

# Tuberculosis in Intensive Care Unit

Dhruva Chaudhry<sup>1</sup>, Diksha Tyagi<sup>2</sup>

## ABSTRACT

About 3.4% of the hospitalized tubercular patients need admission to the intensive care unit (ICU). Patients requiring ICU admission had a poor prognosis and high mortality rate (60 vs 25%) as compared to other causes of severe pneumonia. The most common indication for tuberculosis-related ICU admission is acute respiratory failure due to pneumonia or acute respiratory distress syndrome (ARDS) (with or without miliary tuberculosis) followed by septic shock with multiple organ dysfunction, adrenal insufficiency, and neurological involvement, especially tubercular meningitis. Tuberculosis patients who require admission to ICU are mostly immunocompromised [human immunodeficiency virus (HIV) coinfection] and have underlying miliary tuberculosis or disseminated tuberculosis. Pulmonary tuberculosis presenting as ARDS is a rare phenomenon, but a most common cause of admission of tuberculosis patients to ICU. Tuberculous meningitis is the most severe form of tuberculosis with mortality more than 60% and residual neurological disability in 25% cases. Tuberculosis-related septic shock has been found in only 1% of all septic shock patients admitted to ICU. Patients with tuberculosis with refractory shock should be suspected for adrenal insufficiency. A trial of physiologic stress replacement dose of hydrocortisone (200–300 mg) should be given to all critically ill patients with vasopressor-dependent shock after correcting other causes. Diagnosis and treatment of tuberculosis in critically ill patients has various challenges, namely appropriate sample collection, issues with the route of administration, drug absorption, bioavailability, dose modification in hepatic and renal dysfunction, and interaction with other drugs.

**Keywords:** Acute respiratory distress syndrome (ARDS), Miliary tuberculosis, Septic shock, Tuberculous meningitis.

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## INTRODUCTION

Tuberculosis is one of the most primitive infectious diseases known to mankind and continues to be a major health problem globally. In 2019, an estimated 10 million people were diagnosed with tuberculosis worldwide. The increasing number of drug-resistant tuberculosis has become a matter of concern with a 10% of increase in the incidence in a year. India is in the top position among the high burden countries with an estimated incidence of more than 2.6 million new tuberculosis cases.<sup>1</sup> It is a pandemic disease with a slow and progressive course requiring a long duration of treatment and high mortality if left untreated. Most of the patients can be managed at home if early diagnosis and treatment are done. Hospitalization is required in patients presenting with complications of tuberculosis, that is, pneumothorax, empyema, hypoxemia due to extensive parenchymal involvement, pulmonary hemorrhage, thromboembolic phenomenon, severe extrapulmonary tuberculosis, adverse reactions to tubercular drugs, and admission due to other comorbidities. About 3.4% of the hospitalized tubercular patients need admission to the intensive care unit (ICU).<sup>2</sup> Despite a high burden country, Indian data of the critically ill tuberculosis patients requiring ICU admission are scarce. In a single center study from India, only 1.7% of patients had active tuberculosis. Out of which, 55.5% had disseminated tuberculosis, 30% had miliary tuberculosis, and 28% had tuberculosis-related acute respiratory distress syndrome (ARDS).<sup>3</sup>

## ICU ADMISSION IN TUBERCULOSIS

The most common indication for tuberculosis-related ICU admission is acute respiratory failure due to pneumonia or ARDS (with or without miliary tuberculosis) followed by septic shock with multiple organ dysfunction, adrenal insufficiency, and neurological involvement, especially tubercular meningitis.<sup>2</sup> Various comorbidities that may coexist with tuberculosis are liver

<sup>1,2</sup>Department of Pulmonary and Critical Care, Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana, India

**Corresponding Author:** Dhruva Chaudhry, Department of Pulmonary and Critical Care, Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana, India, Phone: +91 9991101616, e-mail: dhruvachaudhry@yahoo.co.in

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dysfunction (65.5%), chronic pancreatitis (12.1%), chronic renal failure (8.6%), and human immunodeficiency virus (HIV) coinfection (6.9%). Extrapulmonary tuberculosis has been seen in 19% of patients.<sup>4</sup> Patients requiring ICU admission had a poor prognosis and high mortality rate (60 vs 25%) as compared to other causes of severe pneumonia.<sup>5</sup> The factors associated with high mortality in critically ill patients have been found due to the presence of multiorgan dysfunction syndrome, sepsis, need for mechanical ventilation, development of nosocomial pneumonia, cardiogenic shock, and renal failure.<sup>2</sup>

