TB and the Anaesthetist

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INTRODUCTION

Tuberculosis (TB) is undoubtedly one of the world’s most common and formidable communicable diseases and global threats to public health.\textsuperscript{1,2,3} With particular relevance to the developing world, the burden of TB has led it to become the second leading cause of infectious disease-related death worldwide second only to the human immunodeficiency virus (HIV).\textsuperscript{4} It is believed that around 33% of the world's population may be living with latent infection.\textsuperscript{4,5}

Reports from the World Health Organisation (WHO) in 2013, estimated 9 million cases of TB and 1.5 million TB related deaths. 1.1 million (13%) of those who developed TB were HIV-positive as were 360,000 (24%) of the deaths.\textsuperscript{1} The African region accounted for about 25% of the total number of reported TB cases, with remaining cases originating mainly from the South-East Asian and Western Pacific Regions, India and China. Of note, the African region reported the greatest ratio of cases and mortalities relative to its population.\textsuperscript{1}

Tuberculosis is particularly prevalent in developing countries and South Africa finds itself at one of the epicenters of the epidemic, with an incidence of about 1 person in every 100 developing active TB each year. Children account for fifteen percent of cases and two thirds of patients are also HIV positive.\textsuperscript{1,4,6}

Despite the unsettling numbers of TB cases and mortality, two decades since the 1993 WHO pronouncement of TB as a international public health emergency, some promising strides forward have been made. Reported TB mortality rates worldwide have dropped by 45% from 1990 till 2013 and TB incidence rates have fallen in most areas of the world.\textsuperscript{1} It is estimated 37 million lives were saved over past 13 years through prompt diagnosis and treatment. The Stop TB Partnership initiative aims for a 50% decrease by 2015.\textsuperscript{1}

The worrisome emergence of multi drug resistant TB (MDR-TB) poses a major obstacle to achieving these global outcome goals. Worldwide estimates of MDR-TB ranged around 3.5% of new cases and 20.5% of retreatment cases in 2013, and this has remained fairly static. However there exists significant regional variations regarding burden of resistance and suboptimal treatment outcomes. Reports of extensively drug-resistant TB (XDR-TB) have surfaced in over 100 countries. XDR-TB may account for up to 9.0% (95% CI: 6.5–11.5%) of MDR-TB cases currently.\textsuperscript{1} In South Africa it is estimated that 1.8% of new presentations and 6.7% of retreatment cases are multi-drug resistant with over 700 cases of XDR-TB diagnosed in 2013. The burden of MDR-TB and XDR-TB in South Africa is greatest in KwaZulu-Natal, the Western Cape and Eastern Cape.\textsuperscript{6,7}

It is highly likely that anaesthetists will, either knowingly or unknowingly be exposed to a patient with TB, and thus it is essential that we be well informed. To not have insight into this ubiquitous disease in our context is perhaps unforgivable, and so in the following pages we shall explore the disease, its implications for patients and public health as well as those issues of particular relevance to anaesthesia and critical care.\textsuperscript{6}
HISTORICAL PERSPECTIVE

Paleontological studies have found traces of TB strains in the remains of Neolithic human settlers in the eastern Mediterranean dating back as far as 9,000 years ago. Evidence of mycobacterial infection and spinal tuberculosis has been discovered in Egyptian mummies, and references to phthisis, or “wasting,” are found in the medical records of Greek physicians like Hippocrates. In Europe medical literature from the Middle Ages and well throughout the industrial age refer to the “white plague” of TB, also referred to as consumption—alluding to the progressive anaemia and wasting of the victim’s body and vitality as the illness ran its destructive course.8

The term scrofula or “king’s evil” arose in the Middle ages to describe tuberculous lymphadenopathy of the neck and it was widely held that the monarchs of England and France could heal those afflicted simply by touching them. Treatments revolved around regular bloodletting, liberal use of expectorants and purgatives, lifestyle changes such as vigorous horseback riding, dietary adjustments and, in the grim final stages, opiates.9 As time progressed, without a clear appreciation of the pathogenesis or causative organism, there was no recourse for its sufferers except to quarantine them in sanitariums, where it was believed the hygienic surrounds and unfettered air would bolster the body’s natural defences enough to halt or hinder the progress of the disease. Around 1865, Jean Antoine Villemin, a military physician in Paris, demonstrated TB to be a contagious disease though this may have been suggested as early as Aristotle. However discovery of the actual infectious organism, the tubercle bacillus, was accredited to German doctor Robert Koch in 1882. This helped further elucidate the nature of the disease.8,9

