, it may be reasonable not to re-challenge with Z and extend treatment to 9 months [60]. The management of patients with decompensated liver disease and TB is not clear, and the standard regime with close monitoring, or 18 to 24 months of E, a fluoroquinolone and an aminoglycoside is suggested [60].

Nephrotoxicity
Dose adjustments are required with Z and E with a glomerular filtration rate of less than 30 ml/minute/1.73 m². Aminoglycosides and cycloserine may require similar dose adjustments [63]. No data exist for patients on continuous renal replacement therapy, and collaboration between intensivists, pharmacists, TB physicians, renal physicians and monitoring of drug levels is appropriate.

Corticosteroids as adjuvant therapy
Corticosteroids inhibit release of inflammatory cytokines, which may help lessen tissue damage and constitutional symptoms. There have been many studies of corticosteroids in TB, including advanced pulmonary TB. The only indications for steroids recognised in most international guidelines are a) TBM, where corticosteroids
help reduce risk of death or disability [26,31] and b) tuberculous pericardial effusion where corticosteroids decrease the amount and rate of re-accumulation of tuberculous pericardial effusion [31,64]. The largest trial of steroids in TBM used a reducing dose of dexamethasone, initially given intravenously at a dose of 0.3 to 0.4 mg/kg/day (depending on the severity of the meningitis) for a total of 6 to 8 weeks [65]; British guidelines suggest prednisolone (or equivalent) 20 to 40 mg/day with gradual withdrawal. There are no direct comparisons of the dose or type of steroid in TBM. For tuberculous pleural effusion there is some evidence for adjuvant corticosteroids resulting in a faster resolution of pleural effusion at 4 weeks, but no difference in residual
fl uid at 8 weeks or death rates between corticosteroid and non-corticosteroid groups [66]. Many trials of corticosteroids for pulmonary TB were carried out in the 1950s to 1960s and suggested a more rapid clinical and radiological improvement compared to control patients, particularly in severe disease [67], but an absence of longer term effects on survival or risk of long-term lung damage. The implications of this for patients with advanced TB and respiratory failure on an ICU are unclear. A recent meta-analysis suggests a non-significant trend towards benefit of steroids in pulmonary TB [68], and a 2008 study [14] suggested a lower mortality rate in patients with pulmonary TB who received corticosteroids but firm conclusions cannot be drawn due to the retrospective nature of the study.

Paradoxical reactions/immune reconstitution inflammatory syndrome

A paradoxical reaction in TB is defined as a clinical or radiological worsening of pre-existing tuberculous lesions or the development of new lesions in patients receiving ATT in the absence of an alternative explanation such as drug resistance, ineffective drug delivery or a secondary diagnosis [69]. Patients with HIV are more likely to develop these reactions, which are referred to in the context of HIV co-infection as IRIS [40]. The aetiology of these reactions is unknown, but in HIV may relate to HAART causing a reconstitution of immunity leading to an immune response to dead bacilli. The incidence in HIV-negative patients is probably between 2 and 23% [70], and about 32 and 36% in HIV-positive patients, and may be more in patients with advanced TB. Paradoxical reactions are usually mild and may manifest as recurrent fever, deterioration in radiological appearances or lymph node inflammation [70] but may cause significant morbidity, including airway obstruction, splenic rupture, or worsening neurology due to new or enlarging intracranial tuberculosis [69,71]. The median time of onset is about 26 days after treatment [70], but can occur months into treatment. Risk factors for IRIS include a low baseline CD4 count, rapid recovery in CD4 numbers and HAART started within 2 months of diagnosis [40]. There are no firm recommendations on how to treat paradoxical reactions but a tapering dose of corticosteroids is reasonable [69]. Thalidomide may have a role in severe CNS TB paradoxical reactions unresponsive to corticosteroids [72], and montelukast has been used in IRIS. An algorithm for treatment of pulmonary TB on the ICU based on the above review is presented in Figure 4.

Conclusion

Respiratory failure and miliary TB are common reasons for admission of patients with TB to an ICU. The evidence base for diagnosis and management of TB specific to an ICU setting is sparse and what may be true for stable TB patients may not translate to an ICU. These patients have a high mortality and high rates of organ dysfunction. Diagnosis of TB if not confirmed prior to ICU admission may be challenging but culture of mycobacterium TB should be attempted, with radiology, histology and possibly IGRA s contributing to the clinical picture. Treatment is complicated by drug toxicity, erratic absorption and organ dysfunction, and therapeutic drug monitoring and judicious use of alternative regimes may help this problem. Corticosteroids have a role in TBM and pericardial TB and may have a role in far advanced pulmonary TB on a case by case basis. The clinician should be alert to paradoxical reactions as a cause of apparent treatment failure or disease progression.

Abbreviations

AFB, acid fast bacilli; ARDS, acute respiratory distress syndrome; ATT, anti-tuberculosis treatment; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; CXR, chest X-ray; E, ethambutol; H, isoniazid; HAART, highly active antiretroviral therapy; HDU, high dependency unit; IGRA, interferon gamma release assay; IRIS, immune reconstitution inflammatory syndrome; I, MDR TB, multi-drug resistant tuberculosis; HAART, nucleic acid amplification test; NTM, non-tuberculous mycobacterium; PCR, polymerase chain reaction; R, rifampicin; TB, multi-drug resistant tuberculosis; MOF, multi-organ failure; TB, tuberculosis; TBM, tuberculosis meningitis; WHO, World Health Organisation; Z, pyrazinamide.

Competing interests

The authors have no conflicts of interest to declare.

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