Limiting Consumption in Tuberculosis: Current Concepts in anti-Tuberculosis Treatment in the Critically Ill Patient

Mervyn Mer, FRCP, PhD[1]; Alimudin Zumla, FRCP, PhD[2];
Martin W. Dünser, MD[3]

[1], Department of Medicine, Divisions of Critical Care and Pulmonology, Charlotte Maxeke Johannesburg Academic Hospital and Faculty of Health Sciences University of Witwatersrand, Johannesburg, South Africa.

[2], Division of Infection and Immunity, University College London Medical School, and NIHR Biomedical Research Center at University College of London Hospitals, London, United Kingdom;

[3], Department of Anesthesiology and Intensive Care Medicine, Kepler University Hospital, Johannes Kepler University Linz, Linz, Austria.

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Once considered a waning disease, the burden of tuberculosis (TB) has increased around the world over the last decades. Today, TB is the leading cause of mortality associated with a single infectious pathogen [1]. Although treatment regimens as suggested by the World Health Organization (WHO) result in survival rates of 95% under trial conditions [2], the mortality of TB-associated critical illness remains unacceptably high, and exceeds 50% in many cohorts [3]. This makes *Mycobacterium tuberuclosis* one of the deadliest causes of sepsis, a fact often not recognized by many clinicians in high-income countries. The exponential increase in mortality between non-critically and critically ill patients with active TB disease suggests that anti-TB treatment regimens may be inadequate once organ dysfunction and sepsis have occurred. This concise review focuses on novel pharmacokinetic considerations and suggests a potential novel approach to anti-TB treatment in the critically ill patient.

Who should be treated?

Timely initiation of anti-TB therapy is essential for treatment success, particularly in patients with a high disease severity [3]. This crucially depends on early recognition of at-risk populations and rapid confirmation of the diagnosis. Risk factors for active TB disease broadly include poor living conditions, previous infection or contact with TB (e.g. people living in or originating from endemic regions, prisoners, healthcare workers), immunosuppression (e.g. human immunodeficiency virus (HIV) infection, immunosuppressive therapy including biologics, alcoholism), extremes of age, and medical conditions known to increase the risk for TB (e.g. COPD,

silicosis, diabetes mellitus, malnutrition). Acute respiratory failure, altered mental state, septic shock and multiple organ dysfunction are the most common causes of critical illness and intensive care unit admission of patients with TB. Rapid TB tests based on nucleic acid amplification techniques (e.g. GeneXpert MTB/RIF) are sensitive and specific to diagnose active TB disease in both HIV-negative and -positive patients within a few hours [4]. Simultaneously, these tests can identify multi-drug resistant (MDR) strains.

What anti-TB treatment regimen should be started in critically ill patients?

For both adults and children, the WHO recommends an intensive treatment regimen (rifampicin+isoniazid+ethambutol+pyrazinamide) for two months, followed by a continuation regimen (rifampicin+isoniazid) for four to seven months [5]. Treatment regimens for MDR TB include at least four second line anti-TB drugs [5].

Pharmacokinetic considerations in critically ill patients

Although only limited data on pharmacokinetic changes of anti-TB drugs in critically ill patients have been published, those available consistently report inadequate anti-TB drug levels. In a South African population, therapeutic drug levels were detected in <30% of critically ill patients when a standard drug regimen was given as a fixed drug combination dose via a nasogastric tube [6]. Multiple factors alter pharmacokinetics during critical illness [7].

Intestinal drug absorption is commonly delayed or altered by gastroparesis, intestinal paralysis, pharmacological ulcer prophylaxis, and changes in the gut microbiome. Fluid accumulation increases the volume of distribution of anti-TB drugs with consequent reduction in serum and tissue levels. In addition, glomerular hyperfiltration [7] resulting in augmented renal clearance of anti-TB drugs, genetic variations in drug metabolization (e.g. isoniazid), and poor penetration into infected compartments [8] are likely to contribute to sub-therapeutic levels at the site of TB infection. Such sub-therapeutic anti-TB drug levels have been associated with treatment failure and increased mortality [9,10].