Preventive vaccination against tuberculosis, by inoculating attenuated tubercle bacilli was first developed in 1921 by French bacteriologists Albert Calmette and Camille Guérin and the strain was so dubbed the BCG (Bacillus Calmette-Guérin).8

TB continued to pose a threat to global health until the emergence of streptomycin in 1946 and 6 years later, isoniazid (INH).10 This revolutionized the treatment of TB, aided in the following years by the introduction of pyrazinamide (1954), ethambutol (1962), and rifampicin (1963).11,10 By the latter 20th century, the benefits of more widespread education, economic recovery, improved sanitation, and more widespread endorsement of public health measures and infection control led to falling rates of TB in industrialized countries. Tuberculosis was relegated to a disease ‘of the past, of the indigent, and of the Third World’.8

The disease saw a resurgence during the mid-1980s, attributed partially to complacent health care systems, greater urbanisation, immigration in developed countries and prominently the spread of HIV.3,8

NATURAL HISTORY, MICROBIOLOGY & PATHOGENESIS OF TB

The genus mycobacteria encompasses 5 closely related organisms: Tuberculosis: bovis; canetti; microti; and africanum. M. bovis is transmissible through the ingestion of infected cow’s milk. It penetrates the gastrointestinal mucosa or invades the lymphatic tissue of the oropharynx. Pasteurisation of milk and effective tuberculosis control amongst cattle has significantly reduced the incidence of M. bovis infection.5,11

By far the commonest cause of tuberculosis disease in humans is M. tuberculosis. An obligate aerobic rod, it is spread by airborne transmission and has no known animal reservoirs. It thrives in an aerobic environment, at a PO2 of 140 mmHg, and thus typically has a predilection for the lungs (pulmonary TB) however can cause disease in other sites too (extra pulmonary TB)1,3,11,12
Mycobacterium tuberculosis is transmitted primarily through the airborne route via minute droplet nuclei (0.5-5 μm) that are expelled into the environment when an infectious patient coughs, sneezes, talks or sings. Each of these minute infectious droplets may contain 1-5 bacilli and can remain suspended by indoor air currents for periods up to several hours, distributing them throughout a room or closed environment. The infectious dose of tuberculosis is only 1 to 10 bacilli, meaning exposure to only a small number bacteria is enough to establish infection, though prolonged exposure in addition to several other factors (including host immunity and bacterial virulence factors) may favour the acquisition of infection. One cough or sneeze can liberate from up to 600 000 droplet nuclei.

The following patient characteristics increase the risk for transmission: The presence of a cough, productive of smear positive sputum (for acid-fast bacilli - AFB), lung cavitation and laryngeal TB. Extra-pulmonary TB is generally not infectious, unless co-existing pulmonary tuberculosis is present. Cough-inducing or aerosol-generating procedures (e.g. intubation and extubation, bronchoscopy, sputum induction, administering aerosolized medications, or the handling of lesions or processing of samples in the laboratory can all facilitate the dispersal of infectious units.

Environmental factors that predispose to TB include: Small, enclosed spaces with no sunlight (tubercle bacilli are rapidly inactivated by direct sunlight, but in the dark can endure for several hours). Inadequate ventilation – poor dilution or removal, i.e. recirculation of unfiltered air containing droplet nuclei. Inadequate sanitation and decontamination of medical apparatus and improper techniques for handling processing specimens.

The clinical course of tuberculosis post infection can follow 4 possible trajectories: 1) immediate control/clearance of the organism, 2) latency, 3) immediate active primary disease and 4) Reactivation disease – onset of disease following latent infection.

