

# ISCCM Position Statement on the Approach to and Management of Critically Ill Patients with Tuberculosis

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Received on: 02 July 2024; Accepted on: 24 July 2024; Published on: 10 August 2024

## ABSTRACT

Tuberculosis (TB) is an important cause of morbidity and mortality globally. About 3–4% of hospitalized TB patients require admission to the intensive care unit (ICU); the mortality in these patients is around 50–60%. There is limited literature on the evaluation and management of patients with TB who required ICU admission. *The Indian Society of Critical Care Medicine (ISCCM)* constituted a working group to develop a position paper that provides recommendations on the various aspects of TB in the ICU setting based on available evidence. Seven domains were identified including the categorization of TB in the critically ill, diagnostic workup, drug therapy, TB in the immunocompromised host, organ support, infection control, and post-TB sequelae. Forty-one questions pertaining to these domains were identified and evidence-based position statements were generated, where available, keeping in focus the critical care aspects. Where evidence was not available, the recommendations were based on consensus. This position paper guides the approach to and management of critically ill patients with TB.

**Keywords:** Antituberculous treatment, Critically ill, Immunocompromised host, Infection prevention and control, Organ support, Tuberculosis.

*Indian Journal of Critical Care Medicine* (2024): 10.5005/jp-journals-10071-24783

## INTRODUCTION

Tuberculosis (TB) is an important cause of morbidity and mortality globally. In 2021, around 10.6 million people were estimated to be infected with TB and 1.6 million died.<sup>1</sup> This important communicable disease is more prevalent among marginalized socio-economic status communities with limited access to healthcare.<sup>2</sup> In India, 2.77 million people were estimated to be affected with TB in 2022 with a mortality of 0.32 million and an incidence of 196 per 100,000 population.<sup>3</sup> About 3–4% of hospitalized TB patients require admission to the intensive care unit (ICU); the mortality in this subset of patients is around 50–60%.<sup>4,5</sup> Despite the burden of TB and the likelihood of such patients needing ICU care, there is limited literature on the management of patients with TB who require ICU admission. *The Indian Society of Critical Care Medicine (ISCCM)* position paper aims to bridge this gap by providing recommendations on the various aspects of TB in the ICU setting.

## METHODS

The ISCCM convened a conclave meeting on 16th July 2023 to identify the writing group for TB and to set out the objectives for the position statement. The working group comprised 19 members including a chair and co-chair and 4 women with considerable experience in TB, who are working in academic and private institutions across India in critical care, respiratory medicine, infectious disease, neurology, and microbiology. The domains were deliberated and outlined at the conclave and broad questions were constructed. Seven subgroups were created, each with a coordinator, to refine and finalize the questions and work on the domains. The domains were as follows:

- Categorization of TB in critically ill.
- Diagnostic workup.

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- Drug therapy.
- TB in the immunocompromised host.
- Organ support.
- Infection control, and
- Post-TB sequelae.

Relevant articles on the subject were identified by a literature search undertaken by each of the subgroups, using search terms pertaining to the domains allocated to them. A tutorial on how to perform a PubMed® search was done at the conclave to ensure that authors had a clear understanding on how to perform a thorough literature search using the appropriate search terms. The recommendations of the subgroups were made based on available evidence. Grading of recommendations was not done as there was limited research on this topic in terms of randomized clinical trials, and hence it was decided at the conclave that this would be a position paper and not a guideline. Where evidence was not available, the recommendations were based on consensus. Although a Delphi process would have been ideal to make the

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**How to cite this article:** Chacko B, Chaudhry D, Peter JV, Khilnani G, Saxena P, Sehgal IS, *et al.* ISCCM Position Statement on the Approach to and Management of Critically Ill Patients with Tuberculosis. *Indian J Crit Care Med* 2024;28(S2):S67–S91.

**Source of support:** Nil

**Conflict of interest:** None

recommendations where evidence was not available, this was not undertaken. The recommendations of each of the subgroups were reviewed by a three-member core group (DC, BC, JVP), and position statements and the commentary were refined, ensuring that they were accurate and reflected current evidence. Care was taken to ensure that the recommendations focused on the approach to, the evaluation and management of a critically ill patient with TB. The executive summary provides a quick reference guide on the approach to and management of critically ill patients with TB.

### Executive summary

No.	Question	Position statement
Categorization of TB		
1	How should TB be categorized in the critically ill?	In the critically ill patient, TB should be categorized as pulmonary and extrapulmonary TB.
2	When should TB be suspected in critically ill patients?	TB should be considered in ICU patients with risk factors for developing TB, particularly in high endemic areas, in the setting of nonresolving community-acquired pneumonia (CAP), acute respiratory distress syndrome (ARDS), meningitis, intracranial or bony lesions, pleural or pericardial effusion, psoas abscess, and multiorgan failure.
3	What are the reasons for ICU admission in patients with TB?	Patients with TB are usually admitted to the ICU with a process that is directly related to TB or due to secondary processes.
4	What should the diagnostic approach be in patients with suspected pulmonary TB?	Patients with a high risk of TB, with compatible clinical features and radiological abnormalities, should undergo tests for microbiological confirmation of TB.
5	What should the diagnostic approach be in patients with suspected CNS TB?	The diagnostic approach of a critically ill patient with suspected CNS TB is based on clinical features, imaging, and cerebrospinal (CSF) analysis.
6	When would you suspect drug-resistant TB in ICU patients with suspected TB?	Given the high level of drug resistance to TB, drug resistance must be ruled out in all patients who are admitted to the ICU with suspected TB. Multidrug resistance must be particularly considered in patients >40 years, those with prior history of TB, poor compliance, or failure to TB treatment, and in HIV co-infection.
Diagnostic workup		
7	Is there a role of microscopy in the diagnosis of TB?	Microscopy remains the primary method for diagnosing M. tuberculosis infection and is important in detecting patients with high bacterial load.
8	What is the role of molecular testing in the diagnosis of TB in critically ill?	Molecular testing (Xpert MTB/Rif or Xpert Ultra) should be performed initially on ALL samples obtained from pulmonary or extrapulmonary sites to arrive at a rapid diagnosis of TB and for detecting rifampicin-resistance. LPA, recommended by the guidelines for the PMDT in India, must be performed to further evaluate for drug resistance. The current reference for drug resistance is phenotypic DST using solid (LJ) medium and liquid (MGIT) medium cultures.
9	What is the role of cultures in the diagnosis of TB?	Culture remains the gold standard for TB diagnosis for pulmonary and extrapulmonary TB as it enables accurate identification and subsequent susceptibility testing. However, the turnaround time is high.
10	Is there a role for ADA in the diagnosis of extrapulmonary TB?	ADA is a useful adjunct test in the diagnosis of extrapulmonary TB. It must be used in conjunction with other tests to diagnose TB.
11	What is the role of invasive diagnostic tests for TB?	Invasive tests such as bronchoscopic procedures, biopsy techniques, and conventional surgery may be required to diagnose pulmonary and extrapulmonary TB when noninvasive and less invasive tests fail to give a diagnosis

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## Executive summary (Contd...)

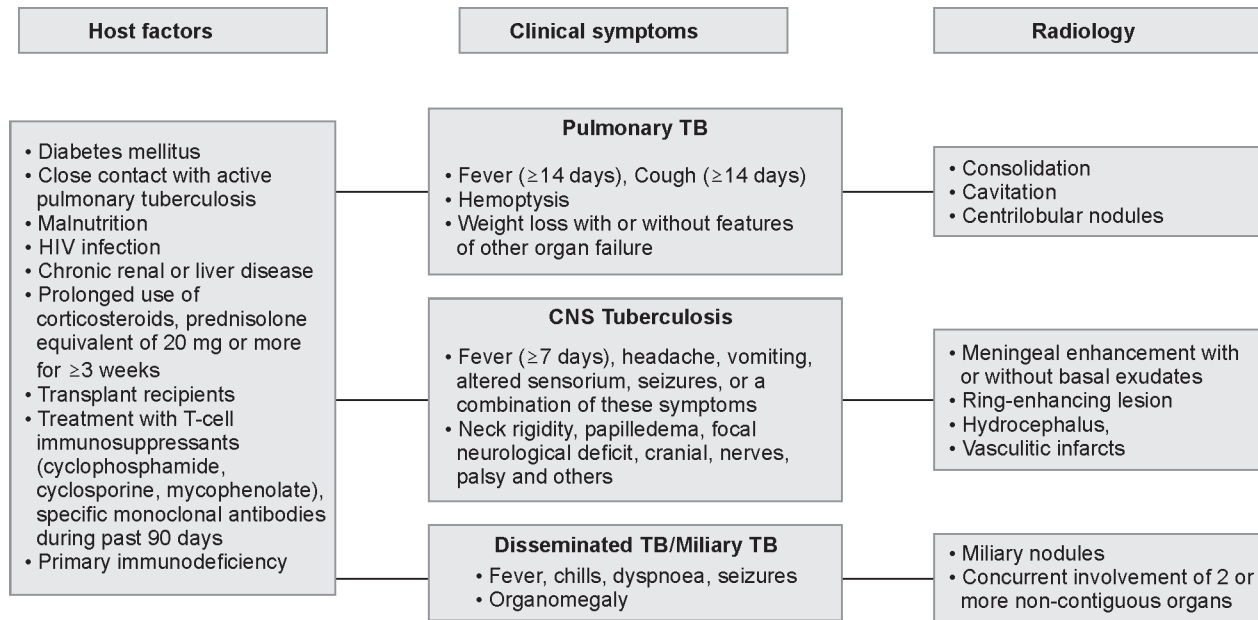
No	Question	Position statement
12	What is the role of imaging in the diagnosis of TB?	Chest radiography is the mainstay imaging for pulmonary parenchymal TB. CT and MRI are used for the evaluation of pulmonary and extrapulmonary TB.
Drug therapy		
13	When should anti-TB be initiated in a critically ill patient?	Timely initiation of anti-TB drugs is essential for treatment success, particularly in those with high disease severity.
14	Which anti-TB regimen should be initiated in a critically ill patient?	As per the National TB Eradication Program (NTEP), a weight based, standard anti-TB regimen with four drugs should be initiated unless drug resistance is suspected or demonstrated. Higher doses of anti-TB drugs may be considered in severe disease.
15	Do enterally administered anti-TB drugs achieve therapeutic levels in critically ill patients?	Absorption of enterally administered anti-TB drugs is reduced in the critically ill patient and if administered when continuous enteral feeds are given. Therapeutic levels may be achieved with enteral pyrazinamide but not with INH, rifampicin, and ethambutol.
16	Is there a role for higher doses of anti-TB drugs or IV anti-TB drugs in TB meningitis and severe illness?	Higher doses of anti-TB drugs or intravenous preparations where available, may be considered in TB meningitis and severe illness.
17	What is the role of other intravenous antibiotics in TB?	Although several IV antibiotics such as aminoglycosides, quinolones, linezolid, and carbapenems are effective against TB, these second-line drugs should be used only in the setting of DR-TB, life-threatening TB, and in those who do not tolerate first-line anti-TB drugs.
18	How should DR-TB be treated in the ICU?	Patients with DR-TB should be enrolled in the NTEP if not already enrolled. The NTEP has adopted bedaquiline-based DR-TB regimen in India based on WHO guidelines. Treatment should be started in consultation with respiratory physicians and NTEP. The recommended drugs and duration of treatment in such patients are guided by program management of DR-TB in India.
19	Is there a risk of drug-drug interaction with commonly used anti-TB drugs?	There are significant drug-drug interactions with the commonly used anti-TB drugs. Clinicians need to be familiar with the common interactions in the ICU setting.
20	What is the role of steroids in TB?	Corticosteroids may be effective in reducing clinically relevant adverse outcomes in some forms of TB.
21	Is there a role for TDM in DR-TB?	There is insufficient evidence to recommend routine TDM during treatment of DR-TB.
22	How do risk prediction scores perform in TB?	Risk prediction scores should not be relied on for mortality prediction in TB.
TB in the immunocompromised host		
23	Does the immunocompromised state predispose an individual to reactivation of latent TB or the acquisition of TB?	Since immunocompromised patients are at risk for TB, the clinical suspicion should be high in patients admitted to the ICU. The interpretation of tests for latent TB infection (such as TST and IGRA) are likely to be influenced by immunosuppression and the severity of critical illness.
24	Is the clinical presentation of TB in the immunocompromised individual similar to that of the immunocompetent host?	In an immunocompromised host, the clinical presentation of TB may be more insidious and likely to be disseminated. TB should be suspected when there is unexplained worsening of clinical status. The surveillance for atypical presentations of TB should be robust in order to pick them up early.
25	What should the diagnostic work be in the immunocompromised host who is suspected to have TB infection?	Taking into consideration the indolent nature of TB in the immunocompromised patient, cross sectional imaging should be considered early to direct diagnostic sampling. Early invasive sampling including bronchial lavage and/or biopsy is advocated in these patients.
26	What would the approach be to the management of TB in the setting of intestinal malabsorption?	In patients with anticipated poor enteral uptake of ATT (short bowel, gut GVHD, severe multiorgan dysfunction with high-dose vasoactive medications), parenteral ATT may be considered along with TDM.
27	What would the approach be to IRIS in TB?	IRIS should be suspected when there is paradoxical worsening of symptoms, typically seen when immunosuppression is reduced or reversed. IRIS can also occur in the immunocompetent host. A course of steroids should be considered.
Organ support		
28	Is the ventilatory management of respiratory failure due to TB different from the ventilatory management of respiratory failure due to other infective etiologies?	There is limited data on the management of respiratory failure in patients with TB. The management of respiratory failure in patients with TB should be along the same lines of management as with other infective etiologies of hypoxemic and hypercapnic respiratory failure.

