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

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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.

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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,

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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

Table 2
Risk factors for acquiring infection with *M.tb* and for developing active TB disease.

Risk factors for acquiring infection with *Mycobacterium tuberculosis*	Risk factors for developing active TB disease after infection with *Mycobacterium tuberculosis*
• Close contact with an active pulmonary TB disease case • Foreign born adult or child, who have migrated within the last 5 years from a high incidence TB country • Low-income group with little access to health care, including homeless people, living in crowded poorly ventilated rooms or settings • People who live or work in high-risk settings (e.g. nursing homes, homeless shelters, mental health institutions, military garrisons, refugee camps or prisons) • Illicit drug use • Sex workers • Health care workers	• HIV infection • Recent treatment for *M.tuberculosis* (within the past two years) • Medical conditions known to increase the risk for TB: - silicosis - chronic respiratory disease - smoking - diabetes mellitus - severe chronic renal insufficiency/-hemodialysis - certain types of cancer (e.g. head and neck) - solid organ transplantation - immunosuppressive therapy (including prolonged use of corticosteroids, chemotherapies and monoclonal antibodies) - malnourished, underweight (body mass index <18) • Pregnancy and post-partum period • Illicit drug use • Alcoholism • Age < 5 or > 65 years • Malnutrition • Vitamin D deficiency

TB, tuberculosis; HIV, human immunodeficiency virus.

about the pharmacokinetic changes of anti-TB drugs in critically ill patients. An observational study from South Africa reported that therapeutic blood levels were achieved in only a minority (<30%) of critically ill patients when rifampicin, isoniazid, pyrazinamide and ethambutol were given as a fixed dose via a nasogastric tube [32]. Case reports observed inadequate blood levels of anti-TB drugs in patients on renal replacement therapy and/or extracorporeal membrane oxygenation [33,34]. Multiple factors may influence pharmacokinetics in critically ill patients. Intestinal absorption may be delayed or altered by gastroparesis, intestinal paralysis, ulcer prophylaxis, enteral nutrition and critical illness-associated changes of the microbiome. Oedema formation and fluid accumulation increase the volume of distribution of anti-TB drugs. Glomerular hyperfiltration or augmented renal clearance, and acute kidney or liver injury can affect anti-TB drug elimination [31]. In addition, genetic variations in drug metabolism [e.g. acetylator status for isoniazid metabolization] play a role as well [35,36]. To avoid inadequate intestinal drug absorption, it appears pragmatic to, at least initially until gastrointestinal function is restored, administer anti-TB drugs intravenously to critically ill patients. Although rifampicin, the drug with the highest sterilizing TB activity, is available in an intravenous formulation, not all drugs are (Table 4), especially the bactericidal isoniazid is not readily available in all regions of the world. In these areas, local regimens of alternative intravenous anti-TB drugs (e.g. a combination of intravenous rifampicin, moxifloxacin and amikacin) may be useful and effective to bridge the period of impaired gastrointestinal function. The use of empirical intravenous fluoroquinolones was suggested to improve survival of critically ill patients admitted for pulmonary TB

Table 3
Diagnostic work-up of TB.

General clinical symptoms		Fever, cough, (night) sweats, chills, weight loss, loss of appetite, lymphadenopathy, asthenia, fatigue, malaise
Pulmonary or laryngeal TB	Specific clinical symptoms Imaging and investigations: chest X-ray, thoracic ultrasound, CT chest, laryngoscopy, bronchoscopy (lavage and or biopsy)	Coughing, haemoptysis, chest pain when breathing or coughing, hoarseness (laryngeal TB) Chest X-ray should be considered in all possible pulmonary and extrapulmonary TB cases. Pulmonary TB classically affects the upper lobes and nodules and cavities are suggestive of the disease. However in immunocompromised individuals with a low CD4 count ($<100/mm^3$) a more disseminated (miliary) pattern or lower or mid zone consolidation may occur. Typical appearance may not be present with more advanced disease; clear chest X-rays have been described in patients with very advanced disease. Chest CT scan may demonstrate "tree in bud" changes, hilar lymphadenopathy and/or cavities and pleural effusions.
	Sputum or induced sputum required for AFB smear microscopy (ZN or auramine) and culture examination	AFB smear microscopy allows for a preliminary confirmation of pulmonary TB and allows for an estimate of bacillary excretion and degree of infectiousness as well as an important marker of TB treatment response or failure. Ideally a smear result should be available within 24 h. Culture is required in most cases to confirm diagnosis of pulmonary and extra pulmonary TB and remains the gold standard, culture can also allow for drug susceptibility of first and second line anti TB drugs as well as typing and whole genome sequencing. Note: If a diagnosis of pulmonary TB cannot be established from sputum smear, other procedures maybe necessary, including culture, NAAT (GeneXpert-Cepheid), bronchoscopy, and gastric aspiration in children for deeper samples. NAAT is a test performed on sputum or lower respiratory samples to detect *Mycobacterium tuberculosis* complex and rifampicin resistance through amplification of the rpoB gene. Ideally NAAT test result should be made available within 72 h. Culture is necessary for species identification of all clinical specimens suspected of containing Mycobacteria. It is required for phenotypic first and second line TB drug susceptibility testing and for subsequent genotyping and whole genome sequencing. Liquid Mycobacterial culture allows for more rapid detection mean 14 days (up to 42 days) than solid culture but is at risk of greater contamination and costs more. Drug Susceptibility Testing (if available) for first-line drugs is generally performed on initial isolates of all patients to identify an effective anti-TB regimen. Testing of second-line drugs may be performed on the initial specimen if drug resistant TB suspected or confirmed by NAAT. Drug Resistance Screening by Sequencing with molecular tool like the Hain line probe

Table 3 (*continued*)