Latent tuberculosis infection refers to infected patients who have mounted an appropriate immune response and have not progressed to symptomatic disease. They are not infectious, but carry dormant bacilli and a lifetime risk of progressing to active TB of approximately 10% if immunocompetent. Of those that progress, half will do so most commonly in the first two years after infection, when the risk is highest, and the other half later on in life. Those most at risk include children less than 5 years, elderly and those with suppressed immunity. The likelihood of progression to disease in patients with HIV, is much greater, with an annual risk of 10% and around 50-60% of HIV infected patients, following infection will progress to active disease.

Passive and active exposure to tobacco smoke and high alcohol consumption (>40g/day) is associated with increased risk of developing TB. BCG immunisation affords variable protection against developing active TB disease. The principal benefit is the prevention of severe disease in children, namely disseminated TB and TB meningitis.

Primary infection most often occurs in childhood but may occur at any age. Due to its high oxygen tension, the most conducive site for primary infection is usually the upper lobe of the lung or apices of the lower lobe. Bacilli reach the alveoli carried by infectious droplets and are phagocytosed by alveolar macrophages. If not eradicated by these preliminary innate defences, it multiplies replicates within the macrophages. Proliferation of the bacilli is slow, dividing roughly every 25 to 32 hours. The tuberculous bacilli carry no known exotoxins or endotoxins, therefore does not incite an immediate host response to the infection. Only after 2 to 12 weeks do sufficient numbers exist (≈104), to elicit a cellular immune response that marks the point of positive response to a Mantoux.

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The liberation of cytokines and chemokines attract other monocytes and macrophages to the area and produce a nodular granulomatous structure referred to as the Ghon focus. From here, TB bacilli and antigens are channelled along lymphatics to the hilar lymph nodes and these constitute the primary (Ghon) complex.

A cell mediated immune response if successful, restricts the replication and spread of phagocytosed bacilli. The inflammatory area is gradually ensconced within fibrous scar tissue, with or without calcification, in which infected macrophages are isolated and perish and the entrapped bacilli lose their viability. Some bacilli remain dormant but viable—in the primary focus and can persist for months or years: this is known as latency. 6,11

A positive tuberculin skin test may be the only outward manifestation in the early stages of primary infection which is usually asymptomatic and generally occurs within 4-6 weeks. Progression of primary infection in the lungs leads to spread throughout the airways or via lymphatics with progressive destruction of the lung. The typical pathological appearance of cavitary tuberculosis, mediated by inflammatory mediators, reactive oxygen and nitrogen intermediates and cytotoxic cell contents, produce a histopathological picture similar to post-primary TB.

Unchecked bacterial growth leads to haematogenous spread to more distant sites resulting in disseminated TB. Certain tissues and organs demonstrate a greater resistance to bacterial multiplication than others. For instance, the liver, spleen and bone marrow, while usually seeded with mycobacteria, do not generally support rampant proliferation. 11

The pattern of post-primary disease as the name implies manifests in a previously sensitised host, occurring after a period of latency, months or even years after initial exposure. It can be a result of re-infection or reactivation of latent bacilli, often prompted by an event such as weakening of the immune system. Upper lobe affection with destructive changes and cavitation are typical of post-primary PTB.

Untreated, TB-related mortality is considerable. Studies detailing the natural course of the disease report a 10 year mortality of approximately 70% among sputum-positive immunocompetent patients with pulmonary TB and 20% among culture-positive (but smear-negative) cases. 1

Pulmonary tuberculosis is the most frequent manifestation of disease, accounting for over 80% of cases. Chronic complications of pulmonary TB include: massive haemoptysis, bronchiectasis, fibrosis, emphysema, obstructive airways disease, pulmonary hypertension and cor pulmonale, lung abscess, aspergilloma, lung/pleural calcification, pneumothoraces and bronchopleural fistula. 5,11

Extra-pulmonary tuberculosis refers to the tuberculous infection of other organs and tissues, most commonly the lymph nodes, pleura, bones, vertebrae, joints, abdomen, nervous system, pericardium or genito-urinary tract. 6,11

**Effect of HIV:**
HIV renders the immune system less able to curtail the propagation and spread of M. tuberculosis. This hastens the progression of latent TB infection to active disease and can also alter the clinical course of TB disease itself, being responsible for a greater incidence of smear negative pulmonary TB as well as disseminated and extra-pulmonary TB disease. These patients have delayed presentation or diagnosis due to atypical presentations and inconclusive investigations as well as poorer treatment outcomes and earlier mortality. 6,11

**Antiretroviral therapy and TB**
Highly active antiretroviral therapy (HAART) is indicated in HIV positive TB patients irrespective of CD4 count.