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## Executive summary (Contd...)

No	Question	Position statement
29	Should noninvasive respiratory support be considered in the management of acute respiratory failure due to TB?	The use of noninvasive respiratory support including HFNC is challenging given their tendency to cause aerosol dispersion and spread of infection to HCWs. It is preferable to use them in isolation facilities with adequate precautions by staff.
30	Is there a role for ECMO support in TB?	There is limited evidence for the use of ECMO in TB. It may be considered in TB in the setting of refractory respiratory or cardiac failure.
31	How should massive hemoptysis be managed?	Patients with massive or life-threatening hemoptysis should be managed in an ICU with focus on airway and hemodynamic stabilization, evaluation of the source of bleed by CT angiogram or bronchoscopy and consideration of bronchial artery embolization as an early treatment option. Nebulized and/or intravenous tranexamic acid may reduce the volume of hemoptysis.
32	When should tracheostomy be considered in patients ventilated for TB?	The indications and timing of tracheostomy in patients admitted to the ICU with TB is similar to that of other patients admitted to critical care. There is inconclusive evidence to recommend early tracheostomy in patients with TB.
33	What is the optimal management of hypotension due to adrenal insufficiency and septic shock with mycobacteremia (Landouzy sepsis)?	In TB, shock may be due to adrenal insufficiency, secondary bacterial sepsis, or mycobacteremia. Shock should be managed along the same lines as the management of septic shock. Early initiation of anti-TB treatment is important. Steroids are indicated for refractory septic shock, adrenal insufficiency, and shock due to mycobacteremia.
34	What is the optimal management of renal failure in patients with TB?	Renal failure in TB should be managed along the same lines as the approach to the management of acute kidney injury in the setting of other infectious diseases. Drug dosing should be optimized for renal function, and nephrotoxic agents should be avoided.
35	Is there a role for first line anti-TB drugs in patients with liver involvement in TB?	Patients with liver involvement due to TB should be started on standard four-drug regimen, irrespective of baseline liver function tests.
36	Is there a role for low-volume PLEX in patients with liver dysfunction due to TB or DILI?	In patients with ALF or ACLF due to anti-TB drugs-induced DILI, low-volume plasma exchange may be considered especially in those who fulfill the King's College criteria for liver transplantation but do not have access to the same.
Infection control		
37	What are the recommended isolation systems for patients with presumed or documented infectious TB in the ICU?	Respiratory isolation of individuals with confirmed or suspected infectious TB is advised, ideally in an AIIR equipped with a HEPA filter and negative pressure. Closed suctioning is recommended for intubated patients. The application of a bacterial filter to the ventilator tubing's expiratory limb may reduce the transmission of infection.
38	What are the key IPC measures for HCWs taking care of patients with suspected or confirmed tuberculosis in the ICU?	Healthcare professionals entering rooms of patients with suspected or confirmed contagious TB disease must wear a properly sized N95 disposable respirator.
39	When can respiratory isolation precautions be discontinued for critically ill patients with pulmonary TB?	For sputum-positive rifampicin susceptible TB patients, a minimum of 2 weeks of isolation is suggested, while on effective anti-TB treatment.
40	Is there a role for routine testing and surveillance of HCWs managing infectious TB patients?	The role and benefit of regular testing and surveillance for TB infection among HCWs in the ICU, using TST or IGRA, in endemic countries like India is unclear.
41	Post TB sequelae: What are the reasons for ICU admission?	Post-TB sequelae patients may present to the ICU with respiratory failure due to exacerbation of obstructive airway disease or restrictive fibrotic lung disease, pulmonary hypertension, hemoptysis due to bronchiectasis, aspergillosis or vascular causes or with secondary infections. There are currently no evidence-based recommendations for the investigation and management of PTLA.

ACLF, acute on chronic liver failure; ADA, adenosine deaminase; AIIR, airborne infection isolation room; ALF, acute liver failure; ARDS, acute respiratory distress syndrome; ATT, antituberculous treatment; CAP, community-acquired pneumonia; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; DILI, drug-induced liver disease; DR-TB, drug resistant TB; DST, drug sensitivity testing; ECMO, extracorporeal membrane oxygenation; GVHD, graft vs host disease; HCW, healthcare worker; HEPA, high efficiency particulate air; HFNO, high frequency nasal oxygen; HIV, human immunodeficiency virus; IGRA, interferon gamma release assay; IRIS, immune reconstitution inflammatory syndrome; ICU, intensive care unit; ICP, intracranial pressure; IV, intravenous; LJ, Lowenstein-Jensen medium; LPA, line probe assay; MGIT, Mycobacteria growth indicator tube; MRI, magnetic resonance imaging, NTEP, National Tuberculosis Eradication Program; TB, tuberculosis, TDM, therapeutic drug monitoring; TST, tuberculin skin test; PMDT, programmatic management of drug-resistant tuberculosis; PTLA, post-TB lung abnormality; PLEX, plasma exchange; WHO, World health organization



**Fig. 1:** When to suspect TB in the critically ill. The figure demonstrates an algorithmic approach to the diagnosis of tuberculosis (TB) in the critically ill. Several risk factors (host factors) predispose to the development of TB. The symptoms in pulmonary, central nervous system (CNS), and disseminated/miliary TB as well as the radiological features in these forms of TB are listed

## CATEGORIZATION OF TB IN CRITICALLY ILL

### Q1: How should TB be Categorized in the Critically ill?

*Position statement:* In critically ill patients, TB should be categorized as either pulmonary or extrapulmonary TB.

*Commentary:* TB is generally categorized as pulmonary and extrapulmonary TB.<sup>6,7</sup> The same classification is applicable to the critically ill.<sup>8</sup>

### Q2: When should TB be Suspected in Critically Ill Patients?

*Position statement:* TB should be considered in ICU patients with risk factors for developing TB, particularly in high endemic areas, in the setting of nonresolving community-acquired pneumonia (CAP), acute respiratory distress syndrome (ARDS), meningitis, intracranial or bony lesions, pleural or pericardial effusion, psoas abscess, and multiorgan failure.

*Commentary:* Patients with pulmonary TB can present acutely or sub-acutely. Tuberculosis should be suspected in a patient who presents with fever and cough of  $\geq 14$  days with hemoptysis, weight loss, or features of organ dysfunction, particularly in high endemic areas and in those with risk factors for developing TB (Fig. 1). Tuberculosis can present as CAP<sup>9</sup> or ARDS<sup>10-12</sup> or life-threatening hemoptysis. The presence of miliary or centrilobular nodules, consolidation with or without cavitation, and pleural effusion should raise the clinical suspicion of TB as a cause of respiratory failure.<sup>13</sup> Patients with extrapulmonary TB may present with acute respiratory failure, septic shock, and multiorgan failure.<sup>14</sup> Those with central nervous system (CNS) TB (meningitis, meningoencephalitis, space-occupying lesion, epidural abscess causing cord compression, or a combination of these) and pericardial TB may require ICU admission.<sup>8,9</sup> Although isolated involvement of other organs such as the liver,<sup>15</sup> gastrointestinal,<sup>16</sup> or urogenital<sup>17</sup> is uncommon in TB patients admitted to the ICU, such patients may require ICU care postoperatively if surgical intervention is required or if they develop

organ dysfunction. Disseminated TB should be suspected when there is concurrent involvement of two or more noncontiguous sites; miliary pattern on chest X-ray is a common finding.<sup>18</sup>

### Q3: What are the Reasons for ICU Admission in Patients with TB?

*Position statement:* Patients with TB are usually admitted to the ICU with a process that is directly related to TB or due to secondary processes.

*Commentary:* Patients with TB may require admission to the ICU for a process that is directly related to TB (pulmonary or extrapulmonary manifestations) or due to secondary processes (Table 1). In pulmonary TB, patients may present with massive hemoptysis that requires airway protection and intubation, severe hypoxia due to superimposed pneumonia or ARDS, or pneumothorax. Patients with pulmonary or extrapulmonary TB can also present with respiratory failure due to pulmonary embolism.<sup>19</sup> Isolated massive pleural effusion as a cause of hypoxia is uncommon in TB. Patients with extrapulmonary TB may present with seizures, electrolyte abnormalities, features of hydrocephalus, pericardial tamponade, sepsis, multiorgan dysfunction, or complications related to drug therapy.<sup>20,21</sup> In a series of 48 patients admitted to the ICU with TB meningitis, 47 patients were referred because of neurological deterioration; 22 were comatose at admission; 36 patients (75%) required ventilatory support, and 16 needed neurosurgery.<sup>22</sup>

### Q4: What should the Diagnostic Approach be in Patients with Suspected Pulmonary TB?

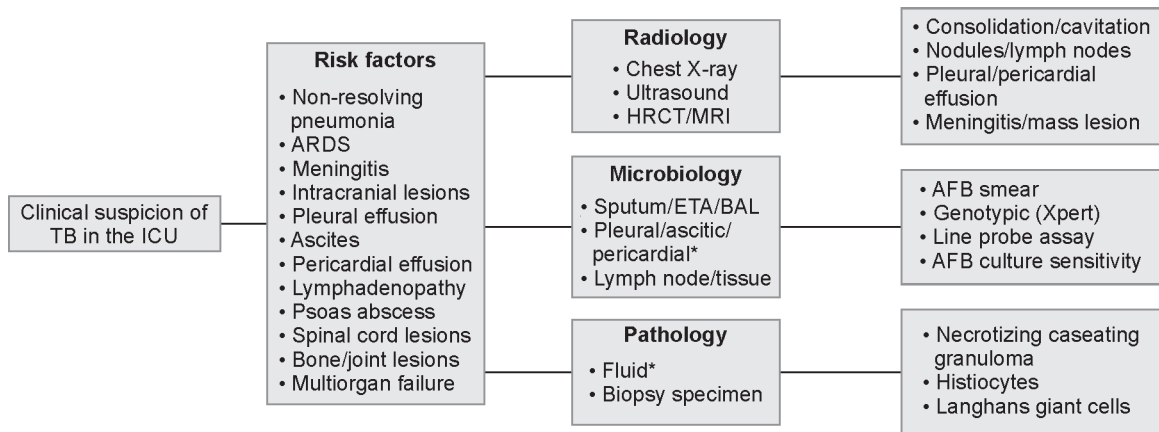
*Position statement:* Patients with a high risk of TB, with compatible clinical features and radiological abnormalities, should undergo tests for microbiological confirmation of TB.

*Commentary:* The guidelines followed in the radiological and microbiological evaluation and confirmation of TB are similar to those of nonICU patients.<sup>23</sup> Patients with a high risk of TB

**Table 1:** Indications for ICU admission in tuberculosis<sup>8</sup>

Site	Primary process	Secondary process*
Parenchymal lung disease	Nonresolving community-acquired pneumonia (CAP)	Superimposed bacterial infection
	TB acute respiratory distress syndrome (ARDS)	Fungal infection (e.g., Aspergillosis)
	Fibro-cavitary disease	TB sequelae (fibrosis, cavitation)
	Miliary TB	IRIS
	TB bronchopneumonia	Hemoptysis (Rasmussen's aneurysm)
Pleural disease	Massive pleural effusion	Pneumothorax
	TB empyema	
CNS disease	Subacute or chronic TB meningitis	Coma or altered conscious state (multi-factorial causes)
	Basal arachnoiditis due to TB	Noncommunicating hydrocephalus
	Tuberculoma	Focal neurologic signs (cranial nerve palsy, hemiparesis)
	TB brain abscess	Seizures
	Spinal arachnoiditis	Electrolyte abnormalities
Pericardial disease	Pericardial tamponade	Heart failure
	Constrictive pericarditis	Organ dysfunction due to heart failure
Abdominal TB	Massive ascites	Secondary bacterial peritonitis
	Intestinal obstruction or perforation (ileocecal TB)	Sepsis
Disseminated TB	Respiratory failure due to miliary TB	Secondary sepsis
	Multiorgan dysfunction	
	Hypotension due to adrenal involvement	
Musculoskeletal TB	Psoas abscess	Paraplegia
		Superimposed bacterial infection

ARDS, acute respiratory distress syndrome; CAP, community-acquired pneumonia; CNS, central nervous system; ICU, intensive care admission; IRIS, immune reconstitution inflammatory syndrome; TB, tuberculosis. \*In addition patients on treatment for tuberculosis (TB) may present with drug toxicity due to antitubercular drugs, intercurrent infections, pulmonary embolism, cardiac or neurological events unrelated to the primary TB process



**Fig. 2:** Diagnostic approach to TB in the critically ill. The figure outlines a diagnostic approach to tuberculosis (TB) in the intensive care unit (ICU). Several clinical features would raise the suspicion of TB. TB may be confirmed with a combination of tests that include radiology, microbiology, and histopathology. ARDS acute respiratory distress syndrome, HRCT high resolution computed tomography, MRI magnetic resonance imaging, ETA endotracheal aspirate, BAL bronchoalveolar lavage, AFB acid fast bacilli. \* Pleural, pericardial, or ascitic fluid can be sent for microbiology and histopathology

with compatible clinical and radiological abnormalities should be investigated further to confirm the diagnosis of TB. For microbiological confirmation, sputum, endotracheal aspirate, bronchial washing, or bronchoalveolar lavage should be sent for microscopy, molecular tests, and cultures (Figs 1 and 2). Biopsy may be required in some situations to confirm the diagnosis. In an intubated patient, microbiological sampling of the lower respiratory tract, by means of bronchoalveolar lavage, is likely to improve the yield and facilitate the diagnosis of pulmonary TB.<sup>24,25</sup>

The role of tuberculin skin test (TST) and interferon-gamma release assay (IGRA) in the diagnosis of TB merit mention. These tests

are used for diagnosing latent TB infection (LTBI).<sup>26</sup> Neither of the tests predicted the subsequent development of active TB among household contacts of pulmonary TB during follow-up.<sup>26</sup> Its role in the diagnosis of LTBI in high-prevalence areas and its relevance in the ICU are questionable.