General clinical symptoms		Fever, cough, (night) sweats, chills, weight loss, loss of appetite, lymphadenopathy, asthenia, fatigue, malaise
		assay. Allows for rapid confirmation of MDR-TB through the identification of genetic mutations associated with rifampicin (rpoB), isoniazid (katG), fluroquinolones (gyr A and B) and injectable amikacin (rrs).
Extra-pulmonary TB	Specific clinical symptoms	Clinical symptoms depend on the part of body affected by TB (see text for details)
	Imaging: X-ray, ultrasound, CT, MRI of affected organ or body site	A high degree of suspicion is generally required to diagnose extrapulmonary TB beyond TB lymphadenopathy. Extrapulmonary TB frequently requires a broad differential diagnosis to exclude malignancy, other granulomatous diseases and non-specific infections.
	Depending on the anatomical site, other clinical specimens are necessary, such as: • Urine • CSF • Pleural fluid • Pus or other aspirated fluid • Biopsy specimens • Blood	AFB microscopy may not provide a good yield from extrapulmonary sources i.e., large quantity of CSF is required to perform a ZN stain. Culture is required in most cases to confirm diagnosis of pulmonary and extra pulmonary TB and remains the gold standard, culture can also allow for drug susceptibility of first and second line anti-TB drugs as well as typing and whole genome sequencing. NAAT has varying sensitivity and specificity for extra pulmonary sites and is highest with lymph node aspirates and lowest with CSF and pericardial fluid.

TB, tuberculosis; CT, computer-tomography; AFB, acid fast bacilli; ZN, Ziehl Neelsen; NAAT, Nucleic Acid Amplification Test; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid.

mimicking severe community-acquired pneumonia [23]. Smaller studies indicated that higher doses of rifampicin (e.g. 15 mg/kg/d) and addition of a fluoroquinolone (e.g. levofloxacin at 20 mg/kg/d) might be associated with improved survival from TB [37,38]. However, a recent large trial failed to confirm these results in adult patients with TBM [39]. Since only 17.4% of study patients presented with a high disease severity in this trial, its conclusions for critically ill patients remain unclear. Others have recommended therapeutic drug monitoring to optimize dosing of anti-TB drugs in critically ill patients [40,41]. This is, however, unlikely to be available in all settings, particularly in those parts of the world where TB is endemic (see Table 5).

Both rifampicin and isoniazid change the activity of cytochrome P450 isoenzymes and are responsible for interactions with several drugs commonly administered in critically ill patients (Table 4). While isoniazid inhibits, rifampicin induces cytochrome activity. Overall, the inductive effects of rifampicin outweigh isoniazid's inhibitory effects. Drug level monitoring and dose adjustments of other drugs are frequently necessary. Notably, rifampicin may reduce blood levels of selected second line anti-TB drugs such as moxifloxacin [42].

Another key challenge of anti-TB drugs relates to their side effects. Some of them (e.g. isoniazid-induced peripheral neuropathy) may be preventable [e.g. by pyridoxine 10 (−25) mg/d] [24,25]. Others are not life-threatening but may have significant impact on the patient's quality of life if not recognized early (e.g. ethambutol-induced retrobulbar neuritis). Drug-induced liver injury is the most dangerous adverse effect of anti-TB drugs and occurs at an incidence of 3–13% with incidence increasing with age [43]. It is commonly triggered by rifampicin, isoniazid, and/or pyrazinamide, especially if combined with other potentially hepatotoxic drugs (e.g. paracetamol, valproic acid). Drug-induced liver injury may develop early after initiation of anti-TB therapy, but may cause critical illness during the subsequent treatment phase. As patients with underlying liver dysfunction are at highest risk, liver function should be judiciously evaluated (incl. hepatitis serology) in all patients before initiation of anti-TB treatment. The first sign of drug-induced liver injury is usually an increase in liver enzymes >3 times of the normal value. The clinical picture may range from an asymptomatic derangement of liver enzymes to acute liver failure. In case of laboratory or clinical signs of liver dysfunction (e.g. right upper quadrant pain, jaundice, coagulopathy, hypoglycemia, encephalopathy), hepatotoxic anti-TB drugs (e.g. rifampicin, isoniazid, pyrazinamide) should be replaced by an aminoglycoside, levofloxacin and ethambutol, or other second-line drugs [44].

4.2. The use of steroids

Glucocorticoids alter the immune response to *M.tb*. Current evidence and guidelines suggest that adjunctive steroid therapy reduces mortality and probably long-term sequelae in HIV-negative patients with tuberculous meningitis and pericarditis [24,25]. An ongoing trial in Southeast Asia evaluates whether this evidence can be translated to HIV-positive patients. The effects of steroids on mortality of patients with pulmonary or extrapulmonary TB other than meningitis or pericarditis remain controversial. A recent meta-analysis reported that steroids could decrease mortality for all forms of TB [45]. It appears that these effects are most consistent in patients with a high disease severity such as miliary TB or TB-associated septic shock [45,46]. Adrenal insufficiency in patients with TB can be caused by an exaggerated pro-inflammatory response [47], tuberculous infiltration or adrenal haemorrhage. Rifampicin increases cortisol metabolism and can precipitate hypocortisolism [48]. Although an inadequate increase in cortisol levels has been observed in 50% of hospitalized patients with TB in India [49], one study reported symptomatic adrenal insufficiency in only 1.4% of patients [50]. The incidence of adrenal insufficiency in critically ill patients with TB is unclear. Similarly, no studies have addressed the question whether steroid replacement improves organ function and/or outcome in patients with TB and critical illness related corticosteroid insufficiency.

4.3. Organ-specific TB – management and support

4.3.1. Pulmonary TB

The most commonly affected organ in TB infection is the lungs. Similar to other infectious diseases (e.g. influenza), the overall rate of acute respiratory failure in hospitalized patients with pulmonary TB is relatively low (1.5–5%) [51,52]. However, in those with HIV infection, extensive (e.g. miliary) or advanced infection, it is the most common cause of critical illness. An intense pro-inflammatory

Table 4
Overview of first-line anti-TB drugs.