Four factors complicate the treatment of the TB patient on HAART:

- Drug interactions due to enzyme induction (rifampicin and effects on NNRTIs and PIs)
- Additive/overlapping adverse drug side effects due to polypharmacy.
- Significant pill burden and consequent difficulties with compliance.
- Paradoxical tuberculosis immune reconstitution inflammatory syndrome (TB-IRIS)

1. **Drug interactions**
   The enzymes of the hepatic cytochrome P450 system, responsible for the metabolism of PIs and NNRTIs, are upregulated by Rifampicin, which can lead to sub therapeutical levels of the former. The effect is more pronounced in PIs than for NNRTIs and more so for nevirapine than efavirenz. The potential consequences of this is perceived failure of antiretroviral therapy and worse, the encouragement of HIV drug resistance. Dose adjustment of lopinavir/ ritonavir is therefore crucial when taken in conjunction with rifampicin-based TB regimens. 11

2. **Paradoxical TB-Immune reconstitution inflammatory syndrome (TB-IRIS)** 11,16
   This syndrome refers to a clinical or radiological deterioration of pre-existing TB in HIV infected patients commenced on ARVs, after having excluded an alternative explanation such as drug resistance, inadequate drug delivery or an alternative diagnosis. Around 1 in 5 HIV-positive patients who are commenced on HAART while undergoing TB therapy will exhibit TB-IRIS.

   The underlying mechanism is most often attributed to a bolstered the immune system upon commencement of HAART driving an inflammatory reaction against remaining TB antigens. Onset usually occurs around 26 days into treatment, but has been reported even months into therapy. It may commonly manifest as enlarging lymph nodes, worsening pyrexia, radiological deterioration and expanding pleural effusions. Risk factors include low CD4 count, rapid recovery in CD4 numbers, disseminated disease and short interval (<2 months) between TB therapy and HAART.

   Paradoxical TB-IRIS is seldom fatal and initiation of HAART should not be deferred in patients with diminished CD4 counts simply to avoid it, as withholding it has been associated with higher mortality. 17 However significant morbidity can occur in the setting of TB meningitis or enlarging neuro- tuberculomas or in the form of airway obstruction or splenic rupture. 11,16

   The diagnosis of paradoxical TB-IRIS is one of exclusion and it is very important to rule out other causes for clinical deterioration (e.g. MDR TB/bacterial pneumonia). There is no firm guidance on the management of IRIS reactions but tapering doses of corticosteroids has been suggested. 4 weeks of Prednisone (1-2 mg), tapered over a further 2 weeks has been used in patients with severe symptoms. Other agents that have been used include thalidomide (possible roles in severe CNS TB paradoxical reactions not improving with steroids, and montelukast. 11,16
CLINICAL MANIFESTATIONS

Symptoms
People with TB often present with vague constitutional symptoms such as fatigue, anorexia, and unexplained weight loss (> 1.5 kg in a month) or failure to thrive in children, as well as cough, fever >2 weeks, and night sweats.

In the later stages of pulmonary disease, chronic cough, shortness of breath (as a result of widespread lung damage or aggravated by large pleural effusions), localised wheeze secondary to tuberculosis bronchitis or bronchial compression by an enlarged lymph node, pleuritic chest pain and hemoptysis may be present. If haemoptysis is present, caseation, consolidation, fibrosis, and cavitation are usually present. 6,9,12

Physical signs
General features that may be encountered often include fever, tachycardia, features of chronic lung disease, stigmata of immunosuppression – wasting, other opportunistic infections. Hypersensitivity phenomena include phlyctenular conjunctivitis, erythema nodosum and Poncet's arthritis related to the T cell-mediated immune response.