### Q5: What should the Diagnostic Approach be in Patients with Suspected CNS TB?

*Position statement:* The diagnostic approach of a critically ill patient with suspected CNS TB is based on clinical features, imaging, and cerebrospinal (CSF) analysis.

**Commentary:** The evaluation of a patient with suspected CNS TB is the same as a nonICU patient. Any patient presenting with fever, headache, altered sensorium, seizures, focal neurological deficits, or a combination of these symptoms for more than 1 week should be investigated for CNS TB. Clinical examination may reveal neck rigidity, cranial nerve palsy, focal neurological deficits, and signs of raised intracranial pressure (ICP), including papilledema. Patients presenting with features of meningitis could also have abnormalities on chest imaging. The diagnostic approach would involve imaging (computed tomography [CT] and/or magnetic resonance imaging [MRI] with contrast), CSF analysis, and microbiological confirmation (Figs 1 and 2).<sup>27-29</sup>

Although molecular diagnostic tests such as the Xpert/Rif can enable rapid diagnosis of CNS TB, CSF culture is likely to increase the sensitivity of TB meningitis diagnosis.<sup>30</sup> Since cultures take 6–8 weeks, anti-TB treatment should be initiated immediately if there is a high probability of TB even when molecular tests are negative as it does not rule out CNS TB given their modest sensitivity. When the index of suspicion is high, it is important to also look for evidence of active TB elsewhere. In immune-deficiency states, it is important to evaluate for a concomitant cryptococcal meningitis.<sup>31</sup>

#### Q6: When would you Suspect Drug-resistant (DR)-TB in Patients Admitted to ICU with Suspected TB?

**Position statement:** Given the high prevalence of DR-TB, drug resistance must be ruled out in all patients who are admitted to the ICU with suspected TB. Multidrug resistance must be particularly considered in patients >40 years, those with prior history of TB, poor compliance, or failure to TB treatment, and in human immunodeficiency virus (HIV) co-infection.

**Commentary:** In 2022 TB was reported as the biggest DR airborne epidemic.<sup>32</sup> The term DR-TB<sup>33,34</sup> encompasses (a) *mono resistance* to a first-line anti-TB drug, (b) *multidrug-resistant TB* (MDR-TB) that are resistant to isoniazid and rifampicin, (c) *pre-extensively drug-resistant TB* (pre-XDR-TB MDR/RR-TB) that are also resistant to a fluoroquinolone, and (d) *extensively drug-resistant TB* (XDR-TB) where the isolates are resistant to other important medications including bedaquiline and/or linezolid.

In India, DR-TB was found to be prevalent in 24.9% of newly diagnosed patients and in 58.4% of patients who had received prior treatment; 18.8% of patients with HIV and TB co-infection had drug resistance.<sup>35</sup> Multidrug-resistant ranged from 3.5 to 26.7% in treatment naïve and in patients who had received prior treatment respectively.<sup>35</sup> A significant increase in MDR ( $p < 0.001$ ) of 12% over time was reported from a tertiary care hospital in New Delhi (4.7% in 2000 to 19.8% in 2012).<sup>36</sup> The global pooled prevalence of MDR-TB was 11.6% (95% CI, 9.1–14.5) in a review of 148 studies<sup>37</sup> with substantial heterogeneity ( $I^2$  99.6) and a sample size of 3,18,430 individuals.

The risk factors for MDR-TB vary depending on the area. An increased risk of MDR-TB was found in a meta-analysis among patients  $\geq 40$  years of age who were unemployed, did not have health insurance, had a positive smear, had not completed or failed their TB treatment, had an adverse drug reaction, were nonadherent, had HIV, COPD, or had an infection with *M. tuberculosis Beijing*.<sup>38</sup> Male gender and a history of prior TB therapy are risk factors for drug resistance in extrapulmonary TB.<sup>39</sup>

## DIAGNOSTIC WORKUP

### Q7: Is there a Role of Microscopy in the Diagnosis of TB?

**Position statement:** Microscopy remains the primary method for diagnosing *M. tuberculosis* infection and is important in detecting patients with high bacterial load.

**Commentary:** The sensitivity of smear and microscopy for diagnosing *M. tuberculosis* ranges from 20 to 80% and is low in pediatric TB, extra-pulmonary TB, or TB with HIV infection.<sup>40</sup> Ziehl-Neelsen stain involving carbol fuchsin for acid-fast staining is rapid, cheap, and affordable in resource-limited settings. Microscopy is important in detecting patients with pulmonary TB with high bacterial load and high risk of transmission. Fluorescent microscopy enhances the sensitivity of smear microscopy as it increases productivity with light-emitting diodes.<sup>41,42</sup> Microscopy cannot distinguish between viable and dead bacilli and is not useful for early detection of treatment failure or drug resistance.

### Q8: What is the Role of Molecular Testing in the Diagnosis of TB in the Critically Ill?

**Position statement:** Molecular testing (Xpert MTB/Rif or Xpert Ultra) should be performed initially on all samples obtained from pulmonary or extrapulmonary sites to arrive at a rapid diagnosis of TB and to detect rifampicin-resistance. Line probe assays (LPAs), recommended by the guidelines for the Programmatic Management of Drug-Resistant Tuberculosis (PMDT) in India, must be performed to further evaluate for drug resistance. The current reference for drug resistance is phenotypic drug susceptibility testing (pDST) using solid Lowenstein-Jensen (LJ) medium and the liquid mycobacteria growth indicator tube (MGIT) medium cultures.

**Commentary:** In a critically ill patient, time is highly crucial so early diagnosis and initiation of treatment is important. In adults with suspected pulmonary TB, Xpert MTB/RIF or Xpert MTB/RIF Ultra or TrueNAT should be used as the initial diagnostic test for TB and for detecting rifampicin resistance in sputum.<sup>43,44</sup> Xpert Ultra performs slightly better than Xpert MTB/Rif (Table 2).<sup>45</sup>

The performance of Xpert for samples obtained from pulmonary and extrapulmonary sites, when compared with culture or composite reference standard (CRS), is summarized in Table 2.<sup>45-48</sup> In adults and children with signs and symptoms

**Table 2:** Performance of the Xpert test in various forms of TB

Type of TB	Number of studies/specimens	Comparator	Sensitivity (95% CI)	Specificity (95% CI)
Pulmonary TB (Xpert) <sup>45</sup>	7	Culture	84.7% (78.6–89.9)	98.4% (97.0–99.3)
Pulmonary TB (Xpert Ultra) <sup>45</sup>	7	Culture	90.9% (86.2–94.7)	95.6% (93.0–97.4)
TB meningitis (Xpert) <sup>45</sup>	5	CRS	37% (25–50)	100%
TB meningitis (Xpert Ultra) <sup>46</sup>	6	CRS	64% (45–80)	100%
<i>Cochrane review</i>				
Pleural (Xpert) <sup>48</sup>	27	Culture	50.9% (39.7–62.8)	99.2% (98.2–99.7)

(Contd...)

**Table 2:** (Contd...)

Type of TB	Number of studies/specimens	Comparator	Sensitivity (95% CI)	Specificity (95% CI)
Pleural tissue (Xpert)	3	Culture	30.5% (3.5–77.8)	97.4% (92.1–99.3)
CSF (Xpert) <sup>48</sup>	29	Culture	71.1% (60.9–80.4)	98.0% (97.0 to 98.8)
Lymph node aspirate (Xpert)	17	Culture	87.6% (81.7–to 92.0)	86.0% (78.4–91.5)
Urine (Xpert) <sup>48</sup>	13	Culture	82.7% (69.6–91.1)	98.7% (94.8–99.7)
Peritoneal (Xpert)	16	Culture	59.2% (45.2–73.5)	97.9% (96.2–99.1)
Pericardial (Xpert) <sup>48</sup>	7	Culture	65.7% (46.3–81.4)	96.0% (85.8–99.3)
Genitourinary–urine (Xpert)	13	Culture	82.7% (69.6 to 91.1)	98.7% (94.8–99.7)
<b>Adults</b>				
Extrapulmonary TB (Xpert) <sup>47</sup>	572*	CRS	75% (70–80)	98% (97–100)
Lymph node (Xpert) <sup>47</sup>	279	CRS	90% (86–94)	71.5 (60–83)
CSF (Xpert)	45	CRS	53% (28 to 79)	100%
Pleural (Xpert)	159	CRS	30% (17–44)	100%
Peritoneal (Xpert) <sup>47</sup>	80	CRS	32% (12–51)	100%
<b>Children</b>				
Extrapulmonary TB (Xpert) <sup>47</sup>	8 (652*)	CRS	71% (63–79)	97% (95–99)
Lymph node (Xpert) <sup>47</sup>	6	CRS	80% (70–88)	94% (89–97)
CSF (Xpert) <sup>47</sup>	5	CRS	42% (22–63)	99% (95–100)

CI, confidence interval/credible interval; CRS, composite reference standard. \*number of specimens

of TB meningitis, the World Health Organization (WHO) strongly recommends that Xpert MTB/RIF or Xpert Ultra should be used in CSF as an initial diagnostic test for TB meningitis rather than smear microscopy and culture.<sup>49</sup> In a meta-analysis of six studies that used a CRS, Xpert Ultra had a pooled sensitivity of 64% and specificity of 100% for TB meningitis.<sup>46</sup> Although Xpert Ultra seems to represent a step forward in TB meningitis diagnosis, it cannot fully exclude TB meningitis.<sup>49</sup> The sensitivity of Xpert was high for lymph node samples (>80%) and low for pleural (30–50.9%) and peritoneal fluid (32–59.2%), while the specificity was generally above 85% for all extrapulmonary sites (Table 2).<sup>47,48</sup>

Testing for resistance to isoniazid (INH) and fluoroquinolone is important in settings where the prevalence of resistance is >5%.<sup>50</sup> Both Xpert MTB/RIF and Xpert Ultra perform similarly in detecting rifampicin resistance.<sup>45</sup> With regards to picking up multidrug resistance, the Xpert MTB/XDR assay<sup>51</sup> has high diagnostic accuracy and meets the WHO's minimum target product profile criteria for a next-generation DST. The performance of the various tests to detect drug resistance is summarized in Table 3. It is necessary to consider the reference sample under examination and the diagnostic accuracy of the test when interpreting the results of the quick diagnostic genomic DST.

Line probe assays are recommended to confirm and further evaluate drug resistance. The LPA test offers an advantage as it is directly performed on clinical samples, has a short turnaround time of 24–48 hours, and detects DR not only to first-line but also to second-line anti-TB drugs.<sup>52,53</sup> It has the advantage of rapid screening for MDR-TB in areas where the prevalence of DR-TB is high and enables timely initiation of appropriate anti-TB drugs. The performance of LPAs against the gold standard is provided in Table 3.<sup>54–59</sup>

The current reference method for assessing DR is pDST,<sup>60</sup> which is a sensitive diagnostic technique that uses cultured isolates exposed to bacterial growth in the presence of antibiotics.

Phenotypic drug susceptibility test is available using both solid (LJ) medium and liquid (MGIT) medium but critical concentrations are limited and available only for rifampicin, isoniazid, levofloxacin, moxifloxacin, bedaquiline, linezolid, clofazimine, amikacin, and streptomycin.<sup>61</sup> In general, a liquid culture medium is preferred. However, the disadvantages of cultures include a long turnaround time, an extremely labor-intensive and complex procedure, and the need for specialized infrastructure, which restricts its impact and accessibility.

Whole genome sequencing is a promising tool that is currently being evaluated to guide individualized clinical decisions for the most complicated TB-resistant cases, predict resistance to first- and second-line anti-TB, characterize hetero-resistance and mixed infections, study taxonomy and transmission dynamics, and discover targets involved in phenotypic resistance and resistance-conferring mutations.<sup>62</sup> Its role in the ICU setting is currently limited.

### Q9: What is the Role of Cultures in the Diagnosis of TB?

**Position statement:** Culture remains the gold standard for TB diagnosis for pulmonary and extrapulmonary TB as it enables accurate identification and subsequent susceptibility testing. However, the turnaround time is long.