Drug	Dose	IV form	Contra-indications	CSF penetration	Side effects	Comment
Rifampicin	Adults: 10 mg/kg/d (max. 600 mg/d) Children: 15–20 mg/kg/d (max. 600 mg/d) No dose adjustment in renal failure	Available	Unstable liver disease, known hyper-sensitivity	10–20%	DILI, vasculitis, nephritis, thrombocytopenia, leukopenia, hemolytic anemia, exfoliative dermatitis	Frequent drug interactions (CYP induction)[a], orange discoloration of body secretions (incl. urine, tears, sweat), monitoring of liver enzymes and bilirubin recommended
Isoniazid	Adults: 5 mg/kg/d Children: 10 mg/kg/d (max. 300 mg/d) No dose adjustment in renal failure	Available (not always accessible)	Unstable liver disease, known hyper-sensitivity	100%	DILI, peripheral neuropathy, lupus-like syndrome, (hypersensitivity) vasculitis, seizures, altered mental state	Drug interactions (CYP inhibition)[b], combine with pyridoxine [10 (−25) mg/d], monitoring of liver enzymes recommended
Ethambutol	Adults: 15 mg/kg/d Children: 20–30 mg/kg/d (max. 1200 mg/d) Dose adjustment in renal failure	Available (not always accessible)	Retrobulbar neuritis, known hyper-sensitivity	25–50%	Retrobulbar neuritis, DILI, thrombocytopenia, leukopenia, myocarditis, pericarditis, altered mental state, exanthema, arthralgia	Visual disturbances often begin with loss of red-green discrimination and then rapidly progress to blindness
Pyrazinamide	Adults: 25 mg/kg/d Children: 35 mg/kg/d (max. 2000 mg/d) Dose adjustment in renal failure	Not available	Unstable liver disease, known hyper-sensitivity, porphyria	100%	DILI, exanthema, rhabdomyolysis, arthritis	Monitoring of liver enzymes recommended

CSF, cerebrospinal fluid; DILI, drug-induced liver injury; CYP, cytochrome P450 system.
Fixed dose combination tablets (containing either rifampicin, isoniazid, pyrazinamide and ethambutol, or rifampicin and isoniazid) are available. There is limited data on the bioavailability if these tablets are crushed and administered via the nasogastric tube. Alternatively, a syrup formulation can be used, particularly in children.
[a] Rifampicin reduces blood levels of the following drugs (relevant to intensive care): azole antifungal agents (e.g. fluconazole, voriconazole, itraconazole), moxifloxacin, clarithromycin, doxycycline, methadone, warfarin, cyclosporine, steroids, anticonvulsants (incl. phenytoin), digoxin, verapamil, diltiazem, nifedipine, propranolol, metoprolol, enalapril, losartan, propafenone, theophylline, statins, sulfonyl ureas, haloperidol, quetiapine, benzodiazepines, zolpidem, non-nucleoside reverse transcriptase inhibitors, protease inhibitors.
[b] Isoniazid increases blood levels of the following drugs (relevant to intensive care): anticonvulsants (e.g. phenytoin, carbamazepine, valproic acid), diazepam, triazolam, theophylline, acetaminophen, warfarin. When isoniazid is combined with rifampicin, the CYP inducing effects of rifampicin predominate.

reaction to *Mycobacterium*-induced injury of the alveolar capillary membrane increases extravascular lung water, induces a ventilation/perfusion mismatch and increases the alveolar arterial gradient (Figs. 1 and 2). Interstitial granulomatous infection and obliterative endarteritis are further contributory factors in the pathophysiology of acute respiratory failure due to pulmonary TB (Fig. 3) [53,54]. Clinically, many of these patients fulfill the criteria of the Acute Respiratory Distress Syndrome (ARDS) [55]. In advanced disease, air spaces become destroyed by caseating granulomas and fibrocavitary lesions [53,54].

The mortality of patients with TB-associated ARDS exceeds that of patients with ARDS from any other cause [56]. Notably, mortality in patients developing ARDS only during anti-TB treatment is lower than in those who present with ARDS at admission [57]. Although non-invasive ventilation has been reported as a useful method to improve respiratory failure in patients with chronic pulmonary sequelae from lung TB [58], the failure rate of non-invasive ventilation in patients with TB-associated ARDS is high. Principles of invasive ventilation (e.g. lung-protective ventilation) in these patients do not differ from those applied in other patients with ARDS. Need for mechanical ventilatory support is often prolonged both in adults and children [10,12].

Complications in patients with pulmonary TB are common and include bacterial infection, pulmonary haemorrhage, pleural effusion/empyema, and/or pneumothorax (Fig. 4). Underlying immunosuppression and prolonged mechanical ventilation make these patients extremely prone to nosocomial bacterial infections. Ventilator-associated pneumonia has been reported to occur in up to two thirds of patients [5,59]. Pneumothoraces developed in 13.8% of patients admitted to the intensive care unit because of TB. Most of these occurred during mechanical ventilation [5]. Drainage of pneumothoraces and pleural effusions can be complicated by pleural adhesions and bronchopleural fistulas. Long-term complications of pulmonary TB include chronic respiratory insufficiency due to fibrotic lung changes or extensive cavitary lesions [58,60].

Major haemoptysis (>200 mL blood expectorated/24 h) is a common complication of pulmonary TB, both in the acute and post-infection

Table 5
Key management differences between children and adults with TB.

	Children	Adults
Typical age	6 months to 5 years and >15 years	Any
Disease type	Primary infection	Primary or post-primary infection[a]
Co-infection with HIV	Rare	Frequent
Chest X-ray	Mostly hilar lymphadenopathy with or without infiltrate	Lymphadenopathy with (upper lobe) infiltrates with or without cavitating lesions
M.tb bacilli load in sputum	Low (paucibacillary)	Low to high (multibacillary)
Risk of transmission to others	Low	High
Need for isolation	Yes	Yes
Extrapulmonary TB	Frequent (>30%) (independent of HIV status)	Rare (except in HIV positive patients)
Tuberculous meningitis	Seizures frequent (~50%), agitation and delirium infrequent	Seizures rare (~5%), agitation/delirium frequent
Diagnostic pathway	Pathway similar to adults but more difficult to sample respiratory specimen	
Treatment	3 or 4 first-line anti-TB drugs (drug sensitive TB)	4 first-line anti-TB drugs (drug sensitive TB)
Pharmacokinetics of anti-TB drugs	Children metabolize many anti-TB drugs faster than adults (higher doses per kg required)	
Side effects of anti-TB drugs	Infrequent	Frequent

[a] Outdated concept as studies showed that many cases of suspected post-primary TB were actually re-infections.

period [14]. The main pathogenetic mechanism is vascular wall necrosis of bronchial arteries adjacent to bronchiolar ulcerations or caseating lymph nodes [61]. When tuberculous lesions invade the chest wall, bleeding may also originate from intercostal, subclavian or mammary arteries. The first management priority in patients with pulmonary haemorrhage is airway control and provision of adequate gas exchange. This frequently necessitates endotracheal intubation and mechanical ventilation [62]. Antitussives (e.g. opiates) and tranexamic acid are adjuncts which are often employed under these circumstances. Bronchoscopy can be used to diagnose and treat pulmonary haemorrhage (e.g. by topical application of epinephrine (adrenaline) 1:10,000 to 1:100,000) [63]. If a bleeding source can be determined on contrast-enhanced computer tomography, angiographic embolization is highly effective in controlling the bleeding [64]. Emergency surgery is associated with high mortality and is reserved for patients who cannot be managed conservatively [63].

