Tuberculosis in Critical Care

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Key Points

- Tuberculosis (TB) uncommonly results in complications such as acute respiratory distress syndrome, septic shock, multiorgan dysfunction, and disseminated intravascular coagulation, which necessitate intensive care unit (ICU) admission.
- Mortality of TB patients requiring ICU care is high compared to other conditions.
- A high index of suspicion and timely initiation of TB treatment are key to improve survival.
- Treatment of TB in ICU patients could be complicated by impaired enteral absorption of drugs.
- Appropriate infection control measures are necessary to prevent airborne spread of TB infection from potentially infectious TB patients admitted to the ICU.

16.1 Introduction

Although tuberculosis (TB) figures among the top 10 causes of mortality globally, it is rather infrequently encountered in the intensive care unit (ICU) setting even in countries where TB is widely prevalent. Patients with TB constitute less than 2% of total ICU admissions (Muthu et al. 2018; Frame et al. 1987). Notwithstanding, these patients pose considerable challenges in terms of timely diagnosis, treatment, and
infection control. Patients with clinically severe forms of TB may require admission to the ICU. Studies from various settings indicate that a broad range of 1–25% of patients with active TB require ICU admission (Patel et al. 2017; Tsai et al. 2008; Levy et al. 1987; Lui et al. 2014; Eveloff et al. 1994; Rao et al. 1998; Silva et al. 2010). The most common reason for transferring a patient with active TB to the ICU is acute respiratory failure (ARF) (Muthu et al. 2018; Frame et al. 1987; Zahar et al. 2001; Valade et al. 2012). Other common indications include mycobacterial septic shock and multiorgan dysfunction syndrome (MODS). However, in some settings, TB meningitis is the most common reason for ICU admission among TB patients. About 40% of patients with TB meningitis would have concomitant pulmonary disease. Less common indications could be massive hemoptysis, pericardial effusion causing cardiac tamponade, Addisonian crisis, airway obstruction in laryngeal TB, disseminated intravascular coagulation (DIC), and seizures caused by tuberculomas in the brain. Importantly, TB patients may also experience acute liver failure due to hepatotoxic drugs and rarely acute renal failure, mainly rifampicin-induced (Hagan and Nathani 2013) (Table 16.1).

These are all settings when a patient already diagnosed with TB or else an obvious possibility of TB (such as chronic meningitis, cardiac tamponade) is shifted to the ICU. The most challenging situation, however, is when patients are admitted to the

| Table 16.1 Common problems encountered in TB patients admitted to the ICU |
|---------------------------------------------------------------|
| **Acute respiratory failure**                                 |
| – ARDS in miliary TB                                         |
| – Tuberculous pneumonia                                     |
| – Extensive parenchymal destruction by untreated pulmonary TB|
| – Massive hemoptysis with pulmonary aspiration               |
| – Airway obstruction in laryngeal TB                         |
| **Acute on chronic respiratory failure**                     |
| – Destroyed lung with intercurrent problems such as bacterial pneumonia, hemoptysis, heart failure |
| **TB meningitis with poor sensorium**                        |
| – Hydrocephalus                                              |
| – Increased intracranial pressure                            |
| – Vasculitic infarcts                                        |
| – Hyponatremia (cerebral salt wasting, inappropriate antidiuretic hormone secretion) |
| – Status epilepticus                                         |
| **TB pericardial effusion with cardiac tamponade**           |
| **Intestinal obstruction/perforation peritonitis**           |
| **Septic shock/multiorgan dysfunction syndrome**             |
| **Disseminated intravascular coagulation**                   |
| **Hemophagocytic lymphohistiocytosis**                       |
| **Acute adrenal insufficiency**                              |
| **Serious adverse drug reactions**                           |
| – Acute liver failure                                        |
| – Acute renal failure                                        |
| – Stevens-Johnson syndrome/toxic epidermal necrolysis        |