**Commentary:** Cultures should be done on all samples even if a rapid diagnosis of TB is made on microscopy or molecular tests, since it enables accurate identification and subsequent susceptibility testing. The traditional LJ medium, the prototype of the traditional solid medium, is cost-effective and less likely to get contaminated. Liquid culture is faster and offers improved sensitivity.<sup>63</sup> The MGIT 960 technique is an advanced and semi-automated method for the cultivation of *M. tuberculosis* in a controlled and monitored system. In a study involving 14,597 isolates, 41% were positive by the MGIT 960 TB system while 24% grew on the conventional



**Table 3:** Performance of molecular tests against culture-based DST to detect drug-resistant TB

Test	Number of studies/specimens	Sensitivity	Specificity
<i>Near patient technology-automated or semi-automated NAAT assay</i>			
Xpert MTB/RIF <sup>54</sup>	48 studies, 8020 participants	Rifampicin resistance: 96% (94–97%)	Rifampicin resistance: 98% (98–99%)
Truenat MTB <sup>55</sup>	1 study, 250 participants	89.3% (66.0–87.4)	92.2% (87.2–95.6)
Truenat MTB <sup>55</sup>	1 study, 250 participants	81.7% (70.7–89.8)	94.9% (89.8–97.9)
Xpert MTB/XDR Cochrane review <sup>56</sup>	Isoniazid resistance 6 cohorts, 1083 participants	94.2% (87.5–97.4)	98.5% (92.6–99.7)
	Fluoroquinolone resistance 6 cohorts, 1021 participants	93.2% (88.1–96.2)	98.0% (90.8–99.6)
	Ethionamide resistance: 4 cohorts, 434 participants	98.0% (74.2–99.9)	99.7% (83.5–100.0)
	Amikacin resistance 4 cohorts, 490 participants	86.1% (75.0–92.7)	98.9% (93.0–99.8)
Xpert MTB/XDR <sup>57</sup>	1 study 497 participants	Isoniazid 96.8% Fluoroquinolones 90.0% Kanamycin, 70.0% Amikacin 83.3% Capreomycin 70.0% Ethionamide 61.8%	Isoniazid 95.8% Fluoroquinolones 98.3% Kanamycin 99.6% Amikacin 99.6% Capreomycin 99.6% Ethionamide 99.6%
Line probe assays			
GenoType® MTBDR assay <sup>58</sup> INH and Rifampicin resistance	10 studies, 3,349 specimens	INH 84.3% (76.6–89.8) Rifampicin 98.1%, (95.9–99.1)	INH Resistance 99.5% Rifampicin resistance 98.7%
GenoType® MTBDR assay <sup>59</sup> Fluoroquinolone resistance	9 studies, 1,771 participants	86.2% (74.6–93.0%)	
GenoType® MTBDR assay <sup>59</sup> Second line injectable drugs	8 studies, 1,639 participants	87.0% (38.1–98.6%)	99.5 (93.6–100.0%)
GenoType® MTBDR assay <sup>59</sup> XDR TB	6 studies, 1,420 participants	69.4 (38.8–89.0%)	99.4 (95.0–99.3%)

Values in parentheses indicate confidence intervals (CI) unless specified.

LJ medium within 6 weeks.<sup>64</sup> Typically, all positive MGIT cultures grow both *M. tuberculosis* complex (MTBC) and most nontuberculous mycobacteria (NTM). These need to be further characterized. Cultures increase the sensitivity in the diagnosis of extrapulmonary TB.<sup>27,48</sup>

### Q10: Is there a Role for Adenosine Deaminase (ADA) in the Diagnosis of Extrapulmonary TB?

**Position statement:** Adenosine deaminase is a useful adjunct test in the diagnosis of extrapulmonary TB. It must be used in conjunction with other tests to diagnose TB.

**Commentary:** Pleural fluid ADA is a useful diagnostic test for tuberculous pleural effusion. In a systematic review of 174 publications, the sensitivity, specificity, and diagnostic odds ratio were 92, 90, and 0.97%, respectively. The threshold used for ADA in the studies ranged from 40 to >65 IU/l. All studies however showed a high risk of bias.<sup>65</sup> In CNS TB, ADA has low to moderate diagnostic utility.<sup>66,67</sup> In one study, the widely used cut-off value of 10 U/l had a specificity of 82% and a sensitivity of 50%.<sup>67</sup> In abdominal TB, a meta-analysis of 24 articles demonstrated a pooled sensitivity and specificity of 93% and 95%, respectively.<sup>68</sup> In a study involving 105 patients with TB pericarditis, the sensitivity and specificity for ADA were 82.1 and 92.4%, respectively when a threshold of 40 U/l was used.<sup>69</sup>

### Q11: What is the Role of Invasive Diagnostic Tests for TB?

**Position statement:** Invasive tests such as bronchoscopic procedures, biopsy techniques, and conventional surgery may be required to diagnose pulmonary and extrapulmonary TB when noninvasive and less invasive tests fail to give a diagnosis.

**Commentary:** In the diagnosis of pulmonary TB, if a diagnosis cannot be made based on sampling of the respiratory tract, bronchoscopic procedures such as (BAL) may be required, targeting areas of radiographic abnormality.<sup>70</sup> Bronchoalveolar lavage is likely to improve the yield and facilitate the diagnosis of pulmonary TB.<sup>24,25</sup> If endobronchial lesions are observed, biopsies may be taken.<sup>70</sup> Transbronchial lung biopsies have now been largely replaced with endobronchial ultrasound (EBUS)-guided needle aspiration of lung lesions as well as paratracheal, subcarinal, and hilar lymphadenopathy.<sup>70</sup> Image-guided or surgical biopsy may be required for peripheral lung lesions.<sup>70</sup>

In extrapulmonary TB involving the pleura, pericardium, lymph nodes, bones and joints, bowel, peritoneum, kidney, fallopian tubes, and epididymis, noninvasive techniques may not be feasible and other methods may not be diagnostic. Many of these sites may be amenable to percutaneous aspiration and/or biopsy.<sup>71</sup> In disseminated TB, a diagnosis may also be obtained through

bone marrow, lung, or liver biopsy.<sup>71</sup> Samples must be subject to histopathological examination and cultures.

### Q12: What is the Role of Imaging in the Diagnosis of TB?

*Position statement:* Chest radiography is the mainstay imaging for pulmonary parenchymal TB. Computed tomography and MRI are used for the evaluation of pulmonary and extrapulmonary TB.

*Commentary:* In parenchymal disease of the lung due to TB, chest radiography remains the main process for the evaluation of TB. Computed tomography is more sensitive than radiography for the detection of lymphadenopathy.<sup>72</sup> Magnetic resonance imaging is superior to CT in the detection and assessment of CNS TB.<sup>72</sup> Contrast MRI is superior to CT for the evaluation of meningitis and its complications, including hydrocephalus as well as characterizing homogeneous or ring-enhancing tuberculoma, and miliary TB involving the brain.<sup>72</sup> Abdominal lymph nodes are best evaluated on CT.<sup>72</sup> F-FDG<sup>18</sup> PET may help differentiate active and inactive pulmonary TB and assess treatment response.<sup>73</sup> Since tubercular lesions demonstrate high F-FDG<sup>18</sup> uptake, it has the potential to be used for the diagnosis of spinal infections and monitoring treatment response in select cases of extrapulmonary TB.<sup>72</sup>

## DRUG THERAPY FOR TB

### Q13: When should Anti-TB be Initiated in a Critically ill Patient?

*Position statement:* Timely initiation of anti-TB drugs is essential for treatment success, particularly in those with high disease severity. *Commentary:* Early diagnosis and treatment are likely to improve outcomes in all forms of TB. In one study of TB patients with septic shock, early and appropriate anti-TB treatment appeared to improve mortality.<sup>74</sup>

### Q14: Which Anti-TB Regimen should be Initiated in a Critically Ill Patient?

*Position statement:* As per the National TB Eradication Program (NTEP), a weight based, standard anti-TB regimen with four drugs should be initiated unless drug resistance is suspected or demonstrated. Higher doses of anti-TB drugs may be considered in severe disease.

*Commentary:* As per the NTEP guidelines, a weight-based, standard anti-TB regimen with four drugs (rifampicin, isoniazid, pyrazinamide, and ethambutol) should be initiated unless drug resistance is suspected or demonstrated (Table 4). Higher doses of anti-TB drugs may be considered in severe disease.<sup>14,75,76</sup> For both adults and children, the WHO recommends an intensive treatment regimen with four drugs for 2 months, followed by a continuation regimen (rifampicin, isoniazid) for 4 months except for CNS TB and bone or joint TB.<sup>77</sup> However, the current RNTCP guideline advocates a three-drug regimen in the continuation phase (rifampicin, isoniazid, ethambutol) because of the risk of isoniazid mono-resistance.<sup>78</sup> Streptomycin is recommended instead of ethambutol in the intensive phase if vision is impaired or cannot be assessed.<sup>78</sup>

In critically ill patients, first-line enterally administered drugs appear to be superior to second-line parenteral drugs plus ethambutol. In a study of 178 critically ill patients, an alternative regimen that included IV levofloxacin plus oral ethambutol plus IM

streptomycin or IV amikacin, without rifampicin and isoniazid was associated with a significantly ( $p = 0.011$ ) higher (63.5%) mortality when compared with the mortality of 51.4% among 284 critically ill patients who were administered of rifampicin, INH, pyrazinamide, and ethambutol enterally.<sup>79</sup> There is some evidence that higher doses of the usual anti-TB drugs (e.g., rifampicin up to 35 mg/kg/d) are safe and may reduce the time to culture conversion and may be associated with better survival in severe disease.<sup>80,81</sup>

### Q15: Do Enterally Administered Anti-TB Drugs Achieve Therapeutic Levels in Critically Ill Patients?

*Position statement:* Absorption of enterally administered anti-TB drugs is reduced in critically ill patients and if administered when continuous enteral feeds are given. Therapeutic levels may be achieved with enteral pyrazinamide but not with INH, rifampicin, and ethambutol.

*Commentary:* Multiple factors alter drug pharmacokinetics in critical illness and include reduced absorption, increased volume of distribution, augmented renal clearance, genetic variations in drug metabolism, and poor penetration into infected compartments.<sup>76</sup> Pharmacokinetic studies in 10 critically ill patients showed that a fixed-dose combination of rifampicin, INH, pyrazinamide, and ethambutol, given according to weight via a nasogastric tube resulted in sub-therapeutic rifampicin plasma concentrations in a majority of patients, while other drugs had a more favorable pharmacokinetic profile.<sup>82</sup> In a study of eight critically ill patients with TB and acute respiratory failure, blood samples were obtained at steady state.<sup>83</sup> The  $C_{max}$  of pyrazinamide was above the recommended concentration of  $>20$  mg/L; for rifampicin, the  $C_{max}$  was below the recommended level of  $>8$  mg/L and the  $C_{max}$  of INH was below the recommended levels of  $>3$  mg/L.<sup>83</sup> In another study involving 20 critically ill patients, rifampicin concentrations were low in all patients receiving continuous enteral feeding.<sup>84</sup> In another study of 81 HIV patients hospitalized for sepsis, with or without meningitis, who were initiated on first-line anti-TB drugs, 49 completed pharmacokinetic studies.<sup>75</sup> Serum  $C_{max}$  targets were achieved in 8.2% with 450 mg of rifampicin, 0% with 300 mg of INH, 89.8% with 1500 mg of pyrazinamide, and 63.2% with 1200 mg of ethambutol.<sup>75</sup> Enteral administration of pyrazinamide results in rapid absorption with peak concentration achieved within 1–2 hours.<sup>85</sup> Only minor changes in bioavailability occur when it is taken with a meal.

### Q16: Is there a Role for Higher Doses of Anti-TB Drugs or Intravenous Anti-TB Drugs in TB Meningitis and Severe Illness?

*Position statement:* Higher doses of anti-TB drugs or intravenous (IV) preparations, where available, may be considered in TB meningitis and severe illness.