4.3.2. *Central nervous system TB*

TB-associated pathologies of the central nervous system include delirium, TBM, tuberculoma of the brain or spinal cord, and stroke. While delirium can complicate the course of any critically patient with TB, TBM is the most frequent neurologic condition induced by TB. It often complicates miliary TB and is particularly common in children (0.5–5 years) and HIV-positive subjects. Hospital mortality rates of 25% (67% in HIV-positive patients) and 65% at one year have been reported [65,66]. Approximately half of the survivors suffer from neurological sequelae [65,67]. The pathophysiology of TBM involves haematogenous spread of TB bacilli to the meninges or brain tissue with secondary penetration in the subarachnoid space [68]. Characteristically, the infratentorial meninges and subarachnoid space are predominantly affected. Initial symptoms of TBM are notoriously non-specific (e.g. fever, headache, loss of appetite, malaise, vomiting) and of subacute onset (12–29 days) [68], although one third of patients may present with symptoms lasting one week or less [69]. Agitation is frequent while clinical signs of meningeal irritation are only inconsistently present. Cranial nerve palsies, mostly involving the abducens nerve, are encountered in one third of patients. Based on the level of consciousness, presence of focal neurological deficits and other aspects (meningism, seizures), the British Medical Research Council defined three clinical stages of TBM that are closely related to mortality [70]. The diagnosis of TBM requires a high index of suspicion and clinical acumen. Further diagnostic methods include fundoscopy (e.g. papilloedema, neovascularization) and lumbar puncture. In case of focal neurological deficits, a tuberculoma of the brain or spinal cord as well as a stroke must be suspected and computer tomography or magnetic resonance imaging performed (Fig. 5) [71]. The cerebrospinal fluid analysis is characterized by an increased cell count with lymphocytic predominance, increased protein (when left standing proteins typically precipitate to a "spider's web clot"), and decreased glucose levels.

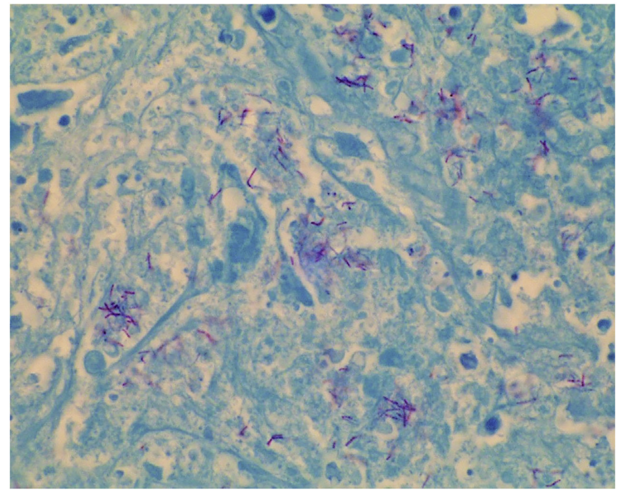

Fig. 1. Lung histology showing *M.tb* bacilli in a patient who died of severe pneumonia.

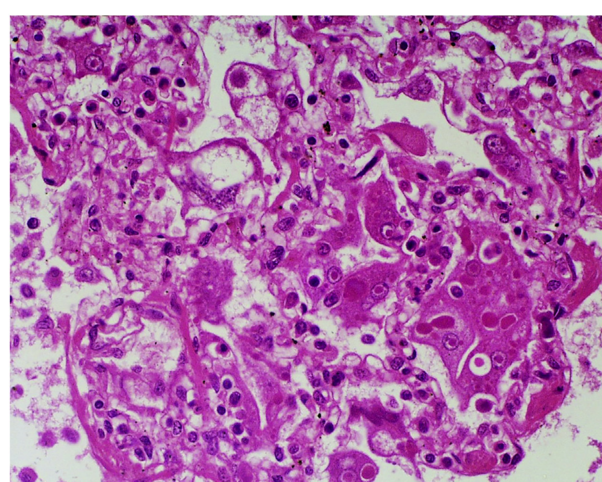

Fig. 2. Autopsy histology of lung of a *M.tb*-HIV co-infected patient showing owl's eyes inclusion bodies of cytomegaly virus.

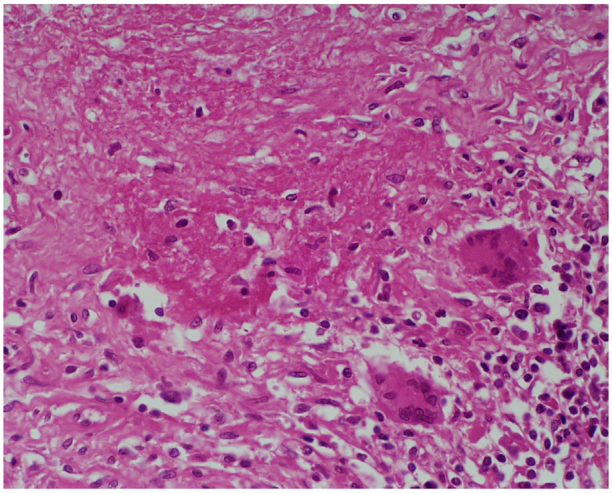

Fig. 3. Autopsy examination of lung tissue in a patient with pulmonary TB - shows Langehan's giant cells and caseous necrosis.