## Acute Respiratory Distress Syndrome

Lungs are the most common site of involvement in tuberculosis. Patients present with acute respiratory failure due to extensive parenchymal involvement, secondary Gram-negative pneumonia or sepsis, chronic obstructive pulmonary disease, history of poor compliance with tuberculosis treatment, and cancer. Pulmonary tuberculosis presenting as ARDS is a rare phenomenon, but it is

**Table 1:** Severity of ARDS depending on PaO<sub>2</sub>-to-FiO<sub>2</sub> ratio

ARDS severity	PaO <sub>2</sub> /FiO <sub>2</sub> * (ratio of partial pressure of arterial oxygen to fraction of inspired oxygen)
Mild	200–300
Moderate	100–200
Severe	<100

\*With PEEP 5 cm H<sub>2</sub>O

the most common cause of admission of tuberculosis patients to ICU.<sup>2</sup> Out of the total ARDS patients presenting in an ICU, only 4 to 5% are secondary to tuberculosis.<sup>6</sup> It is particularly seen in patients with miliary or disseminated tuberculosis, immunocompromised patients, with shorter duration of illness, lymphopenia, and elevated serum alanine aminotransferase.<sup>2</sup>

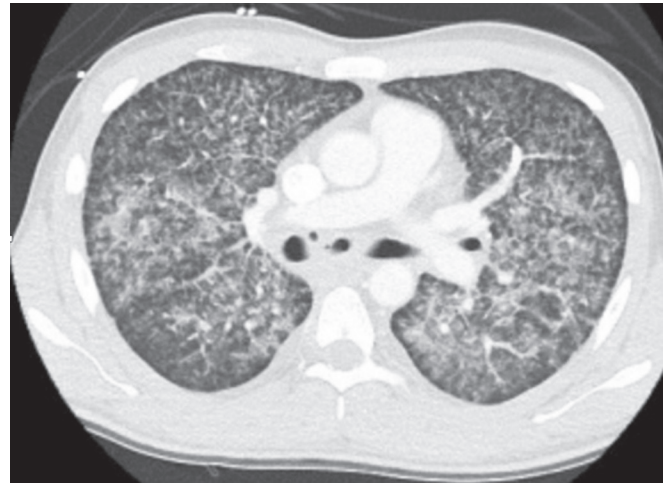
The diagnosis of tuberculosis-related ARDS is based on Berlin's criteria.<sup>8</sup> The severity of ARDS is explained by PaO<sub>2</sub>-to-FiO<sub>2</sub> ratio as follows (Table 1):

The pathogenesis of ARDS in pulmonary tuberculosis has not been clearly established. Direct injury to the alveolarcapillary membrane by the *Mycobacterium* initiating intense proinflammatory response or aggregation of platelets in pulmonary capillaries leading to endothelial injury and leucocyte activation or direct activation of macrophages by the lipoarabinomannan (component of mycobacterial cell wall) leading to release of tumor necrosis factor- $\alpha$  and interleukin-1 $\beta$  are the various postulated hypothesis. Interstitial granulomatous infection and obliterative endarteritis are the other contributory factors.

Patients usually present with sudden onset of respiratory distress with a background history of fever, weight loss, cough, or antituberculosis treatment. Bilateral interstitial infiltrates with underlying miliary nodules, cavitation, or upper lobe consolidation are common radiological findings (Figs. 1 and 2). Diagnosis is difficult in patients with an atypical clinical and radiological presentation, especially in immunocompromised patients. In critically ill patients, a high degree of suspicion and clinical experience is required along with appropriate sample collection and investigations for the diagnosis of tuberculosis-related ARDS. The prognosis is poor with high mortality of 60% in patients requiring invasive mechanical ventilation.<sup>2</sup>



**Fig. 1:** Chest radiograph showing bilateral diffuse infiltrates in a patient with tuberculosis-related ARDS



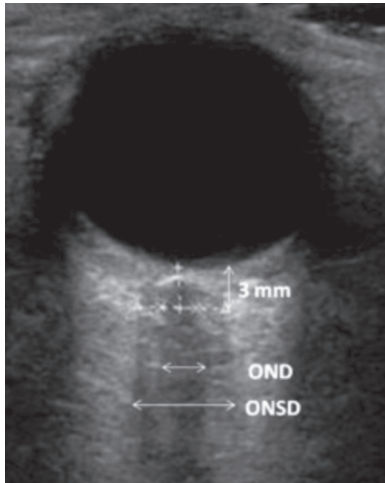
**Fig. 2:** Computed tomography of the chest of a patient with tuberculosis-related ARDS showing multiple nodular opacities with diffuse ground-glass opacities

