Journal of Critical Care 45 (2018) 184–196

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

The critically ill patient with tuberculosis in intensive care: Clinical presentations, management and infection control☆

Akaninyene Otu, MPH, FWACP [a,b], Madiha Hashmi, FFARCSI [c], Ahmed M. Mukhtar, MD [d], Arthur Kwizera, MD [e], Simon Tiberi, MD [f], Bruce Macrae, FRCPath [g], Alimudin Zumla, PhD.FRCP [h], Martin W. Dünser, MD [i,j,*], Mervyn Mer, FRCP, PhD [k]

[a] Department of Internal Medicine, University of Calabar, Calabar, Nigeria
[b] National Aspergillosis Centre, University Hospital of South Manchester, Manchester, United Kingdom
[c] Department of Anaesthesiology, Aga Khan University, Karachi, Pakistan
[d] Department of Anesthesia and Intensive Care, Cairo University, Cairo, Egypt
[e] Department of Anaesthesia and Critical Care, Makerere University College of Health Sciences, Kampala, Uganda
[f] Division of Infection, Royal London Hospital, Barts Health NHS Trust, London, United Kingdom
[g] Department of Microbiology, University College London Hospitals NHS Foundation Trust, London, United Kingdom
[h] Division of Infection and Immunity, University College London Medical School, and NIHR Biomedical Research Center at University College of London Hospitals, London, United Kingdom
[i] Department of Critical Care, University College of London Hospital, London, United Kingdom
[j] Department of Anaesthesia and Intensive Care Medicine, Kepler University Hospital, Johannes Kepler University Linz, Linz, Austria
[k] 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

ARTICLE INFO

Keywords:
Tuberculosis
Latent tuberculosis
Multi-drug resistant tuberculosis
Drug-resistant tuberculosis
Infection control
Intensive care

ABSTRACT

Tuberculosis (TB) is one of the top ten causes of death worldwide. In 2016, there were 490,000 cases of multi-drug resistant TB globally. Over 2 billion people have asymptomatic latent *Mycobacterium tuberculosis* infection. TB represents an important, but neglected management issue in patients presenting to intensive care units. Tuberculosis in intensive care settings may present as the primary diagnosis (active drug sensitive or resistant TB disease). In other patients TB may be an incidental co-morbid finding as previously undiagnosed sub-clinical or latent TB which may re-activate under conditions of stress and immunosuppression. In Sub-Saharan Africa, where co-infection with the human immunodeficiency virus and other communicable diseases is highly prevalent, TB is one of the most frequent clinical management issues in all healthcare settings. Acute respiratory failure, septic shock and multi-organ dysfunction are the most common reasons for intensive care unit admission of patients with pulmonary or extrapulmonary TB. Poor absorption of anti-TB drugs occurs in critically ill patients and worsens survival. The mortality of patients requiring intensive care is high. The majority of early TB deaths result from acute cardiorespiratory failure or septic shock. Important clinical presentations, management and infection control issues regarding TB in intensive care settings are reviewed.

1. Introduction

Tuberculosis (TB) is the leading cause of mortality associated with a single identifiable infectious pathogen globally. The World Health Organization (WHO) estimated that, in 2016, 10.4 million new TB cases occurred worldwide, with about 10% (1 million) of these cases occurring in people living with human immunodeficiency virus (HIV) infection [1]. Sixty percent of new TB cases were reported from six endemic areas (India, Pakistan, Indonesia, China, Nigeria, South Africa), while only 3% of active TB cases were reported from Europe. TB claimed 1.674 million lives in 2016 [1]. The WHO defines death from TB as all-cause mortality during the course of TB treatment. With relevant variations around the world (endemic areas >50% vs. <5% in non-endemic areas), directly TB-related deaths usually occur early after diagnosis [e.g. 20 days following diagnosis] [2]. In 2016, there were an estimated 490,000 cases of multi-drug resistant (MDR) TB worldwide with India, China, South Africa and Eastern Europe carrying the greatest burden [1]. Over 2 billion people have asymptomatic latent *Mycobacterium tuberculosis* (*M.tb*) infection of whom about 10% will develop clinical disease during their lifetime under conditions such as stress, migration,

☆ All authors contributed equally.

* Corresponding author at: Department of Anaesthesia and Intensive Care Medicine, Kepler University Hospital, Johannes Kepler University Linz, Altenbergerstrasse 69, 4040 Linz, Austria.
E-mail address: Martin.Duenser@i-med.ac.at (M.W. Dünser).

https://doi.org/10.1016/j.jcrc.2018.03.015
0883-9441/

poor nutrition, co-morbidities (diabetes, cancer, COPD), use of steroids, biologics and immunotherapies which lead to immunocompromise [3].

Patients infected with *M.tb* raise important management issues in adult and children presenting to intensive care units. A relevant number of these patients clinically present with active (drug-sensitive or MDR) TB disease for single or multiple organ support. In other patients, detection of *M.tb* may be an incidental co-morbid finding as previously undiagnosed sub-clinical disease which only manifests during intensive care. In patients with latent infection, *M.tb* may re-activate to active clinical diseases under conditions of stress and immunosuppression [3]. Cases of active TB disease present special management and infection control requirements in intensive care units worldwide.

The aim of this review is to provide an overview of the clinical presentation, management (TB drugs, treatment regimens, steroids, organ specific TB, and HIV-co-infection) and infection control practices associated with critically ill patients with TB.