ICU with one or more organ dysfunctions such as ARF or MODS, but without any obvious suggestion of TB as the underlying cause. In Taiwan, 4% of patients with culture-confirmed pulmonary TB over the period 2005–2010 presented with clinical and radiographic manifestations similar to severe community-acquired pneumonia that required ICU admission (Tseng et al. 2012). In a study from Hong Kong, 48 of 349 patients with TB admitted to the hospital over a 2-year period died. In about 50% patients (23 of 48) that died by Day 90, a diagnosis of TB was not made antemortem (Lui et al. 2014). In a study on burden of TB done at four South African ICUs, 7 (15%) of 46 patients with confirmed TB died before the diagnosis was made (Calligaro et al. 2015). Possibility of TB was not considered at the time of ICU admission in about 13% of patients with TB admitted to the respiratory ICU of a large teaching hospital in northern India (Muthu et al. 2018). Thus, a diagnosis of TB is missed in a considerable proportion of patients admitted to ICUs across different settings. In a multicentric study involving 34 ICUs in India, of the 456 patients admitted with fever of less than 2 weeks duration and one or more organ dysfunctions, no patient received a diagnosis of TB (Singhi et al. 2017). Notably, a specific etiological diagnosis could not be achieved in about 20% of patients. Hospital mortality was considerably higher in these patients (27% vs 15%) compared to the rest, in whom the most common diagnoses were dengue, scrub typhus, meningoencephalitis, sepsis, pneumonia, and leptospirosis. It is possible that at least some of the patients without a specific diagnosis could have had TB that was not diagnosed antemortem.

Pulmonary TB might be incidentally detected on routinely performed chest radiographs in patients admitted to the ICU for other indications such as alcoholic liver disease, chronic kidney disease, and diabetes complications. Likewise, in endemic countries, it is not uncommon for thrombolysis or anticoagulation for the treatment of acute coronary syndromes to result in hemoptysis, unmasking pauciympomatic or healed pulmonary TB lesions. Further, patients with active TB could be admitted to the ICU with unrelated illnesses like trauma, emergency surgeries, or organ failures.

16.2 Acute Respiratory Failure in TB

Notwithstanding the fact that TB most commonly affects the lungs, often extensively, ARF is an infrequent complication of pulmonary TB. Incidence of ARF among patients with active TB admitted in non-ICU inpatient settings is about 1.5% (Levy et al. 1987; Agarwal et al. 1977). On the other hand, almost 80% patients with TB admitted in the ICU have ARF (Frame et al. 1987; Eveloff et al. 1994; Erbes et al. 2006). Patients with TB could develop ARF by several mechanisms. First, patients with extensive parenchymal destruction from untreated or previously treated pulmonary TB could develop ARF as a complication. Second, miliary TB might be complicated by acute lung injury leading to acute respiratory distress syndrome (ARDS) (Fig. 16.1). Miliary TB is particularly associated with a high risk of ARDS. In a large case series from northern India, about 15% of patients with miliary TB developed ARDS (Sharma et al. 2006).
Third, primary tuberculous pneumonia, characterized by parenchymal consolidation with or without endobronchial spread, in itself could result in ARF necessitating mechanical ventilation (Fig. 16.2) (Kim et al. 2008). This presentation is difficult to differentiate from bacterial pneumonia, the only difference being the longer duration of symptoms before presentation in patients with tuberculous pneumonia as compared to bacterial pneumonia. A high index of clinical suspicion is required in such a situation. Of the 115 patients with ARF caused by TB treated at a South Korean ICU over an 18-year period, ARF was attributable to extensive parenchymal damage by previous episodes of TB in 25 patients (Kim et al. 2008). Of the remainder, 66 patients had tuberculous pneumonia and 24 had miliary TB. Of the

Fig. 16.1 Acute lung injury in miliary TB. A 40-year-old, HIV-negative man presented with fever for 2 months and breathlessness for 10 days. He was tachypneic (respiratory rate 44/min) and his oxygen saturation on room air was 87%. The chest radiograph showed diffuse miliary mottling (Panel a; magnified view of right lower zone in Panel b), and a thin-veil of haziness particularly over the left lung fields (Panel a). High-resolution computed tomographic images (Panels c, d) showed patchy areas of consolidation and ground-glass opacities in a background of randomly distributed micronodules. The patient had clinical and radiographic improvement at 2 weeks (Panel e) following treatment with supplemental oxygen, anti-TB treatment, and adjunctive steroids.
469 patients with ARDS treated over a 16-year period at a teaching hospital in northern India, 18 patients had TB-related ARDS; only six of them had miliary TB (Muthu et al. 2017). It is possible that the rest actually had tuberculous pneumonia.