The cerebrospinal fluid of HIV-positive patients with TBM can have lower cell counts, polymorphonuclear cell predominance and normal glucose levels, a constellation which may be confused with cryptococcal meningitis [72]. Smear microscopy with Ziehl Neelsen staining requires high fluid amounts (up to 10 mLs) and has a low diagnostic sensitivity (10–60% depending on laboratory capacities and technician experience). Similarly, the sensitivity of molecular techniques are only moderate (~50%) but specificity is high (98%), and they require at least 2 mL of cerebrospinal fluid [73]. Cerebral imaging studies of adults with TBM revealed that nearly 80% had one or more cerebral tuberculoma(s), many of which paradoxically developed only during anti-TB therapy [74,75].

Nearly all patients with TBM requiring intensive care do so because of an altered mental state (agitation and more commonly a decreasing level of consciousness). In a French series, 75% of critically ill patients with TBM required intubation and mechanical ventilation [76]. British and WHO guidelines recommend timely initiation of anti-TB treatment with first line drugs [24,25], although new data suggest a promising role of fluoroquinolones [77]. In addition, adjunctive steroid therapy with dexamethasone or equivalent doses of prednisolone is recommended [24,25], as trials suggest that this is associated with improved mortality [78]. The duration of steroid therapy is usually two months, with weaning of the steroid dose over this period [65]. Neurosurgical interventions may be indicated for evacuation of large a tuberculoma/s. General neuro-intensive care principles regarding temperature control, cardiorespiratory management and blood sugar control also apply for patients with tuberculous central nervous system involvement.

Complications of TBM are frequent and include hydrocephalus, seizures (more frequent in children than adults), sodium disturbances (e.g. syndrome of inadequate antidiuretic hormone secretion) and stroke. In approximately 80% of cases, the hydrocephalus is communicating and must be suspected in all patients with a decreased mental state. Although conservative management with diuretics (e.g. acetazolamide 100 mg/kg/d) can be attempted, repeated lumbar drainage or placement of a ventricular drain is required in about one third of patients [76]. For the treatment of seizures, valproic acid should be used with caution as it may increase the risk of drug-induced liver injury [79]. Up to two-thirds of patients with TBM develop radiologic signs of stroke, mostly involving the basal ganglia [70]. The pathogenetic mechanisms of stroke in TBM remain unclear but likely involve

Fig. 4. Chest X-ray in a spontaneously breathing patient with active pulmonary TB disease and pneumothorax presenting with respiratory distress and shock.

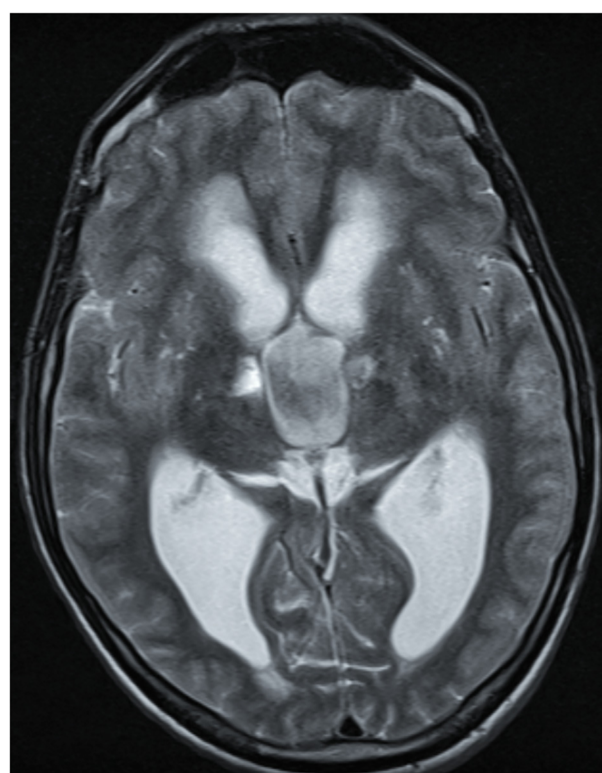

Fig. 5. MRI brain in a patient with central nervous system TB: Leukoaraiosis secondary to TB vasculopathy. Left thalamic parenchymal enhancement and oedema. Focal mature gliosis in the right thalamus.

vasospasm or inflammation of arteries crossing thick subarachnoid exudates (acute phase), as well as proliferative intimal disease and hypercoagulability (chronic phase) [68]. The clinical picture of TBM-associated stroke varies from no signs or only subtle signs, to monoplegia (acute phase) or dense hemiplegia (chronic phase). There is no specific therapy. In a randomized trial from India including 118 patients with TBM, prophylactic aspirin (150 mg/d) resulted in a 19.1% absolute risk reduction of stroke and a lower mortality (21.7 vs. 43.4%; p = 0.02) compared to placebo [80]. Currently, a Vietnamese trial to confirm these findings is ongoing (NCT02237365). A study in children with TBM failed to show benefits of aspirin [81]. Small studies have shown some benefit of thalidomide as a rescue therapy in children with TBM and tuberculomas who do not respond to anti-TB drugs and corticosteroids [82].

4.3.3. Tuberculous pericarditis

Haematogenous seeding, contiguous spread of a lung lesion, or rupture of a caseous lymph node into the pericardium can result in tuberculous pericarditis and pericardial effusion [83]. The incidence of tuberculous pericarditis varies around the globe and is highest in South Africa [84]. The diagnosis is usually based on clinical symptoms, electro-/echocardiography and/or pericardial puncture. The effusion is typically bloody with elevated protein levels and cell count (predominantly lymphocytes). The sensitivity of diagnostic tools (smear microscopy, adenosine deaminase fluid levels >30–60 IU/L, molecular testing) is limited and requires that therapy often needs to be initiated without laboratory confirmation [85,86]. Anti-TB treatment for tuberculous pericarditis is identical to that of pulmonary TB [24,25]. Steroids (prednisolone-equivalent of 60 mg/d for 4 weeks followed by 30 mg/d for four weeks, and then 15 mg/d for two and 5 mg/d for one week) hasten clinical improvement, decrease the rate of constrictive complications and the need for subsequent pericardectomy [87]. Large pericardial effusions with or without tamponade develop in about 10% of patients and require percutaneous puncture and/or surgical drainage (Fig. 6).