*Commentary:* Given the reduced bioavailability of enterally administered anti-TB drugs INH, ethambutol, and rifampicin, it may be preferable to administer these drugs at higher doses, or intravenously when they are available, along with enteral pyrazinamide in critically ill patients.<sup>76</sup> In one of the earliest phase II trials of patients with TB meningitis, a higher oral dose of rifampicin (13 mg/kg) was found to be safe and possibly associated with survival benefits in severe disease.<sup>81</sup> In another study, a higher dose of oral rifampicin (17 mg/kg and 20 mg/kg) resulted in approximately similar  $AUC_{0-24}$ , but lower plasma  $C_{max}$  values compared with 600 mg IV over 1.5 hours.<sup>86</sup> In a phase II study, which was predominantly

**Table 4:** Overview of anti-tubercular drugs and their relevance to critical care<sup>14</sup>

Drug	Dosing	IV	Comments	CSF
Isoniazid	Adults: 5 mg/kg/d Children: 10 mg/kg/d (max. 300 mg/d)	Available*	Enteral absorption is reduced in the setting of sepsis, respiratory failure <sup>75,83</sup>	100%
Rifampicin	Adults: 10 mg/kg/d (max. 600 mg/d) Children: 15–20 mg/kg/d (max. 600 mg/d)	Available*	In critically ill patients with TB and respiratory failure, $C_{max}$ below recommended level (>8 mg/L) when given orally. <sup>83</sup> Higher oral dose (35 mg/kg) or 20 mg/kg IV achieves CSF MIC in >93% of patients <sup>87</sup>	10–20%
Ethambutol	Adults: 15 mg/kg/d Children: 20–30 mg/kg/d (max. 1200 mg/d)	Available*	In TB meningoencephalitis and HIV infection IV INH and ethambutol resulted in better clinical outcomes as compared with oral treatment. <sup>89</sup>	25–50%
Pyrazinamide	Adults: 25 mg/kg/d Children: 35 mg/kg/d (max. 2000 mg)	Not available	Absorption rapid after oral administration, peak concentration in 1–2 hours. Minor changes in bioavailability when taken with meal. Serious adverse events are frequent, particularly in elderly. <sup>91</sup>	100%
Moxifloxacin	Adults: < 30 kg, 400 mg once daily 30–50 kg 600 mg once daily > 60 kg, 800 mg once daily Children: 10–15 mg/kg once daily	Available	Second-line drug; majority of trials, treatment success not in favor of quinolones over standard regimens. <sup>93</sup> Survival benefit for TB meningitis in one trial. <sup>93</sup>	AUC for CSF to plasma 0.82 at 400 mg once day <sup>94</sup>
Amikacin	Adults: 15 mg/kg/day	Available	Effective for MDR-TB; Among 437 MDR-TB of whom 288 were HIV co-infected, 270 (62%) developed hearing loss. <sup>92</sup>	Mean (SD) 1.65 (1.6) mg/L children <sup>92</sup>
Carbapenems	Imipenem, ertapenem and meropenem used in studies.	Available	Bactericidal activity greater with meropenem at 6 gm daily than with 3 gm daily. <sup>96</sup> <i>In vitro</i> studies suggested that activity of carbapenems increases when used with clavulanate. <sup>97</sup>	Low; 79% undetectable <sup>98</sup>
Linezolid	Adults: 600 mg/day	Available	Risk-benefit ratio favors 600 mg/day. <sup>98</sup> Adverse events less and longer tolerance to drug when switched from 600 to 300 mg per day of linezolid. <sup>100</sup>	~ 30% <sup>102</sup>

\*Not available in India; AUC, area under the curve; CSF, cerebrospinal fluid; IV, intravenous; MDR, multi-drug resistant; MIC, minimum inhibitory concentration

done on HIV individuals, standard dosing of rifampicin (10 mg/kg) was able to achieve CSF concentrations above minimal inhibitory concentration (MIC) in only 11% (2/18) of patients when compared with 93% (14/15) in those receiving 20 mg/kg IV of rifampicin and 95% (18/19) in those receiving 35 mg/kg of rifampicin.<sup>87</sup> In another study of 46 HIV individuals, the  $AUC_{0-24}$  for rifampicin was 42.9  $\mu\text{g}\cdot\text{h}/\text{mL}$  for the standard (10 mg/kg) oral dose, 295.2  $\mu\text{g}\cdot\text{h}/\text{mL}$  for high (35 mg/kg) oral dose and 206.5  $\mu\text{g}\cdot\text{h}/\text{mL}$  for IV administration.<sup>88</sup> In one study of patients with TB meningoencephalitis and HIV infection, IV INH and ethambutol resulted in higher sputum conversion, clinical improvement, and improved mortality when compared with oral treatment.<sup>89</sup> In another study of 152 patients with pulmonary TB, 65 patients received parenteral INH, ethambutol, and rifampicin.<sup>90</sup> After the intensive phase, sputum conversion was significantly higher ( $p < 0.05$ ) in patients treated parenterally (100%) when compared with 71% among controls.<sup>90</sup> Given these observations, IV formulations of INH, rifampicin, and ethambutol should be administered where available<sup>14</sup> or a higher dose of enterally administered rifampicin may be justified in the critically ill patient with TB, when IV formulations are not available. Since pyrazinamide is not available as an IV preparation and has a favorable pharmacokinetic profile, a standard dose of pyrazinamide can be administered enterally in the critically ill patient. Serious adverse events are however frequent, particularly in the elderly.<sup>91</sup> The first- and second-line anti-TB drugs and dosing are given in Table 4. Intravenous preparations of rifampicin, INH, and

ethambutol are not available in India. Further studies are required to evaluate the safety and efficacy of higher doses of enterally administered anti-TB drugs in the critically ill.

#### Q17: What is the Role of Other Intravenous Antibiotics in TB?

**Position statement:** Although several IV antibiotics such as aminoglycosides, quinolones, linezolid, and carbapenems are effective against TB, these second-line drugs should be used only in the setting of DR-TB, life-threatening TB and in those who do not tolerate first-line anti-TB drugs.

**Commentary:** Several IV antibiotics commonly used in the treatment of gram-positive and gram-negative organisms are effective against TB (Table 4). However, they are considered only in the setting of drug-resistant TB, intolerance to first-line drugs, or in patients with life-threatening TB. These include aminoglycosides (such as streptomycin, amikacin, and kanamycin), quinolones (such as moxifloxacin, levofloxacin, and gatifloxacin), linezolid and carbapenems (such as ertapenem, imipenem, and meropenem).

IV amikacin is effective in the treatment of MDR-TB. Among 437 MDR-TB of whom 288 were HIV co-infected, 228 (73%) had a good outcome in terms of cure or treatment completion; 270 (62%) developed hearing loss.<sup>92</sup> Quinolones are available as IV formulations and used as second-line drugs in TB. In most trials, treatment success was not in favor of quinolones over standard

regimens.<sup>93</sup> Survival benefit for TB meningitis was observed in only one of three published trials.<sup>93,94</sup>

In a systematic review of the use of carbapenems in TB that included two studies on ertapenem, one on imipenem and four on meropenem, that included patients with XDR-TB, the authors concluded that culture conversion rates ranged between 60 and 94.8% with the proportion of adverse events attributable to carbapenems below 15%.<sup>95</sup> The bactericidal activity of meropenem was greater with 6 gm daily than with 3 gm daily.<sup>96</sup> Although  $\beta$ -lactam antibiotics have achieved overall success, their usage for treating TB is limited due to inherent resistance induced by the existence of a chromosomally-encoded gene (BLaC) in *M. tuberculosis*, which encodes for a Class A Ambler  $\beta$ -lactamase (BLaC). *In vitro* studies suggested that the activity of carbapenems against *M. tuberculosis* was increased when used in combination with clavulanate, a BLaC inhibitor.<sup>97</sup> In TB meningitis, CSF levels were undetectable in 79% of samples.<sup>98</sup>

Linezolid may be effective in treating XDR or pre-XDR-TB. In a recently published study, of the 181 participants enrolled, 88% had XDR or pre-XDR-TB.<sup>99</sup> A favorable outcome was observed in 84–93% of participants who were administered bedaquiline-pretomanid-linezolid (BPaL) combination. The overall risk-benefit ratio favored the group that received a lower dose of linezolid (600 mg/d) for 26 weeks compared with the higher dose (1200 mg/d) for 26 weeks or 600 mg for 9 weeks.<sup>99</sup> In another study involving 69 patients, better treatment outcomes, fever recurring adverse events, and tolerance to longer duration of linezolid were observed when patients were switched from 600 to 300 mg per day of linezolid.<sup>100</sup> There was pharmacokinetic evidence of the potential usefulness of linezolid in TB meningitis,<sup>101</sup> with the extent of CSF penetration around 30% of plasma exposure and correlating with CSF protein concentrations.<sup>102</sup>

It must be kept in mind that the indiscriminate use of these antibiotics as empiric treatment for fever of unknown origin could potentially mask an underlying tubercular infection and may delay its diagnosis.

### Q18: How Should Drug-resistant TB (DR-TB) be Treated in the ICU?

*Position statement:* Patients with DR-TB should be enrolled in The National TB Elimination Programme (NTEP) if not already enrolled. The NTEP has adopted a bedaquiline-based DR-TB regimen in India based on WHO guidelines. Treatment should be started in consultation with respiratory physicians and NTEP. The recommended drugs and duration of treatment in such patients are guided by the program management of DR-TB in India.

*Commentary:* Patients with MDR-TB need a multi-disciplinary approach. The recommended anti-TB drug regimen is based on the findings from the NiX-TB,<sup>103</sup> ZeNiX-TB<sup>99</sup> and TB-PRACTECAL trials.<sup>104</sup> In the NiX-TB trial, the safety and efficacy of an all-oral three-drug BPaL regimen administered over 6 months in patients with treatment-intolerant or nonresponsive MDR-TB or XDR-TB was assessed. With this regimen, 90% (95% CI, 83–95%) of patients had satisfactory outcomes; nevertheless, the daily high dose of linezolid was associated with a significant incidence of side effects, with 48% developing anemia and/or thrombocytopenia and 81% developing peripheral neuropathy.

Linezolid at lower daily doses was better tolerated with fewer adverse events.<sup>99,100,104</sup> Three 24-week BPaL-based therapy regimens with linezolid (BPaL, BPaLC (with clofazimine), and

BPaLM (with moxifloxacin) were compared to standard-of-care treatment in the TB-PRACTECAL trial to assess their efficacy and safety. At 72 weeks, 89% of patients in the BPaLM arm reported treatment success, compared to 52% of patients in the standard-of-care arm.

The WHO updated its DR-TB guidelines in 2022,<sup>33</sup> recommending the BPaLM regimen as the preferred regimen for patients with MDR/RR-TB when fluoroquinolone susceptibility is presumed or documented, and BPaL alone for patients with additional fluoroquinolone resistance (pre-XDR-TB).

### Q19: Is there a Risk of Drug-drug Interaction with Commonly Used Anti-TB Drugs?

*Position statement:* There are significant drug-drug interactions with the commonly used anti-TB drugs. Clinicians need to be familiar with the common interactions in the ICU setting.

*Commentary:* The commonly used anti-TB drugs have significant drug interactions by virtue of inhibition or activation of enzymes. The mechanism of action of the anti-TB drugs, the mechanism of drug-drug interaction, and the important drug interactions are summarized in Table 5. Clinicians must be familiar with the common interactions in the ICU setting, particularly with rifampicin (Table 6). Therapeutic drug monitoring (TDM) may be considered, where available, when significant drug interactions are likely to lead to toxicity or sub-therapeutic effect. For more information, the readers may refer to the exhaustive review of the drug interactions published in 2020.<sup>105</sup>

Multiple drug interactions, particularly with calcineurin inhibitors (CNI), mTOR (mammalian target of rapamycin) inhibitors, and glucocorticoids<sup>106</sup> can occur in post-transplant patients on immunosuppression. These can lead to an increased risk of graft rejection, up to 25%.<sup>107</sup> Based on these, modifications of immunosuppressant medication doses have been suggested to the tune of a three to five-fold increase in CNI or mTOR inhibitors, with doubling of steroid dose.<sup>108</sup> Though some investigators have demonstrated adequate serum levels,<sup>109</sup> other investigators have reported the relative impossibility of such attempts.<sup>110,111</sup>

### Q20: What is the Role of Corticosteroids in TB?

*Position statement:* Corticosteroids may be effective in reducing clinically relevant adverse outcomes in some forms of TB.

*Commentary:* Corticosteroids may be effective in reducing clinically relevant outcomes in some forms of TB (Table 7).<sup>112–116</sup> In patients with pulmonary TB admitted to ICU with acute respiratory failure (ARF) ( $n = 124$ ), steroids were associated with reduced 90-day mortality (OR 0.47; 95% CI, 0.22–0.98;  $p = 0.049$ ) using inverse probability treatment weighting (IPTW) method.<sup>117</sup> Steroids were prescribed in this study for ARDS, shock, wheeze, or disseminated TB. On TB pleural effusions, six trials ( $n = 590$ ) were summarized in a Cochrane review.<sup>112</sup> The risk of residual pleural effusion on chest X-ray reduced by 45% at 8 weeks and 65% at 24 weeks.<sup>112</sup> In TB meningitis, a systematic review of nine RCTs ( $n = 1337$ ), showed a reduction in death (RR 0.75, 95% CI, 0.65–0.87); however, there was no effect on disabling neurological deficits.<sup>113</sup> In HIV-negative individuals, steroids may reduce the risk of death (4 trials,  $n = 660$ , RR 0.80, 95% CI, 0.59–1.09), and the need for pericardiocentesis (RR 0.85, 95% CI, 0.70–1.04) in patients with TB pericardial effusions; there is uncertainty on the effect of steroids on constriction and in HIV individuals.<sup>118</sup> In a small study of 13 patients, high dose methylprednisolone (500–1000 mg/d for 3 days) was associated