Fourth, massive hemoptysis with pulmonary aspiration could also lead to ARF in patients with TB. Finally, in human immunodeficiency virus (HIV)-infected and immunosuppressed patients, TB might uncommonly co-exist with other opportunistic infections such as pneumocystis pneumonia and disseminated cytomegalovirus disease. Nearly two-thirds of TB patients with ARF would satisfy the consensus diagnostic criteria for ARDS, and about a third would have concomitant organ dysfunctions in the form of septic shock, DIC, and multiorgan failure (Sharma et al. 2006; Kim et al. 2008; Muthu et al. 2017).

Clinically these patients present with typical features of pulmonary TB like fever, cough, and weight loss (Deng et al. 2012). Presence of dyspnea could indicate the development of ARDS (Sharma et al. 2006). Of note, hemoptysis is uncommon among TB patients developing ARDS. Duration of symptoms could vary from days to months (Levy et al. 1987). Patients with miliary TB are more predisposed to sudden development of ARF, especially when the diagnosis is delayed by >30 days (Sharma et al. 2006). In a study of 146 HIV-negative patients with pulmonary TB admitted to the ICU of a specialist TB hospital in Iran, the most common finding on computed tomography was ARDS-like bilateral infiltrates (17%), followed by parenchymal nodules (1–2 cm size; 14%), cavitation (11%), consolidation (10%),

Fig. 16.2 Tuberculous pneumonia. Chest radiograph of a man with active pulmonary TB who presented with type 1 respiratory failure. There is a cavitory lesion in the right upper zone and extensive bilateral nodular infiltrates larger than miliary micronodules, which are typically 1–2 mm in size.

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interstitial involvement (9%), ground-glass opacities (7%), pleural effusion or thickening (7%), and miliary nodules (2%). Enlarged lymph nodes were present in about 40% of adults (Hashemian et al. 2015).

Histopathology of the lungs in TB-ARDS may show evidence of widespread parenchymal involvement with caseation necrosis, interstitial granulomatous inflammation, small vessel microthrombi, congestion, edema, and diffuse hyaline membranes (Murray et al. 1978). However, evidence of diffuse alveolar damage in the form of hyaline membrane formation may not be present in all cases of TB-ARDS. Some cases show features of confluent TB bronchopneumonia only (Levy et al. 1987).

16.3 TB Meningitis

Patients with TB meningitis often require endotracheal intubation for airway protection or when the respiratory efforts are poor. The most important determinant of survival in patients with TB meningitis is the stage of TB meningitis, which is largely determined by the Glasgow Coma Scale score. Several factors contribute to impairment of sensorium in TB meningitis. They are, communicating and at times obstructive hydrocephalus, elevated intracranial pressure, vasculitic infarcts, and hyponatremia. The latter is seen in about 40% of patients. Most of these patients have hypotonic hyponatremia, the cause of which could be either syndrome of inappropriate antidiuretic hormone secretion (SIADH) or cerebral salt wasting syndrome. Differentiating these two opposing conditions is often challenging, the only distinction being intravascular volume status, assessment of which could prove difficult in critically-ill patients. Some investigators have reported that cerebral salt wasting is more common than SIADH in patients with TB meningitis (Misra et al. 2016), and that volume depletion caused by salt wasting might contribute to strokes (Misra et al. 2018). Application of high positive end-expiratory pressure (PEEP) levels to maintain oxygenation could potentially decrease cerebral perfusion in patients with TB-ARDS and concomitant meningitis. However, the effect of high PEEP on intracranial pressure may not be clinically significant (Boone et al. 2017).