Examination of the respiratory system may elicit findings concordant with consolidation, fibrosis, bronchiectasis, pleural effusions and cavitation. Extra-pulmonary TB may present with general symptoms or symptoms related to the site or organ affected. 6,11

TB meningitis
Prior to the introduction of effective anti-tuberculosis medications, TB meningitis was invariably fatal. It is responsible for about 6 to 18% of TB related ICU admissions. HIV infection is a risk factor but the clinical presentation and outcomes are similar to those in the HIV-negative population. 11

Clinical presentation involves insidious onset of headache, lethargy, disorientation, depressed consciousness, vomiting and other signs of meningism or raised intracranial pressure. The diagnosis of TB meningitis is based on clinical presentation, risk factors and characteristic cerebrospinal fluid (CSF) results: raised protein content (>1g/l), low glucose and high lymphocyte count (30-300/mm3). Elevated opening pressure and negative India ink stain for cryptococcus and confirmation of TB elsewhere in the body is supportive. Positive cultures of TB are more likely with bigger volumes of CSF (>6 ml) and serial specimens. 11,16

Disseminated / Miliary TB
This occurs as a result of widespread haematogenous dissemination of TB bacilli with resultant seeding of distant organs. This may occur following recent primary infection or the erosion of a tuberculous lesion into a blood vessel. X-ray of the chest may demonstrate the typical pattern of small, widespread, homogenously distributed "millet seeds" miliary nodules. Pancytopenia or anaemia and deranged liver function tests may be present. Microbiological confirmation is uncommon via sputum (usually is paucibacillary), but other options include cerebrospinal fluid, blood culture or bone marrow. 6,11,16

Tuberculous lymphadenopathy
TB lymphadenopathy is a frequent form of extra-pulmonary TB. It occurs more often in children and is usually a complication of primary TB but can also be seen in advanced HIV disease. Mediastinal lymphadenopathy can grow large enough to impinge on the airways. Peripheral TB lymphadenopathy are typically large (>2 cm), irregular, matted constellations of nodes, that are tender and firm or fluctuant to palpation. A differential diagnosis would include persistent generalized lymphadenopathy in HIV-infected individuals. 11
Tuberculous serous effusions
TB is a common cause of exudate in the HIV population and tuberculous effusions can affect any of the serous cavities in the body, e.g. pleural, pericardial or peritoneal collections. The fluid is generally paucibacillary as the effusion is mainly due to a reactive inflammatory process, however, culture may be positive. 5,11

a) TB pleural effusion
TB is the most common aetiology of a unilateral pleural collection in TB stricken countries as well as the commonest manifestation of HIV-related extra-pulmonary disease. It may be associated with a mortality of up to 20%.

Pleural aspiration reveals: straw coloured lymphocyte predominant exudate with protein content >30g/l. Adenosine deaminase (ADA), a marker produced by the activation of lymphocytes, if elevated more than 30 IU is supportive of a diagnosis of TB. 11
Tuberculous empyema usually results when the contents of a tuberculous cavity in the lung erodes into the pleural space.

b) TB pericardial disease
Disease occurs in two main forms: pericardial effusion and constrictive pericarditis. Tuberculosis is responsible for up to 90% of pericardial effusions found in HIV infected patients.
Clinical features include symptoms of chest pain, cough, dyspnoea, syncope and malaise due to low cardiac output. Physical signs include: tachycardia, hypotension, pulsus paradoxus (drop of systolic pressure >10mHg on inspiration), distended neck veins and elevated jugular venous pressure, diffuse apex beat, muffled heart sounds and a pericardial friction rub. Features in keeping with right ventricular failure include bipedal oedema, tender hepatomegaly (liver congestion) and ascites. Additional findings in constrictive pericarditis include atrial fibrillation (in 20% of patients), a raised JVP, an early third heart sound (pericardial knock) and pericardial calcification (25% of patients).

