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WHAT'S NEW IN INTENSIVE CARE

Limiting consumption in tuberculosis: current concepts in anti-tuberculosis treatment in the critically ill patient

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Intensive Care MedIntensive Care MedIntensive Care MedOnce considered a waning disease, the incidence of tuberculosis (TB) has increased around the world over the last decades. Today, TB is the leading cause of death associated with a single infectious pathogen [1]. An increase in the burden of TB has not only been seen in endemic areas but also in high-income countries and intensive care unit populations. The scarce evidence on the epidemiology of TB in critically ill patients has recently been summarized [2]. In the majority of patients, TB-associated critical illness is caused by TB-induced new organ dysfunction and thereby sepsis. Accordingly, acute respiratory failure, septic shock and multi-organ dysfunction are the most common reasons for intensive care unit admission in patients with pulmonary or extrapulmonary TB [2].

Although treatment regimens as suggested by the World Health Organization (WHO) result in survival rates of 95% under trial conditions [3], the mortality of TB-associated critical illness remains unacceptably high and exceeds 50% [4]. This makes *Mycobacterium tuberculosis* 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.

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Who should be treated?

Timely initiation of anti-TB therapy is essential for treatment success, particularly in patients with a high disease severity [4]. This crucially depends on early recognition of at-risk populations and rapid confirmation of the diagnosis. Risk factors for active TB disease are broadly related to impaired immune function. For example, people living in poor or crowded conditions (e.g., prisons, camps) or those with previous TB infection or contact with TB (e.g., people living in or originating from endemic regions, healthcare workers) are at increased risk [2]. Although patients infected with the human immunodeficiency virus (HIV) make up a relevant percentage of patients with active TB disease worldwide (~11%), particularly clinicians in non-endemic areas face a growing number of active TB disease in patients with other immunodeficiencies or on immunosuppressant medication [2]. Furthermore, extremes of age and medical conditions (e.g., COPD, silicosis, diabetes mellitus, malnutrition) both increase the risk for TB and TB-associated critical illness [2]. 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 [5]. 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 2 months followed by a continuation regimen (rifampicin + isoniazid) for another 4–7 months [6]. Treatment regimens for MDR TB include at least four second-line anti-TB drugs [7].

Both the intensive and continuation regimens are based on oral formulations.

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 [8]. Multiple factors alter pharmacokinetics during critical illness [9]. Intestinal drug absorption is commonly delayed or altered by gastroparesis, intestinal paralysis, pharmacologic 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 [8] resulting in augmented renal clearance of anti-TB drugs, genetic variations in drug metabolization (e.g., isoniazid) and poor penetration into infected compartments are likely to contribute to sub-therapeutic levels at the site of TB infection. Sub-therapeutic anti-TB drug levels are associated with treatment failure and increased mortality [10].

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

In view of the aforementioned pharmacokinetic changes during critical illness, it appears pragmatic to modify anti-TB treatment in critically ill patients by adding a third treatment regimen to achieve therapeutic blood levels of anti-TB drugs specifically during the initial period of life-threatening disease (Fig. 1). During this additional "initiation phase," anti-TB drugs should be administered intravenously and probably at higher dosages than currently recommended. 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 survival in critically ill patients with pulmonary TB [11]. Several studies reported that higher than usual doses of anti-TB drugs (e.g., rifampicin up to 35 mg/kg/day [12]) were safe, reduced the time to culture conversion and may be associated with better survival in severe disease [12, 13]. A recent large trial evaluating an intensified regimen including higher-dose rifampicin (15 mg/kg/day) and levofloxacin (20 mg/kg/day) for the first 8 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 has been advocated to optimize dosing of anti-TB drugs relative to minimum inhibitory concentrations (MICs) [15]. Critical drawbacks of such

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
Levofloxacin	Yes
Moxifloxacin	Yes
Amikacin	Yes
Kanamycin	Yes

	IV Form
Linezolid	Yes
Imipenem + cilastin	Yes
Meropenem + clavulanate	Yes

*, inconsistent availability; IV, intravenous.

Fig. 1 Potential novel approach to anti-TB treatment in critically ill patients consisting of three (instead of two) phases of therapy. Asterisk indicates inconsistent availability. *IV* intravenous

a strategy are its restricted availability 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, an infectious disease specialist should assist with the empirical selection and dosing of anti-TB drugs also considering 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 (Fig. 1). The time point for this transition is highlighted 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 2 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 be influential, optimizing therapeutic approaches might very well limit "consumption" in critically ill patients with TB. We eagerly and excitedly await further work in this sphere!

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Compliance with ethical standards

Conflicts of interest

None of the authors has a conflict of interest regarding the drugs, methods or techniques discussed in this manuscript.

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