16.4 Septic Shock and Multiorgan Dysfunction in TB

Rarely, a clinical syndrome characterized by shock and multiorgan dysfunction, mimicking septic shock caused by gram-negative infections, has been described in TB (Pène et al. 2001). Presence of vasodilatory shock characterized by a high cardiac output and decreased systemic vascular resistance in these patients along with renal failure, ARDS, and DIC closely resembles gram-negative sepsis (Ahuja et al. 1992). Adrenal involvement was unlikely to explain these findings. Although a rapidly fatal form of TB was well known in the pre-chemotherapy era, advent of the HIV epidemic brought back this form of TB to attention (Gachot et al. 1990). Apart from HIV infection, such a presentation has been reported in other immuno-suppressed conditions, advanced age, alcohol abuse, malignancy, diabetes, renal
failure, and pregnancy (Jog et al. 2011). *Mycobacterium tuberculosis* is an important cause of bloodstream infection and severe sepsis in HIV-infected patients from sub-Saharan Africa (Cummings and O’Donnell 2015). In the tri-national Cooperative Antimicrobial Therapy of Septic Shock (CATSS) database, 53 patients with TB septic shock, defined as confirmed *M. tuberculosis* infection and hypotension requiring vaspressors in the absence of other pathogens, were identified over a 12-year period (Kethireddy et al. 2013). As compared to other bacterial septic shock, patients with TB septic shock were younger and malnourished, often with normal white cell counts despite overt clinical signs of infection; >90% had respiratory involvement—multilobar consolidation, miliary mottling, occasional nodules, and cavitation were the radiographic findings; and 55% had extrapulmonary involvement (Kethireddy et al. 2013). Although most of these patients had underlying conditions such as diabetes, alcohol/substance abuse, and immunosuppression including HIV infection, the frequency of these conditions was similar to the other septic shock patients. Only 20% of patients with TB septic shock survived to hospital discharge. Historical terminologies such as “sepsis tuberculosa gravissima,” “sepsis tuberculosa acutissima,” and “generalized non-reactive tuberculosis” are often used in contemporary literature to describe such a clinical course of TB. Sometimes this condition is also called Landouzy sepsis, which we think is inaccurate (Landouzy 1908). On post-mortem examination, many organs contain small necrotic foci surrounded by normal parenchymal cells, with very little inflammatory response; these lesions are, however, studded with innumerous TB bacilli (Arends 1950; O’Brien 1954).

16.5  Disseminated Intravascular Coagulation in TB

Like septic shock, DIC also could be encountered in patients with TB, albeit infrequently (Pène et al. 2001; Goldfine et al. 1969; Mavligit et al. 1972). In experimental studies, *M. tuberculosis* infection induces expression of tissue factor in macrophages (Kothari et al. 2012), which might explain the occurrence of DIC in patients with disseminated/miliary TB. In a large series of 833 patients with culture-proven TB, 27 (3%) patients had laboratory evidence of DIC; 16 patients had overt DIC with bleeding manifestations, most commonly upper gastrointestinal bleeding; 3 patients had arterial thrombosis in distal extremities (Wang et al. 2005). Nearly half of the patients with DIC also had ARDS and septic shock, and about two-thirds of patients with DIC died. In a study of hospitalized patients with HIV-TB, 29 (64%) of 45 patients had DIC (Janssen et al. 2017). Of the 128 patients with DIC diagnosed over a 1-year period at a South African hospital, 28 patients had TB; all of them had HIV co-infection (Mayne et al. 2018). All these findings suggest that DIC is fairly common among seriously-ill TB patients, and presence of DIC should not be considered a pointer against a diagnosis of TB. Very rarely, a triad of acute renal failure, autoimmune hemolysis, and DIC has been observed in patients with rifampicin hypersensitivity (Ip et al. 1991; Costiniuk et al. 2011). Rifampicin, particularly when used intermittently, could result in renal failure by other mechanisms also (De Vriese et al. 1998).
16.6 Hemophagocytic Lymphohistiocytosis in TB