Diagnosis is on clinical, radiological and echocardiographic grounds. A pericardial effusion can produce a globular cardiac image on chest x-ray. Examination of the ECG may show tachycardia, ST changes and low or changing QRS voltages. Response to medical therapy is usually good and may achieve resolution without the need for pericardiocentesis. Adjunctive treatment with corticosteroids has proven to be advantageous in treating both forms of pericardial disease. 5,11

c) Abdominal Tuberculosis
TB abdomen can present in a variety of ways, with the ability to affect any part of the gut. Peritoneal TB is the most frequent form of abdominal TB and presents with constitutional symptoms, abdominal distension and pain. Ascitic tap may reveal straw coloured, lymphocyte predominant (> 300 per mm3) exudate. Ileocaecal involvement accounts for a large proportion of abdominal TB cases and may present with a tender right iliac fossa mass. A third of cases present with an acute abdomen. Computed tomography or sonographic assessment may show thickened inflamed bowel wall, abdominal lymphadenopathy, mesenteric thickening or ascitic fluid. Contrast studies may exhibit stricturing, shortening and distortion. Diagnosis rests on obtaining histological specimens at colonoscopy or exploratory laparotomy/laparoscopy. The main differential diagnosis is Crohn's disease.
Low-grade hepatic dysfunction is common in miliary disease and patients may present with a mixed hepatic/cholestatic picture. 5,11
Tuberculosis of the spine (Pott's disease)

Although tuberculosis can manifest in any bone, it more frequently targets the vertebral column. It usually arises as a discitis and then tracks along the spinal ligaments to then infect the nearby anterior vertebral bodies. It is characterized by reduction in bone density and gradual erosion, with preservation of the disc space for a longer period than seen in pyogenic infections. Vertebral osteomyelitis may occur in childhood, with subsequent destruction of the vertebral body with resultant neurological fallout. Collapse of neighbouring vertebral bodies can give rise to an exaggerated kyphotic angulation (gibbus). Transverse myelitis and paralysis may occur due to anterior spinal artery thrombosis incited through local inflammation. Spread into paravertebral tissue may result in a so-called “cold abscess”.

Clinical features include back pain, stiffness, localised swelling, deformity of the spine or neurological sequelae. Spinal cord compression and paraplegia are major concerns requiring prompt intervention. X-rays and CT of the spine show disc space narrowing and erosion of the adjacent vertebral bodies, wedge shaped collapse and angulation. Differential diagnoses comprise other causes of infectious spondylitis, degenerative disc disease, and metastatic disease to the vertebrae. Secondary effects on lung mechanics need to be borne in mind with severe thoracic vertebral deformity.

TB arthropathy

TB can affect any joint, but the hip or knee are most commonly affected. Gradual onset of pain and swelling is usual with or without constitutional symptoms. Reduced joint space and erosions may be seen as disease progresses.

Genitourinary disease

Symptoms are usually mild, with haematuria, frequency and dysuria are often present, and sterile pyuria found on urine microscopy and culture. Females may suffer infertility as a result of endometritis, or pelvic pain due to tubo-ovarian disease. In men, genitourinary TB may present as epididymitis or prostatitis.

Endocrine

Both Tuberculosis and HIV infection can cause primary hypoadrenalism.
DIAGNOSTICS
Microbiological confirmation of TB and drug susceptibility testing is key to ensuring correct diagnosis and effective treatment.

The tuberculin skin test (Mantoux/TST) is conducted by injecting 0.1 mL of purified protein derivative containing 5 tuberculin units intradermally. A positive skin response, read at 48-72 h, shows a hypersensitivity response in the form of an area of induration, greater than 10mm in immunocompetent individuals and greater than 5mm in immunosuppressed patients. The Mantoux has limited utility in endemic areas. It is nonspecific, so may react positive to other mycobacteria. It simply tests previous exposure so may test positive if the person has had a BCG vaccine and does not differentiate between latent infection and disease. BCG use in infants infected with HIV is also controversial, due to the possibility of disseminated BCG disease. 11,16