4.3.4. Abdominal TB

Abdominal TB complicates one third of cases with pulmonary TB [88]. It mainly includes gastrointestinal TB and tuberculous peritonitis. Gastrointestinal TB mainly results from ingestion of infected sputum in acute pulmonary TB and involves the terminal ileum and ileocaecal region in 75% of cases [89]. It is particularly prevalent in the Indian subcontinent and often presents with non-specific gastrointestinal symptoms and a palpable mass in the right iliac fossa [89]. A proportion of abdominal TB cases may be due to *M. bovis* infection. Gastroduodenal or small intestinal ulcerations rather than hypertrophy are seen in patients with post-primary pulmonary TB. Haematogenous seeding and direct spread from infected lymph nodes are the pathogenetic mechanisms leading to tuberculous peritonitis. Clinical symptoms of abdominal TB depend on the underlying pathology. While up to 30% of patients present with an acute abdomen (due to obstruction or rarely perforation) (Fig. 7), the majority manifest with abdominal pain (75%), ascites (60%), and weight loss (50%). from abdominal pain (75%), ascites (60%), and weight loss (50%) [88]. Data from the largest series of acute abdominal TB revealed that abdominal distention and tenderness was frequent, but guarding was not [69,90]. The diagnosis of gastrointestinal TB is made clinically or by imaging (e.g. computer tomography). Ascitic puncture in tuberculous peritonitis has a low diagnostic yield. Laparoscopic or blind peritoneal biopsies have a sensitivity of about 75% [91,92]. Treatment strategies for abdominal TB are largely based on anti-TB drugs and supportive measures. Endoscopic balloon dilatation has successfully been used in patients with colonic or ileocaecal strictures [93]. Surgery is reserved for patients with perforation, complete obstruction or massive bleeding. The rates of perioperative complications are high [88].

4.3.5. Further extrapulmonary TB manifestations

Haematogenous seeding can involve essentially all body tissues and organs such as the liver, spleen and kidneys including the urinary tract (with the potential to cause ureteral strictures and hydronephrosis). Tuberculous laryngitis resulting in hoarseness, cough and in severe cases pain and airway obstruction can complicate pulmonary TB [94]. Of all bones and joints, the lower thoracic spine is affected most frequently (Pott's disease in which long-term sequelae are common) [95]. Tuberculous uveitis can cause acute blindness, lymphadenitis (Fig. 8) with or without lymphocutaneous fistulas [83]. Conjunctivitis and erythema nodosum represent hypersensitivity reactions to bacilli antigens in patients with acute TB [83].

4.3.6. Disseminated TB

Disseminated TB, also referred to as miliary TB due to the characteristic miliary pattern seen on chest X-ray (Fig. 9), is associated with mycobacteraemia and multiple organ involvement. Most commonly affected organs are the lung, liver, spleen, meninges, and kidneys. Characteristic skin lesions (erythematous macules and papules, also referred to as TB miliaria cutis) and choroidal tubercles on fundoscopy can give valuable clues in the diagnosis of miliary TB [96]. Many patients present with ARDS and shock [27]. Disseminated intravascular coagulation and multiple organ dysfunction are common. The mortality of disseminated TB is high [97].

4.4. Management of HIV-co-infected patients

HIV infection increases the risk of TB infection/re-activation and death [98]. Every patient with newly diagnosed TB should therefore undergo testing for HIV. TB accelerates HIV replication and disease progression. It is the leading cause of death among HIV-positive persons and causes 26% of AIDS-related deaths [99]. At decreased CD4 counts (<200 per cubic millimeter) the presentation of TB may be atypical. At CD4 counts <75/mm^3, pulmonary symptoms are usually absent and mycobacteremia with miliary TB common [97]. Antiretroviral therapy increases treatment success, significantly reduces all-cause mortality and recurrence rate in *M.tb* and HIV co-infected patients [100,101]. The WHO recommends initiation of antiretroviral therapy within the first eight weeks after start of anti-TB treatment [24]. As patients with a low CD4 count are at a particularly high risk of short-term death, antiretroviral therapy should be initiated within two weeks once anti-TB therapy is commenced and tolerated. As one trial indicated that HIV positive patients with TBM who were started on early antiretroviral therapy had more severe adverse events, antiretroviral therapy is suggested to be initiated only after eight weeks of starting anti-TB drugs [66]. HIV-positive patients who are already on antiretroviral therapy at TB diagnosis should be continued on antiretrovirals without interruption.

Relevant drug interactions and an increase in the rate of adverse drug-related events must be considered when administering anti-TB and antiretroviral medications together. As rifampicin reduces the serum levels of protease and to a lesser degree non-nucleoside reverse transcriptase inhibitors [102], antiretroviral regimens with non-nucleoside reverse transcriptase inhibitors (e.g. efavirenz) are recommended [24]. All patients with *M.tb* and HIV co-infection should receive trimethoprim-sulfamethoxazole prophylaxis as this substantially reduces the risk of *Pneumocystis jirovecii*, toxoplasmosis, malarial and bacterial infections, as well as mortality [24,103].

The immune reconstitution inflammatory syndrome (IRIS) is characterized by worsening of clinical symptoms after initiation of antiretroviral therapy. Mild forms with fever and lymph node enlargement develop in one third of HIV-positive patients with active TB and a CD4 count <50/mm^3 who were started on antiretroviral therapy early [104]. Severe forms are rare but can manifest as increasing tuberculomas, worsening of pulmonary gas exchange