TB is a relatively common cause of secondary hemophagocytic lymphohistiocytosis (HLH) in endemic countries (Brastianos et al. 2006; Chen et al. 2017). Till date, more than 70 cases of TB-associated HLH have been reported (Padhi et al. 2015). This, however, does not reflect the true magnitude of the problem. Presence of cytopenias and jaundice should arouse the possibility of HLH in patients with TB. Hemophagocytosis in the bone marrow and elevated serum ferritin levels are common as isolated findings in patients with TB (Visser and van de Vyver 2011). However, further evidence of cytopenias and organ dysfunction is required to make a diagnosis of HLH. Bone marrow examination demonstrates histiocytosis and hemophagocytosis in more than 90% of cases, but not invariably. Most of these patients were treated with adjunctive immunosuppressive treatment in addition to anti-TB treatment (Brastianos et al. 2006; Padhi et al. 2015). Despite early diagnosis and appropriate treatment, TB-HLH is associated with a mortality of about 50%.

16.7 When to Suspect TB in ICU Patients

A diagnostic possibility of TB should be considered in patients admitted to the ICU with severe pneumonia and underlying risk factors for TB such as old age, alcoholism, chronic renal failure, diabetes, HIV infection, and a history of immunosuppressive medications. In the absence of any of these predisposing factors, one should also consider a possibility of TB if the presenting illness is sub-acute. Duration of symptoms >1–2 weeks, white cell counts <12,000/μL, nodular/cavitating infiltrates, and upper lobe involvement are predictive of pulmonary TB among patients presenting as community-acquired pneumonia (Liam et al. 2006; Chon et al. 2013). Lower than expected levels of serum C-reactive protein and procalcitonin could be indicative of TB as the etiology (Kang et al. 2009; Ugajin et al. 2011). TB should be considered among the differentials in patients with MODS of unclear etiology particularly when the preceding illness is sub-acute. Identifying miliary TB in patients presenting with ARDS is very challenging. Careful reading of the chest radiograph for the presence of miliary nodules is required. Presence of cytopenias and elevated serum alkaline phosphatase levels should heighten the suspicion. When doubtful, high-resolution computed tomographic imaging of chest should be performed. One needs to be mindful of the potentially destabilizing effect of shifting a patient requiring high PEEP settings for CT imaging.

In a seminal study, Eveloff et al. retrospectively analyzed the hospital charts of 14 patients with culture-confirmed TB, who were admitted to the ICU in a low-prevalence setting, to determine the reasons for diagnostic delay (Eveloff et al. 1994). The time to diagnosis ranged from 3 days to 3 months, and in 5 patients the diagnosis of TB was established only post-mortem. They concluded that

- Diagnostic delay was not due to a failure to consider the possibility of TB. In fact, adequate attempts were made to diagnose TB after sputum specimens were found to be negative for acid-fast organisms.
However, most invasive diagnostic procedures such as bronchoscopy and bone marrow examination were negative for acid-fast organisms.

- Often co-existent bacterial infections acted as confounders, making clinicians believe that clinical worsening was due to bacterial sepsis rather than TB.
- Chest radiographs were often misinterpreted since typical findings of reactivation TB were seldom encountered.

This study was conducted before the advent of Xpert MTB/RIF assay, which is more sensitive and rapid than smear microscopy. To what extent this diagnostic delay could be improved by Xpert MTB/RIF testing is a matter of conjecture. In a randomized evaluation done in South Africa (Calligaro et al. 2015), Xpert MTB/RIF testing on tracheal aspirate samples of mechanically ventilated adults with suspected pulmonary TB had much better sensitivity than concentrated fluorescent smear microscopy for diagnosing culture-confirmed TB. This translated into faster treatment initiation at 48 h (92% vs 53%). However, there was no appreciable effect on mortality. About 30% of Xpert MTB/RIF-positive samples were negative by culture. At present, it is unclear whether these discordant results are false- or true-positives (Calligaro et al. 2015).