**Interferon gamma release assays (IGRAs):**
The last 10 years has seen some advances in the detection of latent TB, with the advent of interferon gamma release assays. These tests boast comparable and possibly better sensitivity and specificity than the TST (90% sensitivity and 99% specificity) and so may be considered an acceptable alternative. These include the QuantiFERON TB Gold In-Tube test and the T-SPOT.TB test. These blood tests work on the basis of detecting the release of a cytokine, interferon gamma from sensitized T cells in response to two synthetic peptides from the TB bacillus.11 Results of these tests are not affected by prior BCG immunization and don’t cross-react with common environmental mycobacteria. It still however cannot distinguish latent TB from active TB. The test takes approximately 16-24 hours for a result as the whole blood specimen needs to incubate in the presence of M. tuberculosis antigens. WHO however does not currently suggest these investigations for protocolised use in low to middle income settings such as South Africa. Specific applications in specialised settings such as screening in neonates with TB exposure and patients receiving TNF – alpha antagonists are being explored. 6,11,12,16,21

**Microscopy:**
The most widely utilised technique for detecting TB worldwide is sputum smear microscopy. Two staining methods can be utilised to detect acid-fast bacilli (AFB); Ziehl-Neelsen staining or fluorescent auramine staining. Acid fast bacilli are so named on the basis of the ability of mycobacteria to take up and retain neutral red stains after an acid wash.1,6,11,12 Negative sputum microscopy does not definitively rule out tuberculosis, and cultures should still be conducted. Findings should generally be reported within 48 hours. Positive detection on smear microscopy requires around 10 000 TB bacilli per ml of sputum, hence its limitation in paucibacillary specimens. Further limitations are that alone, it allows no comment on the viability and drug susceptibility of the organism, and it cannot differentiate from non-tuberculosis mycobacteria. Procuring an adequate sputum specimen can also be problematic in children, and gastric aspirates are often substituted, but provide a poorer pick-up rate(< 40%). 1,6,11,16

Culture is the current reference standard, more sensitive than smear microscopy, and hence more useful in paucibacillary tuberculosis, such as HIV positive patients and children. Culture requires only 10 – 100 TB bacilli per ml of sputum for positivity. Culture is also critical for drug susceptibility testing (currently advocated as a universal standard for patient care) and observing patients’ response to treatment for drug-resistant cases. However, it is a costly and slow diagnostic technique. Time to positive results relates to bacillary load and in most cases should be demonstrable by 4 weeks; although a formal report as negative can only be confirmed upon completion of a 6 week incubation. It necessitates a well-resourced laboratory, well trained dedicated staff, and a proficient transport system to ensure viable specimens. 1,11
Culture Mediums: may be solid or liquid. Solid media include coagulated egg (e.g. Löwenstein-Jensen); or agar (e.g. Middlebrook 7H10). These methods are easy as well as less expensive. Drawbacks include sluggish bacterial growth (up to a month) and inaccuracies from manual interpretation of results. More labs are favouring liquid culture media techniques as they provide shorter incubation times, usually within 7 to 14 days, however are more at risk to contamination than solid media techniques. 11,16

Molecular Testing
Rapid molecular tests are recent advances in TB diagnostics. In October 2013, WHO released a policy update which expanded the recommendation of Xpert MTB/RIF as the first line investigation in all patients being assessed for pulmonary TB to include its use in children and some types of extra pulmonary TB. The technology involves the use of real-time polymerase chain reaction to identify relevant DNA sequences. It is endorsed for use directly on unprocessed sputum and results are achievable in only two hours. It also provides rapid genotypic information on rifampicin resistance.

Two different PCR technologies are available locally. 1,6,11

These are:
1. **The Xpert MTB/RIF:** The test itself is called Xpert MTB/RIF and the device which is an automated real-time molecular platform is the GeneXpert (GXP). It is used for rapid diagnosis of TB and screening for rifampicin resistance by identifying particular mutations in the rpoB gene. It thus can expedite diagnosis and enable early initiation of treatment. About 130 TB bacilli per ml of sputum are needed for positive detection. It is a more sensitive test than smear microscopy (Sensitivity= 97%; Specificity = 99% with a sensitivity of about 70% in smear negative TB). A closed system, it reduces risk of cross-contamination and human error. It can distinguish MTB from non tuberculous mycobacteria). 11,18,19