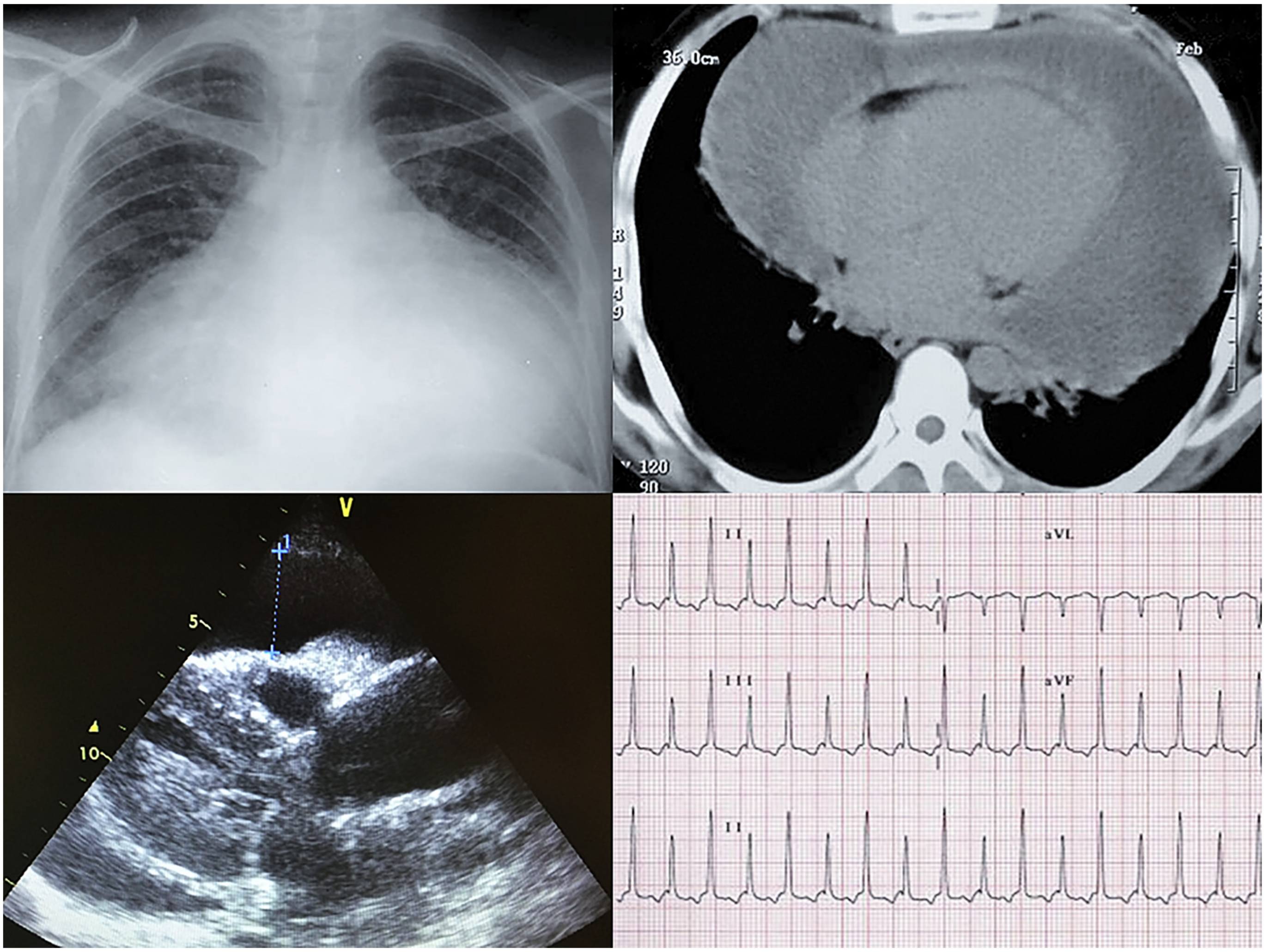

Fig. 6. Chest X-ray (upper left), computertomography (upper right) and echocardiography (lower left) image of a patient with a large TB-induced pericardial effusion and tamponade. The electrocardiogram of the patient (lower right) shows an electrical alternans.

and ARDS [105]. It has been suggested that the propensity to develop IRIS was linked to the quantity of mycobacteria in circulation [106]. This could account for the higher rates of IRIS in patients with disseminated or extrapulmonary TB who have a considerable load of mycobacteria [107]. Specific diagnostic criteria for IRIS have been published [108]. Most importantly, (opportunistic) infections

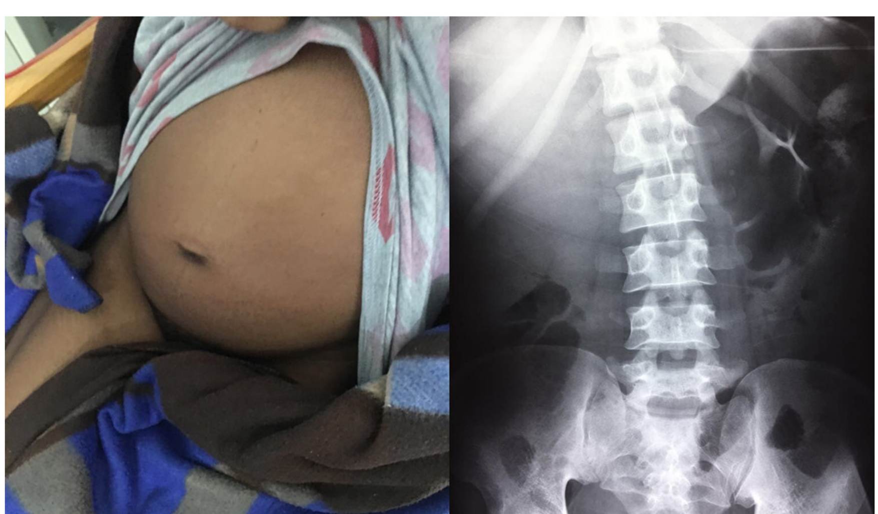

Fig. 7. Clinical appearance and abdominal X-ray in a patient with abdominal TB and intestinal obstruction.

Fig. 8. Axillary lymphadenitis in a patient with TB disease.

and drug-resistant TB need to be excluded as important differential diagnoses. No standard treatment for IRIS has been recommended. Management is usually symptomatic and includes steroids in severe cases. Prednisolone at 1.5 mg/kg/d for two weeks followed by 0.75 mg/kg/d for two weeks reduced the length of hospitalization, hastened recovery and improved outcome in patients with TB-associated IRIS [109]. It is rarely necessary to interrupt antiretroviral therapy on account of IRIS unless symptoms are life-threatening [110].