**Table 5:** Important drug-drug interactions and mechanisms<sup>105</sup>

Drug	Mechanism of action/mechanism of drug interaction	Important drugs interactions
Isoniazid	Destruction of cell wall, generating RO <i>Drug interaction:</i> Inhibits cytochrome P450 system and acts as a mild monoamine oxidase inhibitor	Disulfiram, acetaminophen, antacids, rifampicin, oral hypoglycemic agents, anticonvulsants, theophylline
Rifampicin	Inhibits DNA-dependent RNA polymerase; decreases affinity of RNA polymerase for short RNA transcripts. <i>Drug interaction:</i> Induces P450 cyto-chrome oxidases (CYP3A4, CYP2A, CYP2B, CYP2C, CYP3A), and human P glycoprotein ABC transporter	Morphine, antacids, antiarrhythmics, several antibiotics, anticoagulants, anticonvulsants, antidepressants, INH, pyrazinamide, bronchodilators, steroids, tacrolimus, cyclosporin, retrovirals, thyroid hormones
Ethambutol	Inhibits arabinosyl transferases involved in synthesis of mycobacterial cell wall	Coadministration with aluminum salts delays and reduces the absorption of ethambutol. Other drugs potentially causing optic neuritis should be avoided
Pyrazinamide	Nicotinamide analog; inhibits the coenzyme A biosynthesis	Concomitant administration of pyrazinamide with isoniazid and/or rifampin is associated with an increased risk of hepatotoxicity
Fluroquinolones	Inhibits DNA gyrase	Antacids, antiarrhythmics, rifampicin, warfarin, insulin, bronchodilators, cyclosporin, tacrolimus
Amikacin	Blocks 30S ribosomal subunit	Diuretics, cephalosporins, cyclosporin, colistimethate sodium, tacrolimus
Carbapenems	Inhibiting BlaC beta-lactams	Caution in patients with TB meningitis and when coadministered with ganciclovir and valproic acid
Linezolid	Binds 50S subunit of prokaryotic ribosome, prevents formation of initiation complex, inhibits protein synthesis <i>Drug interaction:</i> Reversible inhibitor of monoamine oxidases A and B and serotonin agonists	Rifampicin, warfarin, antidepressants (SSRI like fluoxetine, sertraline), fentanyl, morphine derivatives

ROS, reactive oxygen species; SSRI, selective serotonin reuptake Inhibitor

**Table 6:** Drugs frequently prescribed in the ICU and their interaction with rifampicin

Drugs	Comment
Oral anticoagulants	Avoid newer oral anticoagulants (dabigatran, rivaroxaban, apixaban), warfarin may be used with international normalized ratio monitoring (dose escalation likely required)
Glucocorticoids	Increase dose of glucocorticoid 2–3-fold
Azoles	If possible, avoid (voriconazole, itraconazole, posaconazole). Fluconazole has less reduction in serum concentration compared to other azoles. Monitor for response
Atorvastatin	Monitor lipid panel; increased dose will likely be needed
Phenytoin	Monitor serum phenytoin concentrations and seizure activity, dose escalation likely required
Midazolam	Preferably avoid with rifampin, use alternatives
Tacrolimus	Monitor serum tacrolimus concentrations and clinical response, increased dose may be required, use alternatives if possible
Cyclosporine	Monitor serum cyclosporine concentrations, dose escalation likely required
Anti-retroviral drugs	Use dolutegravir-based regimen, double the dose of dolutegravir

with higher 3-month survival in miliary TB complicated by ARDS.<sup>114</sup> Steroids may also be indicated in immune reconstitution inflammatory syndrome (IRIS) and adrenal insufficiency. The role of steroids in the various forms of TB is summarized in [Table 7](#).

### Q21: Is there a Role for TDM in DR-TB?

*Position statement:* There is insufficient evidence to recommend routine TDM during the treatment of DR-TB.

*Commentary:* There is currently little evidence to support TDM for medications used to treat MDR/RR-TB. Even though there is good reason to use TDM, it is unclear if this enhances treatment outcomes and lowers resistance risk. However, given that rifampicin exhibits a significant amount of pharmacokinetic variability and

that the exposures resulting from the recommended doses lie on the steep side of the dose-response curve, ensuring adequate drug concentrations, either through TDM or higher dosing, may play a significant role in DR-TB prevention strategies.<sup>119</sup> TDM may be considered in patients who are slow to respond to treatment, have drug-resistant TB, are at risk of drug-drug interactions, or have concurrent disease states that significantly complicate the clinical situation.<sup>120</sup>

### Q22: How do Risk Prediction Scores Perform in TB in the Critically Ill?

*Position statement:* Risk prediction scores should not be relied on for mortality prediction in TB.

**Table 7:** Steroids for tuberculosis

Type of TB	Steroid type and dose	Comments and supporting evidence
Pulmonary <sup>a</sup>	Adults: Prednisolone 50 mg or equivalent; duration unclear	Pulmonary TB admitted to ICU with ARF ( $n = 124$ ), steroids reduced 90-day mortality (OR 0.47; 95% CI, 0.22–0.98; $p = 0.049$ ) using IPTW method. <sup>117</sup> Steroids prescribed for ARDS, shock, wheeze or disseminated TB. Meta-analysis suggested that steroids could be effective in reducing mortality for all forms, including pulmonary TB. <sup>115</sup>
TB pleural effusion	Prednisolone 1 mg/kg reduced after 1–2 weeks, total duration max up to 3 months	Six trials ( $n = 590$ ) summarized in a Cochrane review. Risk of residual pleural effusion on chest X-ray reduced by 45% at 8 weeks and by 65% at 24 weeks. <sup>112</sup>
TB meningitis	Dexamethasone 0.6 mg/kg children, 0.4 mg/kg adults intravenously to be tapered on a weekly basis by 0.1 mg/kg—then oral therapy starting at 4 mg per day decreasing by 1 mg every 7 days; <sup>113</sup> Prednisolone 2–4 mg/kg children, adults 2.5 mg/kg for 6–8 weeks and then taper <sup>116</sup>	Systematic review of nine RCTs ( $n = 1337$ ), reduction in death (RR 0.75, 95% CI, 0.65–0.87); no effect on disabling neurological deficits. <sup>113</sup>
Pericardial	Adults: prednisone 60 mg/day (or equivalent) for 4 weeks, followed by 30 mg/day for 4 weeks, 15 mg/day for 2 weeks, and 5 mg/day for 1 week	In HIV-negative individuals, may reduce risk of death (4 trials, $n = 660$ , RR 0.80, 95% CI, 0.59–1.09), need for pericardiocentesis (RR 0.85, 95% CI, 0.70–1.04); uncertainty on effect on constriction and in HIV individuals. <sup>118</sup>
TB-associated IRIS	Prednisone 40 mg per day for 14 days, followed by 20 mg per day for 14 days	RCT on prophylactic prednisolone to reduce IRIS in patients with TB and HIV infection who were ART naïve was associated with lower incidence of TB-associated IRIS than placebo, without evidence of an increased risk of severe infections or cancers. <sup>143</sup>
Adrenal insufficiency	Hydrocortisone 50–100 mg 6–8 hourly acute phase; maintenance prednisolone	Adrenal insufficiency can be confirmed by diminished response to synthetic adrenocorticotropin. Should be suspected when there is hypotension needing high-dose vasoactive agents

<sup>a</sup>includes pulmonary and tuberculosis (TB) acute respiratory distress syndrome (ARDS); ART, anti-retroviral therapy; HIV, human immunodeficiency virus; ICU, intensive care unit; IPTW, inverse probability of treatment weighted; RCTs, randomized controlled trials; RR, risk ratio; IRIS, immune reconstitution inflammation syndrome;

**Commentary:** Tuberculosis requiring ICU admission has high mortality. In a systematic review of 17 studies, APACHE II, SOFA, and SPAS II scores underestimated mortality in pulmonary TB.<sup>121</sup> Factors associated with negative outcomes included hospital-acquired infections, need of mechanical ventilation and vasopressors, delay in initiation of anti-TB treatment, more than one organ involvement, and higher severity score.

## TUBERCULOSIS IN THE IMMUNOCOMPROMISED HOST

Among patients admitted to the ICU with TB, immunocompromised patients comprise 6.9–68.7% of the cases.<sup>122,123</sup> The umbrella term of “immunocompromised individual” includes patients with acquired or primary immune deficiency, patients on glucocorticoids, other immunosuppressant drugs for the treatment of connective tissue disorders, post solid organ transplant, and hematological malignancies in the pre- and post-transplant periods.<sup>124</sup> The increasing efficacy of treatment for these diseases has resulted in a change in the scenario from uniformly fatal diagnoses to treatable or manageable chronic comorbid conditions. At the same time, the presence of immune deficiency of a chronic nature and the ubiquitous presence of TB bacilli (especially in countries with high prevalence of TB) makes the risk of infection with TB several-fold higher.<sup>122</sup> Understanding the risks of infection and clinical syndromes that tuberculosis manifests with, in the

immunocompromised critically ill individual is essential to diagnose TB and to provide optimal care.

### Q23: Does the Immunocompromised State Predispose an Individual to Reactivation of Latent TB or the Acquisition of TB?

**Position statement:** Since immunocompromised patients are at risk for TB, the clinical suspicion should be high in patients admitted to the ICU. The interpretation of tests for latent TB infection (such as the TST and IGRA) are likely to be influenced by immunosuppression and the severity of critical illness.

**Commentary:** Immunocompromised hosts have a 10–110-fold higher risk of latent TB reactivation in HIV infection and 20 times higher risk in solid organ transplants than the general population.<sup>125,126</sup> While latent TB screening by TST or IGRA is advised before the use of immunosuppressive drugs such as anti-TNF alpha, and prior to solid organ and hematological transplants,<sup>125,126</sup> in severely ill patients with coexisting immunological insufficiency (acquired or primary), these tests may yield more ambiguous results.<sup>127,128</sup> After recovery from critical illness, 48% of results remain ambiguous.<sup>127</sup> These results were related with higher severity of critical illness and lower blood albumin levels.

Solid organ transplant recipients have the highest TB risk compared to allogenic hematopoietic stem cell transplant (HSCT) recipients and the general population.<sup>129</sup> Lung transplant recipients

have a 5.6-fold higher risk of TB than other stem cell recipients.<sup>130</sup> Allogeneic transplant with unrelated donor (RR 23.9), prior total body irradiation (RR 4.9), and persistent GVHD (RR 3.6) should raise clinical suspicion for TB in post-HSCT patients.<sup>131</sup>

Tuberculosis symptoms typically appear in the first year after solid organ transplantation, albeit the timing varies.<sup>130</sup> Up to 30% of patients may acquire TB later in the post-transplant phase, with renal transplants causing symptoms later than lung and liver transplants.<sup>130</sup> Pulmonary was the most common site in renal transplant recipients, with a median presentation period of 46–196 days. Post-allogeneic HSCT recipients average 150 days of symptoms,<sup>129</sup> with a median gap of 6–7 weeks between symptoms and diagnosis.<sup>132</sup>

#### **Q24: Is the Clinical Presentation of TB in the Immunocompromised Individual Similar to that of the Immunocompetent Host?**

*Position statement:* In an immunocompromised host, the clinical presentation of TB may be more insidious and likely to be disseminated. TB should be suspected when there is unexplained worsening of clinical status. The surveillance for atypical presentations of TB should be robust in order to pick them up early.

*Commentary:* In the immunocompetent host, the most common reason for admission due to TB is acute respiratory failure, followed by septic shock with multiorgan dysfunction.<sup>4</sup> In contrast, the clinical presentation of TB infection in the immunocompromised patient is more insidious. The symptoms are limited in intensity even though TB may be of a disseminated nature.<sup>122</sup> In patients with HIV co-infection, lower CD4 counts are associated with a higher prevalence of extrapulmonary infections and miliary TB, which signifies hematogenous dissemination.<sup>133</sup>

In the immunocompromised post-solid organ transplant recipient, about one-third to one-half of all cases of active TB are disseminated or occur at extrapulmonary sites. Atypical presentation of TB such as pyomyositis, cutaneous ulcers or abscess, and tenosynovitis also occurs.<sup>108,134</sup> Clinical suspicion for TB should be high in patients with respiratory failure after treatment for acute rejection.<sup>124,135</sup>

The absence of fever in about 20–31% of patients could confound the diagnostic paradigm.<sup>124,135</sup> As in other groups of immunocompromised patients, clinical presentation is indolent. Atypical presentations including diffuse alveolar hemorrhage have been reported.<sup>131</sup>

#### **Q25: What should the Diagnostic Work be in the Immunocompromised Host Who is Suspected to have TB Infection?**

*Position statement:* Taking into consideration the indolent nature of TB in the immunocompromised patient, cross-sectional imaging should be considered early to guide diagnostic sampling. Early invasive sampling including bronchial lavage and/or biopsy is advocated in these patients.

*Commentary:* In post-renal transplant patients, the pattern of pulmonary involvement was found to be miliary nodules (40%), cavitation and centrilobular tree-in-bud nodules (22.5%), ground-glass attenuation and consolidation (15%), mediastinal lymph node enlargement (12.5%) and pleural effusion (10%) constituted the major HRCT patterns.<sup>136</sup>

In post-HSCT patients, most common pattern of pulmonary involvement of the chest X-ray was that of consolidation (100%) and nodules (80%).<sup>82</sup> On cross-sectional imaging, the most common

imaging findings were consolidation (100%), nodules (71%), tree-in-bud appearance (43%), and ground-glass opacity (43%).<sup>136</sup> In contrast, cavitations were only found in 14% of patients and lymphadenopathies in 71% of patients.<sup>136</sup>

In post-renal transplant recipients, respiratory samples yielded microbiological evidence of TB, but the culture of at least one sample from other areas was positive in 53% of patients.<sup>124</sup> In a study of patients with HIV co-infection, invasive sampling in the form of BAL and organ biopsy were needed in 11% and 25% of the patients respectively.<sup>137</sup>

#### **Q26: What would the Approach be in the Management of TB in the Setting of Intestinal Malabsorption?**

*Position statement:* In patients with anticipated poor enteral uptake of antituberculous treatment (ATT) [short bowel, gut graft vs host disease (GVHD), severe multiorgan dysfunction with high-dose vasoactive medications], parenteral ATT may be considered along with TDM.