Management strategies are similar to that of the other patients with ARDS. An initial trial of noninvasive mechanical ventilation may be given to patients with mild and moderate ARDS (PaO<sub>2</sub>/FiO<sub>2</sub> >150 cm H<sub>2</sub>O). Patients with moderate to severe ARDS (PaO<sub>2</sub>/FiO<sub>2</sub> <150 cm H<sub>2</sub>O) will need mechanical ventilation without any delay.<sup>7</sup> Ventilation strategies include low tidal volume with a high positive end-expiratory pressure (PEEP) combination to keep plateau pressure  $\leq$ 30 cm H<sub>2</sub>O (lung-protective ventilation). Initial use of neuromuscular agents and conservative fluid administration should be followed. Patients with severe refractory hypoxemia should be considered for early prone positioning. Recruitment maneuvers should be used with caution as tuberculosis lungs are prone to air leaks. Any sudden increase in airway pressures (both peak and plateau pressure) should be evaluated for the development of pneumothorax.

### Tubercular Meningitis

Tuberculous meningitis is the most severe form of tuberculosis with a mortality of more than 60% and residual neurological disability in 25% of cases.<sup>8,9</sup> It is the second most common cause of admission to ICU after acute respiratory failure. It accounts for around 6 to 18% of all tuberculosis-related ICU admissions.<sup>10,11</sup> Children and patients suffering from miliary tuberculosis or disseminated tuberculosis, and HIV coinfections are the most commonly affected. Clinical presentation is usually indolent with nonspecific features like fever, headache, loss of appetite, weight, and seizures, but it may also present with acute bacterial meningitis-like symptoms. Patients with low Glasgow Coma Scale (GCS) due to increased intracranial pressure, acute hydrocephalus, basal arachnoiditis, acute hydrocephalus, tuberculomas, and cerebral infarction require admission to ICU.

The management of tubercular meningitis is challenging with no clear guidelines for diagnosis and treatment. Diagnosis of tuberculous meningitis requires lumbar puncture and cerebrospinal fluid (CSF) analysis (high opening pressure), cell count (lymphocytic predominant pleocytosis), high protein (100–500 mg/dL), low glucose (<45 mg/dL or CSF-to-plasma sugar ratio <0.5), high adenosine deaminase (ADA) (>10), and isolation of *Mycobacterium tuberculosis*. Brain imaging, such as contrast-enhanced computed tomography (CECT) of the brain and magnetic resonance imaging



**Fig. 3:** Ultrasonographic measurement of optic nerve sheath diameter for the evaluation of intracranial pressures in patients with tubercular meningitis

(MRI) of the brain, is done to evaluate the cause of raised intracranial pressure (hydrocephalus, tuberculous masses, and cerebral edema) and associated midline brain shift or ischemia. Routine follow-up with brain imaging is not recommended but may be required in patients with worsening neurological status.

Invasive mechanical intubation is required in patients with GCS <8, refractory seizures, and coexisting respiratory failure. Early initiation of antituberculosis treatment, optimization of intracranial pressure, prevention of secondary insult to the brain, and ICU-related complications are the important components of management of tuberculous meningitis. Intracranial pressure monitoring can be done by noninvasive methods like ultrasonographic measurement of optic nerve sheath diameter or by transcranial Doppler (TCD) ultrasound. Normal optic nerve sheath diameter is 5 mm (measured 3 mm posterior to eye globe) (Fig. 3). An increase in optic nerve sheath diameter correlates with increased intracranial pressure. TCD ultrasound measurements are less reliable because the cerebral blood flow and pulsatility index can be affected by various other factors like blood pressure and changes in partial pressure of carbon dioxide.

Intracranial pressure can be optimized by medical therapy with or without surgical intervention. Acetazolamide and hyperosmolar therapy can be used to reduce intracranial pressure. There are no clinical trials comparing the benefit of hypertonic saline and mannitol in tuberculous meningitis. Hypertonic saline has been recommended over mannitol because it rapidly and strongly reduces intracranial pressures without causing hypovolemia. In a meta-analysis on the patients with traumatic brain injury, the use of mannitol is potentially harmful.<sup>12</sup> Corticosteroids are used in addition to antituberculosis drugs to decrease cerebral edema and have been found to reduce short-term mortality.<sup>13</sup> In patients with HIV coinfection, the role of steroids is controversial. Neurosurgical interventions, that is, ventriculoperitoneal shunting and ventriculostomy, are indicated in patients with noncommunicating hydrocephalus and communicating hydrocephalus, which is unresponsive to medical therapy. Supportive therapies include head-end elevation for CSF and cerebral venous drainage, use of antiepileptics, avoidance of hyperthermia, hypotension, hyponatremia, hypernatremia, hypoglycemia, hypoxemia, and

hypercapnia, and sudden increase in intracranial pressure due to coughing while doing airway suction to prevent secondary neuronal damage. Despite adequate treatment, tuberculosis meningitis has high mortality and morbidity. Factors associated with poor outcomes are delayed diagnosis, delayed treatment, high Medical Research Council disease severity grade, lower CSF lymphocyte count, high CSF protein level, presence of hydrocephalus, and antitubercular drug resistance.<sup>14-16</sup>