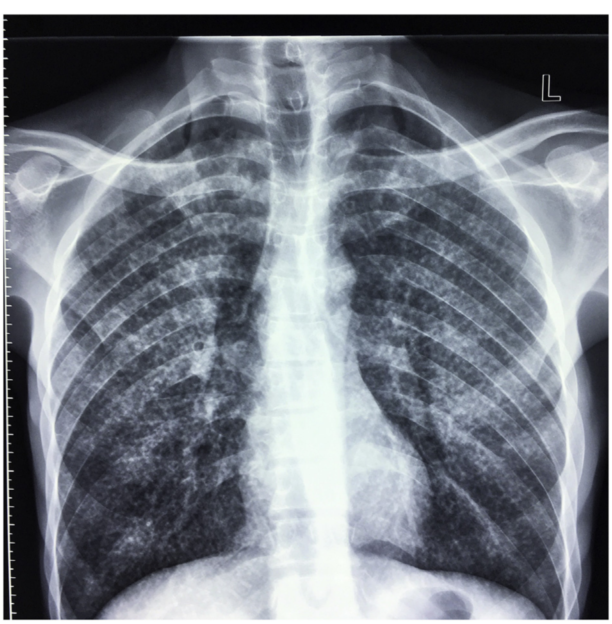

Fig. 9. Chest X-ray in a patient with disseminated TB showing the characteristic miliary pattern.

4.5. Infection control and preventing spread of infection

M.tb bacilli are aerobic, non-spore forming and slow growing bacteria which are resistant to severe adverse environmental conditions. Humans are the only reservoir for *M.tb*, and it is predominantly spread by airborne droplets expectorated by talking, sneezing or coughing of patients with pulmonary TB [111]. *M.tb* containing droplets remain airborne for several hours. Infection control measures (Table 6) are crucial to prevent infection of other patients or staff. Rarely, TB is transmitted via ingestion, inoculation or vertical transmission. One of the most important measures to prevent the spread of infection is early diagnosis and rapid implementation of airborne infection isolation. A high index of suspicion and awareness are essential, particularly in non-endemic areas.

Infection control measures include isolation of patients with TB in a single room [112] whose air should ideally be under negative pressure relative to the other and with air changes greater than six times per hour or more. Staff should adhere to strict hand hygiene standards and wear N95 (FP2) masks when entering the room. N98 (FP3) masks should be worn during handling of respiratory secretions, in- or extubation. Closed suction systems and filters (in the expiratory limb) should be used in mechanically ventilated patients. Diagnostic and therapeutic interventions outside of the isolation area should be kept to a minimum, particularly in patients with MDR-TB. If considered vital these interventions should be scheduled at the end of the day as this reduces exposure to other patients and allows for adequate disinfection and removal of airborne contamination [113]. Spontaneously ventilating patients should wear a surgical mask when leaving the isolation room [111]. De-escalation of isolation can occur when three consecutive sputum smear microscopy are negative. Pragmatically, de-isolation may be considered after a two week-course of anti-TB drugs, however diabetic patients, patients with drug resistance can be smear positive for longer and may require a longer period of isolation [25]. High-level room disinfection (including ultraviolet light) is recommended for adequate environmental decontamination [114]. Suspected or confirmed cases must be reported to regional or national health departments and active contact tracing of household members performed [112].

5. Conclusions and perspective

TB remains a global problem of immense proportion with factors such as HIV infection, migration, drug resistance and iatrogenic immunosuppression driving the disease. An escalation in the numbers of critically ill patients with TB has been observed over the past several years. Mortality remains unacceptably high, and suffering and morbidity enormous. Altered pharmacodynamics and pharmacokinetics in these patients using conventional therapeutic approaches may be a contributing factor to adverse outcome, and further work is required to define optimal treatment strategies. Rapid diagnostic tests have represented a major advance and assisted in expediting management. Several new agents are in development and various clinical trials are underway in an attempt to improve the precarious situation that currently exists. Infection prevention measures are crucial and form an integral component of the management process. Preventive measures moving forward include developing a novel TB

Table 6
Key infection control recommendations.

Setting	Environmental control	Respiratory-protection control
Intensive care units	• In settings with a high volume of patients with suspected or confirmed TB disease, at least one room should meet requirements for an airborne infection isolation room to be used for such patients. • Bacterial filters should be used routinely in breathing circuits of patients with suspected or confirmed TB disease and should filter particles 0.3 μm in size in unloaded and loaded situations with a filter efficiency of ≥95%.	• For HCWs, visitors, and others entering the airborn infection isolation room of a patient with suspected or confirmed infectious TB disease, at least N95 disposable respirators should be worn. • If the patient has signs or symptoms of infectious TB disease and is suspected of being contagious (positive AFB sputum smear result), consider having the patient wear a surgical or procedure mask, if possible (e.g., if patient is not using a breathing circuit) during transport, in waiting areas, or when others are present. • When endotracheal suctioning is performed a closed suction apparatus should be used and a N98 respirator worn
Surgical suites	• If a surgical suite has an OR with an anteroom, that room should be used for TB cases. • If surgery is needed, use a room or suite of rooms that meet requirements for airborne infection isolation rooms. • If an airborne infection isolation or comparable room is not available for surgery or postoperative recovery, air-cleaning technologies (e.g., HEPA filtration and UVGI) can be used to increase the number of equivalent air change per hour. • If the health-care setting has an anteroom, reversible flow rooms (OR or isolation) are not recommended. • Bacterial filters should be used routinely in breathing circuits of patients with suspected or confirmed TB disease and should filter particles 0.3 μm in size in an unloaded and loaded situation with a filter efficiency of ≥95%.	• For HCWs present during surgery of a patient with suspected or confirmed infectious TB disease, at least N95 disposable respirators, unvalved, should be worn. • Standard surgical or procedure masks for HCWs might not have fitting or filtering capacity for adequate protection. • If the patient has signs or symptoms of infectious TB disease (positive AFB sputum smear result), consider having the patient wear a surgical or procedure mask, if possible, before and after the procedure. • Valved or positive pressure respirators should not be used because they do not protect the sterile surgical field.

TB, tuberculosis; OR, operating room; HEPA, high efficiency particulate air; UVGI, ultraviolet germicidal irradiation; HCW, health care worker; AFB, acid fast bacilli.

vaccine, but this represents a daunting task. In the meanwhile, ready recognition and high index of suspicion should be maintained by all, to diagnose and most optimally manage critically ill patients with this perennial problem, irrespective of geographic location of practice.

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