A novel approach to anti-TB treatment in critically ill patients

In view of the aforementioned pharmacokinetic changes, it appears pragmatic to modify the initial anti-TB treatment in critically ill patients to optimize and achieve therapeutic blood levels of anti-TB drugs (Figure 1). During the phase of critical illness, anti-TB drugs should be administered intravenously and probably at higher dosages than recommended by current guidelines. Although rifampicin, the drug with the highest sterilizing TB activity, is available in an intravenous formulation, it and other standard anti-TB drugs are not universally available in this form. Consequently, modified regimens including intravenous formulations of alternative and highly effective anti-TB drugs (e.g. rifampicin+moxifloxacin+amikacin) may be administered. Empirical intravenous fluoroquinolone use improved the survival of critically ill patients admitted for pulmonary TB [11]. Several studies have reported that higher than usual doses of anti-TB drugs (e.g.

rifampicin up to 35 mg/kg/d [12]) were safe, reduced the time to culture conversion in liquid media, and may be associated with better survival in patients with severe disease [12,13]. A recent large trial evaluating an intensified regimen including higher-dose rifampicin (15 mg/kg/d) and levofloxacin (20 mg/kg/d) for the first eight weeks, however, failed to confirm these results in adults with TB meningitis [14]. Since only 17.4% of study patients presented with a high disease severity, the implications of this trial for the management of critically ill patients remain unclear. The use of therapeutic drug monitoring (TDM) has also been advocated to optimize dosing of anti-TB drugs relative to minimum inhibitory concentrations (MICs) [15]. Critical drawbacks of such a strategy are the restricted availability of this useful adjunct in many endemic regions, and the fact that MICs are only known after culture and resistance testing. In all critically ill patients and especially in those with MDR TB disease, infectious disease specialist should assist with the empirical selection and dosing of anti-TB drugs, as well as their interactions with other drugs (e.g. HIV therapy). During recovery from critical illness, high-dose intravenous anti-TB therapy can be switched to currently recommended enteral, fixed dose regimens (Figure 1). The time point for this transition is clinically highlighted and determined by improvement of organ function, in particular gastrointestinal function (e.g. full tolerance of enteral feeds), and reversal of fluid accumulation.

Conclusions

TB remains an enormous healthcare problem with a billion lives having been consumed over the last two centuries. Scores of critically ill patients with TB are encountered globally on a daily basis. It is incumbent on intensive care practitioners to be aware of the problem and focus on efforts to address the unacceptably poor outcomes associated with this disease entity. Although various factors may influence, optimizing therapeutic approaches may very well limit "consumption" in critically ill patients with TB. We eagerly and excitedly await further work in this sphere!
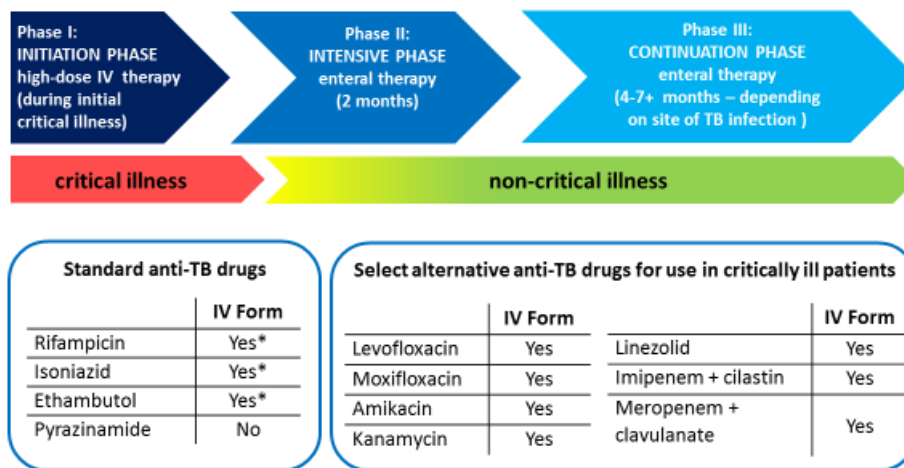
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Figure 1. Potential novel approach to anti-TB treatment in critically ill patients consisting of three phases of therapy.

Standard anti-TB drugs	
	IV Form
Rifampicin	Yes*
Isoniazid	Yes*
Ethambutol	Yes*
Pyrazinamide	No

Select alternative anti-TB drugs for use in critically ill patients			
	IV Form		IV Form
Levofloxacin	Yes	Linezolid	Yes
Moxifloxacin	Yes	Imipenem + cilastin	Yes
Amikacin	Yes	Meropenem + clavulanate	Yes
Kanamycin	Yes		

*, inconsistent availability; IV, intravenous.