### Septic Shock with Multiorgan Dysfunction Syndrome

Patients with tuberculosis presenting with shock are not uncommon. In most of the cases, the reason for the shock is a secondary bacterial infection in the lungs or other sites. Tuberculosis-related septic shock is extremely rare in immunocompetent patients. It has been reported to have higher incidence in patients with HIV coinfection and disseminated tuberculosis. In a large cohort of culture-positive septic shock patients admitted to ICU, only 1% had tuberculosis-related septic shock with a mortality of around 80% in contrast to 49% in patients with shock due to other causes.<sup>17</sup> Delay in diagnosis and initiation of treatment have been found to be the main reasons for high mortality. The presence of septic shock in a confirmed case of tuberculosis with no evidence of any other plausible pathogen is required for the identification of tuberculosis-related septic shock. Diagnosis can be delayed and challenging in patients presenting with acute illnesses complicated by septic shock and multiple organ dysfunction. Other causes of septic shock were ruled out by retrieving appropriate samples and testing. In patients with high clinical suspicion of tuberculosis based on clinical symptoms and radiology, early initiation of empirical antituberculosis therapy is recommended. Treatment involves standard management protocol for septic shock. Initial fluid resuscitation with early initiation of antituberculosis drugs and vasopressors is the basic principle of the management. Any other cause of hypotension was ruled out, contributing to the pathology, namely adrenal insufficiency and cardiogenic shock in cases of disseminated tuberculosis.

### Adrenal Insufficiency

Patients with tuberculosis with refractory shock may have adrenal insufficiency. Tuberculosis is still the second most common cause of chronic adrenal insufficiency after autoimmune disease. It is seen in 6 to 10% of patients with active tuberculosis. Tuberculous infection can precipitate adrenal insufficiency by direct involvement of the adrenal glands or hematogenous spread of infection from a distant site. The use of antituberculosis drugs like rifampicin that increases the metabolism of cortisol may lead to functional adrenal insufficiency. Acute life-threatening adrenal insufficiency due to tuberculosis is rare and may result from acute stress in a patient with chronic adrenal insufficiency, when not appropriately treated. It is characterized by hypotension and shock, fever, confusion, nausea, and vomiting. Diagnosis requires a high degree of suspicion in patients with vasopressor-dependent shock. Skin hyperpigmentation, anemia, hyponatremia, hyperkalemia, and eosinophilia are the associated findings. Fasting plasma serum cortisol levels may be normal or decreased. Adrenal insufficiency can be confirmed by diminished response to synthetic adrenocorticotropin. Treatment involves administration of high-dose glucocorticoids and fluid resuscitation. Intravenous hydrocortisone in doses of 300 to 400 mg per 24 hours given as a continuous infusion or in divided doses at 6-hour interval provides both glucocorticoid and mineralocorticoid coverage. Sample for plasma cortisol levels should be taken before the administration

of hydrocortisone. Prednisolone can be used, if hydrocortisone is unavailable. The use of dexamethasone should be avoided because of the increased incidence of cushingoid side effects. Fludrocortisone should be added in patients with associated aldosterone deficiency. A trial of physiologic stress replacement dose of hydrocortisone (200–300 mg) should be given to all critically ill patients with vasopressor-dependent shock after correcting other causes.<sup>18</sup>

## CHALLENGES IN THE DIAGNOSIS AND TREATMENT IN ICU

Diagnosis of tuberculosis requires microbiological confirmation from the appropriately collected sample. In critically ill patients, appropriate sample collection can be challenging due to poor general conditions. Pulmonary samples like sputum or induced sputum in patients on noninvasive ventilation or endotracheal aspirate or bronchoalveolar lavage in patients on invasive mechanical ventilation should be evaluated for acid-fast bacilli staining (Ziehl Neelsen stain). Mycobacterial cultures should be done for confirmation of diagnosis and drug sensitivity testing to exclude drug-resistant tuberculosis. Culture usually takes a minimum of 2 to 6 weeks for the results. Therefore, molecular testing (GeneXpert) should be done in all critically ill patients, in addition to cultures for the early diagnosis and rapid detection of rifampicin resistance.