16.8 Treatment

The general principles of chemotherapy of TB apply to critically-ill patients as well. Since a delay in treatment initiation could adversely impact survival in critically-ill patients with TB (Lui et al. 2014; Zahar et al. 2001; Calligaro et al. 2015; Deng et al. 2012), clinicians should consider initiating presumptive treatment based on imaging findings alone, pending microbiological and/or tissue confirmation of diagnosis. However, critical illness per se may not be a valid indication for adding second-line drugs to presumptively treat TB. Standard combination of four first-line drugs should be sufficient in situations where drug-resistant TB is unlikely. The recently published first-ever national level survey of drug-resistance in India indicates that frequency of multidrug-resistant TB is quite uncommon (2.8%) among patients without a prior history of TB treatment, while it is 11.6% among previously treated patients (Ministry of Health and Family Welfare, India 2014–16). We do not recommend routinely adding second-line drugs to presumptively treat TB in the ICU setting. A history of TB treatment in the past and appropriate use of rapid diagnostic tests such as XpertMTB/RIF could help decide whether to add second-line agents or not (Calligaro et al. 2015).

On the other hand, while standard first-line drugs are sufficient in terms of coverage, one needs to bear in mind that the absorption, distribution, and elimination of most antimicrobials are considerably altered in a critically-ill patient (Shah et al. 2015). Anti-TB drugs are no exception. Typically, TB drugs are administered in ICU patients through a nasogastric tube after crushing the tablets. Enteral absorption is likely to get affected in the presence of circulatory shock, and enteral route may not be feasible in patients with intestinal obstruction or peritonitis caused by TB. While the pharmacokinetics of anti-TB drugs have been reasonably well
studied in healthy persons and those with active TB, very little data is available on the pharmacokinetics of first-line TB drugs in critically-ill patients. In a small study from South Africa (Koegelenberg et al. 2013), of 10 adult ICU patients administered TB drugs via enteral route, the maximum plasma concentration ($C_{max}$) was below the therapeutic level in 6 patients for rifampicin, 3 patients for ethambutol, and 2 patients for isoniazid; all had adequate plasma concentrations of pyrazinamide. Thus, in an ideal setting, anti-TB drugs should be administered via parenteral route in critically-ill patients. However, injectable preparations of isoniazid and rifampicin are not widely available. Hence, some experts suggest that “local regimens of alternative intravenous anti-TB drugs (e.g. a combination of intravenous rifampicin, moxifloxacin and amikacin) may be useful and effective to bridge the period of impaired gastrointestinal function.” (Otu et al. 2018).

Notably, in a study of 77 patients with severe tuberculous pneumonia requiring admission to a Taiwanese ICU, empirical use of fluoroquinolones before the diagnosis of TB was associated with improved survival (Tseng et al. 2012). If injectable rifampicin is unavailable and the likelihood of TB diagnosis is high, one could consider using injection linezolid in lieu of rifampicin in seriously-ill patients until the time gastrointestinal tract function is restored. Linezolid has good bactericidal and sterilizing activity in TB. Other antibiotics commonly used in clinical practice such as meropenem and amoxicillin-clavulanic acid also have some useful antimycobacterial activity (Caminero et al. 2017).

The other question to be addressed is whether use of corticosteroids could help improve the outcomes in critically-ill TB patients. Patients with TB meningitis and possibly those with TB pericardial effusion experience a survival benefit from adjunctive steroid treatment (Prasad et al. 2016; Wiysonge et al. 2017). Reliable evidence from controlled clinical trials to inform the use of steroids in other forms of TB including those with ARF/ARDS, septic shock, and MODS caused by TB is lacking. Notwithstanding, one cannot rule out a beneficial effect in these groups of patients. Given this, the best possible solution would be to reconcile the observational evidence available on this group of patients with the larger body of trial evidence available on similar clinical conditions and arrive at an informed decision.

Of the 55 patients with miliary TB admitted during 1954–1978 at a Chinese hospital, 5 (18%) of 28 patients treated with chemotherapy alone died as compared to 2 (7.4%) of 27 patients treated with a combination of chemotherapy and prednisone (10 mg QID for Week 1, 20 mg OD Weeks 2–7, tapered off weekly over 3–5 months) (Sun et al. 1981). The difference in mortality could not be explained by a difference in meningeal involvement. Of the 14 patients with meningitis, 9 received prednisone—2 of them died; and 5 did not receive prednisone—1 of them died. Most of these patients were treated with a combination of isoniazid, paraaminosalicylic acid, and streptomycin; a few of them had received ethambutol or rifampicin. On the other hand, among children with miliary TB treated with HRZE/Eth at a South African hospital, 6 (14%) of 43 patients given prednisolone (2 mg/kg/day for 1 month, tapered off over the next month) died, whereas 7 (14%) of 51 patients who did not receive adjunctive steroids died (Hussey et al. 1991). Thus, it
is unclear whether routine use of steroids in miliary TB in the absence of meningeal disease is beneficial in patients receiving HRZE combination chemotherapy.