*Commentary:* Data is lacking on ATT in patients with anticipated poor enteral uptake of ATT. This includes critically ill patients on organ support, short bowel syndrome, and gut GVHD. Case reports and expert opinions are the sources of information for these patients.<sup>138,139</sup> Expert opinion has advocated pragmatically to initially use an IV regimen in critically ill patients.<sup>76</sup> The suggested regimens include rifampicin along with moxifloxacin and amikacin,<sup>76</sup> IV fluoroquinolones with oral anti-TB drugs,<sup>140</sup> or higher doses of rifampicin (15 mg/kg/day) along with fluoroquinolone (levofloxacin 20 mg/kg/day).<sup>81</sup>

#### **Q27: What would the Approach be to IRIS in TB?**

*Position statement:* IRIS should be suspected when there is paradoxical worsening of symptoms, typically seen when immunosuppression is reduced or reversed. IRIS can also occur in the immunocompetent host. A course of steroids should be considered.

*Commentary:* IRIS describes the paradoxical worsening of a pre-existing infectious process, typically seen when immunosuppression is reduced/reversed. Although it is seen in patients with HIV-TB co-infection, it can also be seen in immunocompetent patients diagnosed with TB, solid organ transplant, and post-HSCT. In one study, the prophylactic use of prednisolone in patients with TB and HIV infection who were ART naïve was associated with a lower incidence of TB-associated IRIS than placebo, without evidence of an increased risk of severe infections or cancers.<sup>141</sup> However, evidence or treatment protocols for solid organ transplants are nonexistent, with case reports suggesting the continuation of ATT<sup>142</sup> and high-dose corticosteroids,<sup>143</sup> with some advocating the use of NSAIDs and tocilizumab.<sup>144</sup>

### **ORGAN SUPPORT**

#### **Q28: Is the Ventilatory Management of Respiratory Failure due to TB Different from the Ventilatory Management of Respiratory Failure due to Other Infective Etiologies?**

*Position statement:* There is limited data on the management of respiratory failure in patients with TB. The management of respiratory failure in patients with TB should be along the same lines of management as with other infective etiologies of hypoxemic and hypercapnic respiratory failure.

*Commentary:* In a case series published in 1987, of the 15 patients admitted with respiratory failure due to TB, 11 required mechanical ventilation and 4 patients had evidence of hypercapnic respiratory failure.<sup>145</sup> The radiological features ranged from lobar pneumonia, pleural effusion, bronchopneumonia, and miliary involvement to the destruction of lungs; 33% died in ICU.<sup>145,146</sup> In a study from North India<sup>21</sup> involving 63 patients, 90.5% were ventilated and the mortality was 44.4%. In a larger study of 212 patients, 87.7% were ventilated and the mortality was 50%.<sup>8</sup>

In the absence of studies that have focused on invasive mechanical ventilation for respiratory failure due to TB, the current guidelines for safe ventilatory strategies that were summarized in the recent 2023 European Society of Intensive Care Medicine (ESICM) should be followed.<sup>147</sup> This includes low tidal volume (LTV: 4–8 mL/kg predicted body weight), titration of positive end-expiratory pressure (PEEP), maintenance of a plateau pressure of <30 cm H<sub>2</sub>O, avoidance of prolonged high-pressure recruitment maneuvers (airway pressures maintained  $\geq$ 35 cm H<sub>2</sub>O for at least 1 minute), judicious use of continuous infusion of neuromuscular blocking agents and the use of prone positioning in patients with moderate-severe ARDS (defined as PaO<sub>2</sub>/FiO<sub>2</sub> < 150 and PEEP  $\geq$  5 cm H<sub>2</sub>O), despite optimization of ventilation settings.<sup>147</sup>

### Q29: Should Noninvasive Respiratory Support be Considered in the Management of Acute Respiratory Failure Due to TB?

*Position statement:* The use of noninvasive respiratory support including HFNC is challenging given their tendency to cause aerosol dispersion and spread of infection to HCWs. It is preferable to use this in isolation facilities with adequate precautions by staff.

*Commentary:* A recent study examined the extent of exhaled air dispersion with the use of noninvasive ventilation (NIV) devices.<sup>148</sup> They observed that continuous positive airway pressure (CPAP) dispersed air up to 366 mm in the sagittal plane, with the use of positive end-expiratory pressure (PEEP) up to 20 cm H<sub>2</sub>O via nasal pillows, whereas HFNO dispersed up to 205 mm with flow up to 60 L/min. The dispersion on HFNO increased to 620 mm when the interface became loose. A meta-analysis showed that NIV was a significant risk factor for transmission of acute respiratory infections, with an odds ratio of 3.1 (1.4–6.8), while HFNO was not.<sup>149</sup> However, these studies were done in the non-TB setting.

In a small case series of 3 patients, published in 2005, NIV was used to successfully treat patients with moderate-severe ARDS due to TB with PF ratios in the range of 110–120.<sup>150</sup> In another study of 58 patients with acute exacerbation of pulmonary TB sequelae, 86.2% were successfully weaned off supports.<sup>151</sup> In a more recent study of 44 patients with TB and respiratory failure who required mechanical ventilation, the use of NIV post-extubation was associated with a significant ( $p < 0.001$ ) reduction in the duration of ventilation (–36.2 hours, 95% CI, –53.6 to –18.8 hours) and a significant reduction in the risk (RR 0.44, 95% CI, 0.24–0.83) of ventilatory associated pneumonia.<sup>152</sup>

### Q30: Is there a Role for Extracorporeal Membrane Oxygenation (ECMO) Support in TB?

*Position statement:* There is limited evidence for the use of ECMO in TB. It may be considered in TB in the setting of refractory respiratory or cardiac failure.

*Commentary:* A systematic review of case reports on the use of ECMO in 43 cases of TB over 47 years, was published in 2024.<sup>153</sup> The indications for ECMO were ARDS in 83.4% ( $n = 30$ ) and cardiac failure

in 9 patients. Twenty-seven patients were exclusively on veno-venous ECMO (VV ECMO), while 5 patients were exclusively on veno-arterial ECMO (VA ECMO). In 4 patients, VA ECMO was commenced for respiratory failure coupled with hemodynamic instability. At the end of the observation period, 81.4% survived. The authors concluded that ECMO could have a positive effect on overcoming ARDS or bridging the time until response to anti-TB drugs.<sup>153</sup>

### Q31: How Should Massive Hemoptysis be Managed?

*Position statement:* Patients with massive or life-threatening hemoptysis should be managed in an ICU with a focus on airway and hemodynamic stabilization, evaluation of source of bleed by CT angiogram or bronchoscopy, and consideration of bronchial artery embolization as an early treatment option. Nebulized and/or intravenous tranexamic acid may reduce the volume of hemoptysis.

*Commentary:* Patients presenting with massive hemoptysis should be initially stabilized with a focus on airway, breathing and circulation and correction of coagulopathy. The evaluation of the source of bleeding should be done by bronchoscopy or CT angiogram. In one study of 28 patients with massive hemoptysis of diverse etiology, bronchoscopy was essential in making the diagnosis in only 10.7% of cases and it was comparable with radiographs in 82% of the patients.<sup>154</sup> Although bronchoscopy and CT were comparable in identifying the site of bleeding (73 vs 70%), CT was more efficient in identifying the cause of bleeding.<sup>155</sup> If the airway is compromised, intubation will be required; selective intubation of one bronchus and single lung ventilation using double lumen endotracheal tube may be required to prevent aspiration of blood into the normal lung.<sup>156</sup>

Nebulized and/or intravenous tranexamic acid at the dose of 500 mg thrice daily may be associated with a reduction in the volume of hemoptysis. Inhaled tranexamic acid is safe<sup>157</sup> and may be associated with a reduction in the volume of hemoptysis in nonmassive hemoptysis.<sup>158</sup> Its role in massive hemoptysis is unclear.

The definitive management for life-threatening hemoptysis is bronchial artery embolization. In a systematic review of the role of bronchial arterial embolization for hemoptysis, 22 studies were included.<sup>159</sup> The common indications included TB, post-TB sequelae, and aspergillomas. The overall success of embolization, defined as complete cessation of bleeding, ranged from 70 to 99%; recurrence rates were high at 10–57% and attributed to incomplete initial embolization, recanalization of previously embolized arterial, and the development of new collaterals.<sup>159</sup>

### Q32: When Should Tracheostomy Considered in Patients Ventilated for TB?

*Position statement:* The indications and timing of tracheostomy in patients admitted to the ICU with TB are similar to those of other patients admitted to critical care. There is inconclusive evidence to recommend early tracheostomy in patients with TB.

*Commentary:* A proportion of patients admitted to the ICU for the management of TB may require tracheostomy. In one study published in 2018, of the 63 patients admitted to the ICU, 9 patients (14.3%) required tracheostomy.<sup>21</sup> In another study of patients with TB-ARDS, 5 out of 47 (10.4%) required tracheostomy.<sup>10</sup> There are no studies that have addressed the question of timing of tracheostomy in TB patients admitted to the ICU. However, two recent systematic reviews on tracheostomy in critically ill patients, which have included 15 studies with 3,003 patients<sup>160</sup> and 17 studies enrolling 3,145 patients,<sup>161</sup> respectively, showed that early tracheostomy ( $\leq 7$  days) was associated with a reduced in ventilator-associated



pneumonia (VAP); however, there was significant heterogeneity of treatment effects ( $I^2 > 60\%$ ). The duration of ventilation was reduced by about 1 day with early tracheostomy. There was no effect of early tracheostomy on mortality. In the Indian setting, where there may be financial constraints on prolonged hospitalization and the challenges of managing a tracheostomy at home, the decision on tracheostomy should be made with much deliberation.

### Q33: What is the Optimal Management of Hypotension due to Adrenal Insufficiency and Septic Shock with *Mycobacteremia* (Landouzy Sepsis)?

*Position statement:* In TB, shock may be due to adrenal insufficiency, secondary bacterial sepsis, or mycobacteremia. Shock should be managed along the same lines as the management of septic shock. Early initiation of anti-TB treatment is important. Steroids are indicated for refractory septic shock, adrenal insufficiency, and shock due to mycobacteremia.

*Commentary:* Adrenal insufficiency can occur in the setting of TB due to involvement of the adrenal gland due to TB or due to relative adrenal insufficiency during critical illness. It can be confirmed by diminished response to synthetic adrenocorticotropin. Adrenal insufficiency should be suspected when there is hypotension requiring high-dose vasoactive agents. In the acute setting, replacement should be done with IV hydrocortisone. Subsequently, replacement doses of oral steroids (prednisolone) may be required.

Very few case reports of mycobacterial septicemia exist, and most are documented in those with HIV.<sup>162</sup> Immunocompetent patients may also present with fulminant multiorgan failure and vasoplegic shock, indistinguishable from bacterial sepsis. The overall management of this condition is the same as that of septic shock, in general. Anecdotal reports on the use of pulse steroids exist.<sup>163</sup> However, the disease is almost always fatal.<sup>162–164</sup>

### Q34: What is the Optimal Management of Renal Failure in Patients with TB?

*Position statement:* Renal failure in TB should be managed along the same lines as the approach to managing acute kidney injury in the setting of other infectious diseases. Drug dosing should be optimized for renal function, and nephrotoxic agents should be avoided.

*Commentary:* Renal failure may occur as part of the multiorgan dysfunction syndrome in TB or as a result of secondary infections. It should be managed along standard guidelines for the management of renal failure. Drug dosing would need to be adjusted in the setting of renal failure. Isoniazid and rifampicin do not require any dose adjustment in renal failure.<sup>165</sup> Although pyrazinamide is largely cleared by the liver, due to possible delayed elimination of the drug and its metabolite, a dose of 25–30 mg/kg thrice weekly is recommended in stage IV and V chronic kidney disease (CKD) and in patients on hemodialysis.<sup>165</sup> The dose of ethambutol needs to be reduced to 15–25 mg/kg thrice weekly in CKD stages IV and V.<sup>165</sup>

### Q35: Is there a Role for First-line Anti-TB Drugs in Patients with Liver Involvement in TB?

*Position statement:* Patients with liver involvement due to TB should be started on standard four-drug regimen, irrespective of baseline liver function tests.

*Commentary:* Patients with liver involvement due to TB (based on imaging or biopsy) should be started on standard four-drug regimen, irrespective of baseline liver function tests. In case of

subsequent clinical or biochemical worsening, close monitoring, and possible biopsy is warranted to differentiate between hepatic TB and drug-induced liver injury (DILI) and TB-related IRIS. If DILI is suspected, hepatotoxic anti-TB drugs should be discontinued and rechallenged. If the diagnosis is TB-related IRIS, the drugs may be continued with close monitoring and steroid cover. A meta-analysis published in 2015 showed inferior outcomes in patients with hepatic TB treated with monotherapy or nonhepatotoxic regimens compared to those with full-dose multi-drug therapy with INH, rifampicin, pyrazinamide, and ethambutol.<sup>166</sup>

### Q36: Is there a Role for Low-volume Plasma Exchange (PLEX) in Patients with Liver Dysfunction due to TB or DILI?

*Position statement:* In patients with acute liver failure (ALF) or acute on chronic liver failure (ACLF) due to anti-TB drugs induced DILI, low-volume plasma exchange may be considered especially in those who fulfill the King's College criteria for liver transplantation but do not have access to the same.