In patients with suspicion of extrapulmonary tuberculosis, an adequate and appropriate sample should be taken from respective sites. Fine needle aspiration from peripheral lymph nodes for AFB staining, GeneXpert, mycobacterial cultures, and histopathological examination should be done. Pleural fluid, ascitic fluid, and CSF should be evaluated for cell counts, protein, sugar, and ADA levels. Radiological imaging (CECT/MRI) of the specific site helps in supporting the diagnosis. Despite all evaluations, in patients with inconclusive reports and high clinical suspicion of tuberculosis based on symptoms and radiology, clinical diagnosis of tuberculosis can be made with the decision to administer a trial of empiric antituberculosis treatment.

Isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin are first-line antituberculosis drugs for the treatment of drug-susceptible tuberculosis. Administration of these drugs in critically ill patients has always been full of challenges ranging from issues with the route of administration, drug absorption,

bioavailability, dose modification in hepatic and renal dysfunction, and interaction with other drugs. Treatment of multidrug resistance tuberculosis requires administration of a greater number of drugs with increased risk of drug interaction and adverse effects. Most of the tuberculosis drugs are available in peroral formulations, making them difficult to administer in patients on invasive mechanical ventilation. Variable drug absorption through the enteral route and unpredictable bioavailability in critically ill patients leads to inadequate drug levels in plasma. Isoniazid, rifampicin, and pyrazinamide are the most potent antituberculosis drugs with hepatotoxic potential and need to be replaced with a prolonged regimen of streptomycin and levofloxacin with ethambutol in patients with liver dysfunction. The dose of pyrazinamide, ethambutol, and streptomycin requires modification in renal dysfunction (Table 2). Rifampicin is known to cause thrombocytopenia and shock, further worsening the condition of the patients. Adverse effects of some drugs like ocular toxicity of ethambutol and peripheral neuropathy of isoniazid are difficult to be monitored in critically ill patients. Hence, pyridoxine should be administered to all patients. Rifampicin is a strong enzyme inducer that increases the metabolism of the concomitantly administered drugs, that is, antibiotics and steroids making them less effective and require dose modification.

The role of steroids has been well established in reducing the mortality in patients with tuberculous meningitis and pericardial effusion. Some benefit has been reported in patients with tuberculosis-related septic shock and multiple organ dysfunction, but the evidence is lacking in patients with ARDS due to tuberculosis.

The paradoxical reaction is defined as rapid clinical deterioration after initiation of antituberculosis drugs because of the reconstitution of immunity leading to an immune response to dead bacilli. The patient develops sudden worsening of preexisting tuberculous lesions or the development of new lesions, airway obstruction, splenic rupture, and neurological deterioration in the absence of an alternative cause. Corticosteroids are the mainstay of treatment. In severe cases with neurological involvement, thalidomide has been found to be effective.

Other challenges in the management of tuberculosis patients in ICU are to prevent the spread of the disease, proper isolation, and nursing of the patient. Patients should ideally be treated in negative pressure isolation rooms. All the procedures promoting droplet formations like endotracheal suction, bronchoscopy, and nebulization should be reduced to a minimum. Closed suction

**Table 2:** Dose modification of first-line antituberculosis drugs in patients with renal dysfunction

Antimycobacterial agent and normal dose	Dosage adjustment according to estimated degree of renal function				
	Creatinine clearance 30–60	Creatinine clearance 10–29	Creatinine clearance <10	Intermittent hemodialysis (HD)	Peritoneal dialysis (PD)
Rifampicin 10 mg/kg/day up to 600 mg	No dose adjustment required	No dose adjustment required	No dose adjustment required	No dose adjustment required	No dose adjustment required
Isoniazid 5 mg/kg/day up to 300 mg	No dose adjustment required	No dose adjustment required	No dose adjustment required	No dose adjustment required	No dose adjustment required
Pyrazinamide 30–40 mg/kg/day 1.5 gm for <50 kg 2 gm for >50 kg	No dose adjustment required	30–40 mg/kg q48 hr	30–40 mg/kg three times weekly	30–40 mg/kg three times weekly after dialysis sessions	No dose adjustment required
Ethambutol 15 mg/kg/day	15 mg/kg q24 hr	15 mg/kg q48 hr	15 mg/kg q48 hr	15 mg/kg three times weekly after dialysis sessions	15 mg/kg q48 hr



should be used. N95 masks should be provided to the personnel managing the patient.

## ORCID

Dhruva Chaudhry  <https://orcid.org/0000-0001-5138-2908>

Diksha Tyagi  <https://orcid.org/0000-0003-2739-6909>

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