In a systematic review on the effect of steroids in pulmonary TB, the radiological and clinical improvement was faster with the use of steroids (Smego and Ahmed 2003). However, rifampicin-based chemotherapy was used in only 2 of the 11 trials included in this review. The incremental benefit of steroids in pulmonary TB as an adjunct to the present-day HRZE regimen is unclear (Critchley et al. 2014). Nonetheless, anecdotal evidence suggests that steroids might improve clinical outcomes in patients with TB-related ARF. In a study from South Korea (Kim et al. 2008), among patients with ARF caused by tuberculous pneumonia, the mortality was 57% among 30 patients treated with steroids as compared to 78% among 36 patients who were not treated with steroids. In an extended cohort of patients from the same center (Yang et al. 2016), unadjusted 90-day mortality did not differ by steroid use in 124 patients who had pulmonary TB with ARF, including 33 patients with miliary TB. However, adjunctive steroid use was associated with a lower odds of death on propensity score adjusted analysis. Further, use of steroids was associated with an increased risk of nosocomial infections mostly pneumonia. On the other hand, ICUs with a policy of not using steroids have reported a lower mortality of 28% in patients with TB-ARDS (Muthu et al. 2017). However, most probable reason for this lower mortality was that the patients were much younger compared to previous studies which have reported a high mortality, often in excess of 50% (Erbes et al. 2006; Deng et al. 2012; Yang et al. 2016; Duro et al. 2017).

The benefit of routine use of steroids in patients with ARDS (not TB-related) is a matter of disagreement and debate, with some evidence to suggest that early use might be beneficial (Bein et al. 2016; Thompson and Ranieri 2016; Seam and Suffredini 2016; Meduri et al. 2016). On the other hand, there is some evidence for modest mortality benefit when steroids are used in hospitalized patients with community-acquired pneumonia (Siemieniuk et al. 2015). As stated earlier, while it is widely known that adjunctive steroids are beneficial in TB meningitis and possibly pericarditis, a meta-analysis indicated that steroids might confer a mortality benefit irrespective of the organ affected by TB and whether rifampicin-based regimen is used or not (Critchley et al. 2013). In the face of this uncertainty, clinicians might consider using steroids in patients with TB-related ARF provided there are no contraindications and drug-resistant TB is unlikely.

Ventilatory management of ARF/ARDS in TB is no different from that caused by other etiologies. These patients are managed according to the standard ARDSnet mechanical ventilation protocol. The initial severity of hypoxemia, static lung compliance, and other physiological parameters such as PEEP and $P_{\text{plateau}}$ in patients with TB-ARDS were found to be similar to non-TB patients with ARDS (Muthu et al. 2017). The time-trends in lung mechanics were also similar. Non-invasive ventilation, if effective, could obviate the need for endotracheal intubation in carefully selected patients (Agarwal et al. 2005; Utsugi et al. 2006). While there are only a few reports of successful use of NIV in TB-related ARDS, handful of large case series suggest that NIV could be effective in acute exacerbations of chronic
respiratory failure in patients with pulmonary TB sequelae (Esquinas et al. 2014). Extracorporeal membrane oxygenation (ECMO) has been successfully used in TB-ARF patients with refractory hypoxemia (Omote et al. 2016). Sivelestat sodium is an inhibitor of human neutrophil elastase approved for clinical use in Japan and the Republic of Korea. Utsugi et al. had described the successful use of sivelestat in an elderly patient with confirmed miliary TB and ARDS (Utsugi et al. 2006). However, subsequent reports were not encouraging. In a meta-analysis of six randomized trials, sivelestat did not improve the survival in patients with ARDS due to other causes (Pu et al. 2017).