2. Search strategy

We searched the Medline (using PubMed) and other scientific databases (Google Scholar, EMBASE, Cochrane) from Jan 1, 2000 until October 30, 2017 for publications in English by use of the terms 'tuberculosis' or TB, and combined this individually with 'intensive care, 'critical care', 'ITU', 'HDU'. Furthermore, reviews and other relevant literature published before the year 2000, intensive care and infectious disease textbooks, national and international guidelines were screened for relevant information. References of the most relevant publications were retrieved to improve the search sensitivity.

3. Clinical presentation in intensive care

Reports from Brazil, Germany, and Taiwan, indicate that the majority of early TB deaths results from acute cardiorespiratory failure [2,4,5]. In Sub-Saharan Africa, where co-morbidity with HIV and other communicable diseases are highly prevalent, TB is one of the most frequent clinical management issues in all healthcare settings [6-8]. Acute respiratory failure, septic shock and multi-organ dysfunction are the most common reasons for intensive care unit admission of adult and paediatric patients with active TB [9-12]. Further common causes of critical illness in patients with active TB are bacterial co-infections (e.g. chest infections), anti-TB drug toxicity, thromboembolic complications (Table 1), post-surgical status, and pulmonary haemorrhage [18]. Patients with TB admitted to a Portuguese intensive care unit required a high degree of organ support [mechanical ventilation (66.7%), vasopressors (35.9%), renal replacement therapy (7.7%), extracorporeal membrane oxygenation (5.1%)] [19]. The mortality of patients with confirmed TB requiring intensive care is high [up to 68.7%] [11,20]. Several models to predict mortality have been published. The score with the highest predictive value [area under the receiver operator curve, 0.92 (95%CI, 0.85–0.98)] identified miliary TB, need for mechanical ventilation and presence of shock as the main determinants of death [21]. Other documented risk factors for mortality include nosocomial pneumonia, multi-organ failure, TB destroyed lung, an APACHE II score >20 and duration of symptoms >4 weeks [11,22,23].

4. Management of patients in intensive care

4.1. Anti-TB drugs and treatment regimens

Anti-TB drugs are the mainstay of TB treatment. Both for children and adults with drug-sensitive TB, national and international guidelines recommend a standard treatment regimen including four anti-TB drugs (Table 3) [24,25]. This regimen consists of an intensive (two months of four drugs) followed by a continuation phase (four months of isoniazid and rifampicin). Treatment extension to nine months (and in some cases longer) should be considered in patients with TB of joint or bone, or those with a high risk of relapse (e.g. extensive disease, cavitations, immunosuppression, sputum culture positive >8 weeks), and 12 months or longer in patients with tuberculous meningitis (TBM) [3,26]. Early initiation of anti-TB treatment is essential and appears to be associated with improved survival, particularly in patients with a high disease severity [27]. This does not only require a high index of clinical suspicion but also means that, in many cases, anti-TB drugs must be initiated empirically based on individual patient factors (Table 2) and the clinical presentation, even in the absence of a positive sputum smear. Rapid TB tests (e.g. based on nucleic acid amplification techniques) can critically shorten the time to confirmation of the diagnosis (Table 3) [28].

Infection with MDR (resistant to at least isoniazid and rifampicin) and extensively resistant (resistant to at least isoniazid, rifampicin, fluoroquinolones and one second line injectable) strains of *M.tb* carries an exceptionally high mortality and is a growing challenge in many parts of the world [1,3]. Rapid molecular diagnostic tests (e.g. GeneXpert MTB/RIF assay) yield fast results on *M.tb* resistance to rifampicin, which by proxy indicates resistance to isoniazid in the majority of cases [28]. Standard phenotypic culture-based drug susceptibility tests yield results within two weeks and should be performed routinely wherever available [3]. Clinically, the intensivist must consider infection with a resistant *M.tb* strain if the patient originates from a high-risk region, has undergone a treatment course of first-line anti-TB drugs or fails to respond to standard anti-TB regimens [3,26]. As a rule-of-thumb, further drugs should not be added to a failing regimen but a new regimen consisting of four to five second-line anti-TB drugs or drugs the pathogen is susceptible to should be implemented instead. Treatment of drug-resistant TB should prompt input from an infectious disease specialist, and MDR-TB WHO guidelines should be followed where possible. Initial treatment regimens for drug-resistant TB includes at least four second line drugs (e.g. core drugs: later generation fluoroquinolones, amikacin, capreomycin, kanamycin, ethionamide/prothionamide, cycloserine, linezolid, clofazimine and non-core drugs like delamanid, bedaquiline, *p*-aminosalicylic acid, imipenem-cilastatin/meropenem, amoxicillin-clavulanate, thioacetazone) administered over eighteen months or more [3,24,28].

The treatment success of standard regimens under trial conditions in drug-susceptible TB is 95% in non-critically ill patients [3]. Treatment success critically depends on adequate blood levels of anti-TB drugs [29], while pharmacokinetic variability to a single drug of the regimen can cause treatment failure or induce drug resistance [30]. Pharmacokinetics is extensively altered by physiological and pathophysiological changes occurring during critical illness [31]. So far, little is known

Table 1
Factbox – Venous thromboembolism (VTE) in patients with TB disease.

Background

- VTE is one of the most common medical complications of TB [13].
- Incidences of 1.5–3.4% have been reported in patients with TB disease [13,14].
- VTE can occur early or late in the course of the disease [13].
- Early VTE often occurs after initiation of anti-TB drugs (median interval 14 days) [15].

Pathogenesis [13,16]

- TB-induced hypercoagulability (further exacerbated by HIV co-infection)
- Venous vessel wall inflammation (due to adjacent infectious process)
- Venous compression by lymph nodes
- Endothelial dysfunction due to TB-induced host response and rifampicin [17]
- immobilization

Diagnosis and treatment

- Comparable to patients without TB