*Commentary:* There is emerging evidence that shows that low-volume PLEX in specific sub-populations of liver failure may provide a mortality benefit over standard medical therapy, especially in patients with limited access to liver transplantation. A recent meta-analysis has shown promising results in ALF and ACLF, not specific to TB or TB-DILI. Preliminary data from a prospective trial conducted to assess the role of PLEX in DILI (which had 14% of patients with TB-DILI) showed survival benefit over standard medical care and improvement in hepatic encephalopathy. Based on this, it may be reasonable to consider PLEX as an option in ALF and ACLF, especially in areas without access to liver transplantation.<sup>167–170</sup>

## INFECTION CONTROL

There is evidence that primary transmission of drug-resistant bacteria is the main mechanism for the global spread of drug resistant TB, rather than acquired resistance. So, identifying the source of infection quickly and halting its spread by effective infection prevention and control (IPC) measures are therefore imperative. Infection prevention and control strategies focus on lowering the concentration in airborne particles and the duration of exposure among healthcare providers.

Healthcare workers (HCWs) have an increased risk of contracting *M. tuberculosis* infection when compared with the general population.<sup>171</sup> It is therefore critical to implement and maintain effective strategies for controlling TB infections.<sup>172</sup> Administrative control implementation,<sup>173,174</sup> utilizing triage, and patient isolation, are the fundamental and essential components of any IPC strategy. Furthermore, the strategies prioritize the implementation of respiratory hygiene and the timely initiation of effective treatment. Additional methods encompass engineering and environmental controls. While the evidence for the effectiveness of IPC measures is limited, the deployment of numerous measures has shown a definite decrease in the risk of TB occurrence among HCWs and those visiting healthcare facilities.<sup>174</sup>

### Q37: What are the Recommended Isolation Systems for Patients with Presumed or Documented Infectious TBs in the ICU?

*Position statement:* Respiratory isolation of individuals with confirmed or suspected infectious TB is advised, ideally in an airborne infection isolation room (AIIR) equipped with a

high-efficiency particulate air (HEPA) filter and negative pressure. Closed suctioning is recommended for intubated patients. The application of a bacterial filter to the ventilator tubing's expiratory limb may reduce the transmission of infection.

*Commentary:* Patients diagnosed or suspected to have pulmonary TB should be isolated in an AIIR to mitigate the potential transmission of TB particles. It was found that respiratory isolation of patients with putative or confirmed infectious TB reduced the risk of active TB infection among HCWs by 2% and latent TB infection by 45%,<sup>172</sup> respectively. It is recommended that AIIR implement negative pressure ventilation, with a minimum of 6 air changes per hour (ACH) and a maximum of 12 per day.<sup>175</sup> High-efficiency particulate air filters are recommended to handle the exhaust from the room. Therapeutic interventions and diagnostic assessments that necessitate patients to be transferred from the isolation facility must be limited and preferably performed within the AIIR as far as possible.

Although animal models have demonstrated a reduction in latent TB infection in rooms treated with upper room ultraviolet germicidal irradiation (UVGI) with ultraviolet-C light to kill or inactivate airborne *M. tuberculosis*,<sup>176</sup> the evidence is scant, and its efficacy may be compromised when the relative humidity in the room exceeds 50–60%.<sup>177</sup>

Nonventilated patients diagnosed or suspected of having TB who are coughing should be provided with surgical masks.<sup>175</sup> Although studies have demonstrated a decline in latent TB infection among HCWs,<sup>178</sup> there is no evidence indicating a reduction in active TB infection. Drawing a parallel from the patients wearing masks to decrease transmission, we recommend that closed suctioning is used for intubated patients to reduce the dispersal of respiratory secretions that contain infectious *M. tuberculosis*. Furthermore, to prevent the spread of pathogens, endotracheal tubes or the expiratory side of the ventilator may be equipped with a bacterial filter capable of capturing particles as small as 0.3 µm with an efficacy of at least 95%. Standard environmental cleaning of the ICU room should be sufficient to disinfect the room given that *M. tuberculosis* is transmitted exclusively through airborne transmission and not through surface contact.<sup>179</sup>

### Q38: What are the Key IPC Measures for HCWs Taking Care of Patients with Suspected or Confirmed Tuberculosis in the ICU?

*Position statement:* Healthcare professionals entering rooms of patients with suspected or confirmed contagious TB disease should wear a properly sized N95 disposable respirator.

*Commentary:* Although surgical masks can reduce the number of infectious particulates in the air, their filtration efficiency is only 50% and they fail to form a secure seal on the face; therefore, they are unsuitable for HCWs. Specific respiratory protection, including properly fitted N95 masks, filters at least 95% of particulate 1 µm in diameter when utilized appropriately and with a snug facial seal. In order to achieve this, medical facilities that treat TB patients should establish protocols for periodic respirator fit testing, initial respirator fit testing, and annual respirator training.<sup>175</sup>

Sputum induction and nebulization therapy provoke coughing, heightening the risk of transmission of *M. tuberculosis*.<sup>180,181</sup> While doing procedures that generate aerosols, such as intubation, bronchoscopy, or sputum induction, HCWs should wear at the barest minimum, N95 respirators.<sup>182</sup> However, for these procedures, it is advisable to use a higher level of respiratory protection, such as

an elastomeric full-facepiece respirator or a powered air-purifying respirator (PAPR), instead of a N95 disposable respirator.<sup>175,182</sup>

### Q39: When can Respiratory Isolation Precautions be Discontinued for Critically Ill Patients with Pulmonary TB?

*Position statement:* For sputum-positive rifampicin susceptible TB patients, a minimum of 2 weeks of isolation is suggested, while on effective anti-TB treatment.

*Commentary:* There is a lack of distinct, unequivocal guidelines and insufficient evidence regarding the de-isolation of patients with sputum-positive pulmonary tuberculosis.<sup>183</sup> The 2 weeks of isolation is based on a review article by Rouillon et al. in the 1970s, which suggested that with effective treatment, patients may lose infectivity in probably less than 2 weeks.<sup>184</sup> Dharmadhikari et al. found that patients on successful treatment lose infectivity, even if they are AFB microscopy and culture positive.<sup>185</sup> There is evidence to suggest that isolation may be needed for patients with negative smears, as they too possess the capacity to transmit the infection; research has shown that smear-negative culture-positive tuberculosis is responsible for approximately 17% of TB transmission.<sup>186</sup>

### Q40: Is there a Role for Routine Testing and Surveillance of HCWs Managing Infectious TB Patients?

*Position statement:* The role and benefit of regular testing and surveillance for TB infection among HCWs in the ICU, using TST or IGRA, in endemic countries like India is unclear.

*Commentary:* At present, there is no gold standard test for establishing the diagnosis of LTBI. Two screening tests, TST and IGRAs, are recommended for diagnosing LTBI. Although IGRA may aid in the early detection and mitigation of potential exposures in high-income countries with low TB prevalence, their application in low- and middle-income countries with high endemicity lacks definitive guidelines. Data from high endemic countries have yielded mixed conclusions with regards to active screening. While a study from South India suggested a potential role for screening of HCWs based on a higher annual risk of TB infection,<sup>187</sup> a recent individual patient meta-analysis of individual patients found that the efficacy of both IGRA and TST was inferior in countries with a high incidence of TB.<sup>188,189</sup>

## POST-TUBERCULOSIS SEQUELAE

The term post-tuberculosis describes the range of pathological conditions experienced by TB survivors involving various organ systems.<sup>190</sup> These post-TB sequelae mainly arise from the disease process or the side effects related to TB treatment.

### Q41: Post-TB Sequelae: What are the Reasons for ICU Admission?

*Position statement:* Post-TB sequelae patients may present to the ICU with respiratory failure due to exacerbation of obstructive airway disease or restrictive fibrotic lung disease, pulmonary hypertension, hemoptysis due to bronchiectasis, aspergillosis or vascular causes or with secondary infections. There are currently no evidence-based recommendations for the investigation and management of post TB lung abnormality (PTLA).

**Commentary:** One of the most common post-TB sequelae is post-TB lung illness, which can result in respiratory failure and the need for ICU admission. This can happen because of post-TB issues linked to the vascular system, parenchyma, pleura, mediastinum, or airway. Airflow limitation, restrictive diseases, or a combination of both, occasionally linked to respiratory failure, are functional conditions affecting patients.

Studies have shown that up to 50% of patients experience health issues due to PTLA.<sup>191,192</sup> Fibrosis accounts for 25.0–70.4%, cavitation for 8.3–83.7%, and bronchiectasis for 4.3–11.2% of the imaging-defined PTLA.<sup>193</sup> Younger individuals, patients without HIV and people from high endemic areas are at risk of developing PTLA. In a review of 17 studies among HIV-infected and uninfected individuals, HIV individuals with low CD4 counts and TB were four times more likely to have normal chest radiographs and less cavitation than individuals with higher CD4 counts.<sup>194</sup> The extent of impairment in lung functions is more in DR-TB when compared with drug-sensitive TB.<sup>195</sup>

Exacerbations of chronic obstructive pulmonary disease (COPD), bronchiectasis, and pneumonia are also more frequent after pulmonary TB.<sup>196,197</sup> Population-based studies PLATINO and BOLD suggest that prior TB doubles the risk of developing COPD.<sup>196,198</sup> According to a recent review, persons over 40 years of age who had a history of TB were significantly more likely to get COPD (odds ratio (OR) 3.05, 95% CI, 2.42–3.85).<sup>197</sup> Lung involvement in post-TB COPD is heterogeneous<sup>199,200</sup> and may not respond as well to bronchodilators as a regular COPD patient; the use of inhaled corticosteroids in post-TB COPD may increase the risk of reactivation of TB.<sup>201</sup>

A cross-sectional study of 100 patients indicated a 2.13-fold increase in the chances of pulmonary hypertension post-TB with each further TB episode (CI: 1.17–3.88;  $p=0.013$ ).<sup>202</sup> Post-TB studies have shown that the prevalence of pulmonary hypertension ranges from 6.3% in outpatients to 42.4% in hospitalized patients and 67% in patients with chronic respiratory failure.<sup>203</sup>

Patients with a history of TB may present with hemoptysis either from airway-related broncholiths, bronchiectasis, pulmonary aspergillosis, and vascular causes from rupture of Rasmussen's aneurysm or from dilated bronchial arteries. Chronic pulmonary aspergillosis commonly complicates treated pulmonary TB with residual cavitation. Other presentations of aspergillosis that may complicate PTLA include aspergilloma, allergic bronchopulmonary aspergillosis, invasive and chronic pulmonary aspergillosis or asymptomatic colonization. Based on symptoms of cough, weight loss, hemoptysis, CT chest features of cavitation, a fungus ball, pleural thickening, and pulmonary fibrosis, and positive IgG to *A. fumigatus*, a cross-sectional prospective study from Uganda found that 4.9% of patients who had finished TB treatment 2 years prior had "definite" and another 2.3% had "probable" chronic pulmonary aspergillosis. This increased to 26% among patients with a cavity on CXR.<sup>204</sup>

## FUTURE DIRECTIONS

There is paucity of good trials on TB in the critically ill. Given that an increasing number of patients are admitted to ICUs with TB and its complications in our country, it is incumbent on ICU practitioners to not only be aware of the problem but also channel efforts to reduce mortality. It is important to focus on studies that will explore rapid diagnostic tests in the ICU setting, particularly for extrapulmonary TB where delays in diagnosis and treatment

may result in worse outcomes. Studies on the use of IV anti-TB drugs and/or the use of higher doses of anti-TB drugs in ICU patients is important to address the problems of subtherapeutic concentrations of drugs which are common due to a multiplicity of factors. Therapeutic drug monitoring would be another vital area that would need to become integral to the management of TB in the critically ill. Awareness and knowledge on the key aspects of TB and its management will go a long way in improving outcomes of TB in the critically ill.

## CONCLUSION

Tuberculosis continues to be a major problem in developing countries including India. The more recent increase has been attributed to the COVID-19 pandemic, due to the disruption of services because of the lockdown and diversion of healthcare resources to tackling the pandemic. Newer therapies for the management of cancers and immune disorders, particularly the use of highly potent immunosuppressive agents, have contributed to re-activation of TB in these patient cohorts. These factors have resulted in an increase in the number of patients with TB in the ICU setting. Mortality continues to be unacceptably high among patients with TB admitted to the ICU at 50–60%. Newer diagnostic tests with faster turnaround are likely to help with the early diagnosis of TB including drug-resistant TB. The possibility of use of higher doses of anti-TB drugs in critically ill patients, the availability of IV preparations and the options of TDM of anti-TB drugs is likely to improve diagnostics and management in the ICU patients. More studies are required in the ICU setting to inform decision making in critically ill patients.

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