16.9 Prognosis of TB Patients Requiring ICU Admission

Patients with TB-ARF often require mechanical ventilation for prolonged periods. A few studies indicate that TB-ARF is associated with a high mortality of up to 88% when compared to other causes of ARF (Levy et al. 1987; Mansoura et al. 2014; Piqueras et al. 1987). However, some studies do indicate that mortality due to TB-ARDS is not worse as compared to other causes of ARDS (Muthu et al. 2017; Penner et al. 1995). Factors like underlying destroyed lung, higher APACHE II/ SOFA scores on admission, hyponatremia, lower PaO₂/FiO₂ ratio, advanced age, and sepsis have been identified as risk factors for mortality (Sharma et al. 2006; Kim et al. 2008; Ryu et al. 2007; Lin et al. 2009). In a study of 85 miliary TB patients with ARDS from China, a shorter time to diagnosis, time from diagnosis to mechanical ventilation, and time to initiation of TB treatment were associated with survival (Deng et al. 2012). Complications which may be anticipated in mechanically ventilated TB patients include ventilator-associated pneumonia, pulmonary hemorrhage, pleural effusion or empyema and pneumothorax (Otu et al. 2018). A small study from Germany found that ICU-acquired complications like sepsis, nosocomial pneumonia, and acute renal failure contribute to mortality in TB patients admitted to the ICU (Erbes et al. 2006). Pneumothorax was observed in 14% of patients. It appears that pneumothoraces are common in TB patients receiving mechanical ventilation.

16.10 Recent Advances

Latent infections such as cytomegalovirus and herpes simplex virus are known to get reactivated in critically-ill patients (Walton et al. 2014). It has been recently suggested that reactivation of latent TB infection might occur in critically-ill patients as a result of stress and immunosuppression (Otu et al. 2018). However, no data exist to confirm or refute such a possibility. Of note, in a study from Taiwan, more than half of the ICU patients had indeterminate interferon-gamma release assay (IGRA) results due to a low mitogen response (Huang et al. 2016). Such indeterminate IGRA results were seen among patients with more severe illness.
16.11 TB Infection Control in the ICU

TB is spread by airborne droplet nuclei. Patients with active pulmonary TB admitted to ICU could transmit the infection to healthcare workers and visitors. ICU environments typically lack natural cross ventilation and are hotspots for nosocomial TB transmission. Moreover, aerosol generating procedures are frequently performed in the ICU setting, increasing the risk of TB transmission. Under ideal circumstances, patients with presumed or diagnosed infectious TB disease should be placed in an airborne infection isolation room constantly maintained at a negative pressure of at least 0.01 in. water gauge (2 Pa) lower than its surroundings with at least 12 air changes per hour, and the exhaust air from these rooms should not be recirculated or else done so only after HEPA filtration (Jensen et al. 2005). Unfortunately, such isolation rooms are seldom available in most resource-limited settings where TB is prevalent. In such situations, every attempt should be made to house the patient in a single room with sufficient natural ventilation and facilities for appropriate life support. In intubated patients, bacterial or heat and moisture exchange (HME) filters, capable of filtering particles of 0.3 μm size with an efficiency of >95%, should be placed on the expiratory limb of the breathing circuits and periodically replaced (Jensen et al. 2005). All persons entering the isolation room should wear at least a properly fitting disposable N95 respirator. For infection control purposes, a patient with TB is considered infectious for up to 14 days of effective TB treatment (Jensen et al. 2005).

Endotracheal intubation of TB patients carries a high risk of exposure to infectious aerosols. Likewise, aerosols are likely to be generated during airway suctioning, non-invasive ventilation, high-frequency oscillatory ventilation, tracheostomy, chest physiotherapy, nebulizer treatment, sputum induction, and bronchoscopy (Canadian Agency for Drugs and Technologies in Health 2011). A recent study on aerosol production during such medical procedures, however, did not support this notion (Li et al. 2017). The findings of this study should be interpreted with caution, and should not change current infection control practices.

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