   The shortfalls of this test are its inability to distinguish between live and dead bacilli makes it unsuitable for monitoring response to treatment and that a fraction of Rifampicin resistant results may not correlate with physiological/phenotypic resistance (as seen in formal drug susceptibility testing). The test is still subject to laboratory errors, machine failure or invalid result, necessitating repeat testing. 11

2. **Line Probe Assays**
These tests require smear positive specimens or cultured isolates. The instrument currently used in South Africa is called the Genotype® MTBDRplus assay. It is a PCR based hybridisation assay capable of simultaneously confirming MTB and detecting mutations conferring both rifampicin resistance (rpoB gene) and isoniazid resistance (katG gene). These rapid detection of these resistance patterns can guide therapeutic decisions whilst awaiting phenotypic DST confirmation. Results are generally reported within 2 days in a laboratory setting and within a week in healthcare facilities on smear positive specimens. Time to result on smear negative samples hinges on time to positive culture after which the test can be conducted. Cost:R886 (Path Care 2010) Drawbacks include poor performance in smear negative TB (sensitivity < 50%), being time consuming and an the fact that it is an open system makes it at risk of contamination. It also requires at different rooms for the various steps 11,18

**Blood culture**
Useful in HIV-infected patients with advanced immunosuppression. Specific MTB appropriate culture bottles should be used. 11
**TB LAM**
This urine assay detects lipoarabinomannan (LAM), an antigen derived from the mycobacterial outer cell wall which is shed from metabolically active or degrading cells and is excreted renally. Reasonable sensitivity has been reported in HIV-infected patients with low CD4 counts (<50 cells/mm3). In the setting of advanced immunosuppression this test may provide additional supportive evidence of TB. It has a sensitivity of ~50% alone or ~70% when combined with smear microscopy. 11,18

**Histological examination**
Includes fine needle aspiration from lymph nodes and tissue biopsies from various sites including serous membranes, dermatological lesions, uterine tissue and hepatic samples. Histopathological examination may reveal characteristic granuloma. 11

**Radiology**
Chest radiographs (CXR’s) can provide important supportive evidence and serve as an adjunct to clinical diagnosis in patients were bacteriological confirmation cannot be attained. CXR’s are fast and readily available although complete reliance on them may result in both over and misdiagnosis of TB due to their poor specificity. Therefore clinical correlation and risk factors are still very important. Chest x-rays may also not distinguish well between the changes of old TB and active TB. 1,11,16

In general, upper lobe disease in the form of apical or subapical patchy/nodular infiltrates, cavitation or calcification is suggestive of TB. Disseminated fine nodular lesions present throughout the lung fields is typical of miliary TB. Other findings include; hilar or mediastinal lymphadenopathy, pneumothorax, pleural effusions and pericardial TB. 10,11,16

HIV co-infected patients may have atypical x-rays and a normal radiograph does not exclude TB. Confounders include the presence of superimposed pneumonias or Pneumocystis Jerovecii pneumonia. 9

Computed tomography (CT) scanning though less available in our setting is better at identifying active TB from old fibrotic changes, with centrilobular nodules and a ‘tree in bud’ pattern often indicative of active disease. Other suggestive features that may be present include mediastinal lymphadenopathy and cavitory changes and miliary lesions not seen on CXR may be picked up on CT. 16

**Adjunctive tests**
**Erythrocyte Sedimentation Rate (ESR)**
May be raised in several disease states, therefore carries low specificity for TB.

**Adenosine Deaminase (ADA)**
ADA is an enzyme involved in purine catabolism, catalysing the deamination of adenosine. Found in most cells, including lymphocytes, it is in raised concentrations in tuberculous effusions (>30μl). It has some value in supporting a diagnosis of TB as the cause of an effusion. 11 Other causes include cancer (particularly lymphomas), pulmonary embolus, sarcoidosis, or systemic lupus erythematosus.
DEFINITIONS OF RESISTANCE

The following definitions were adopted by WHO for use since March 2013.\(^1\)

Mono resistance: Resistance to one of the first line TB medicines (rifampicin, isoniazid, pyrazinamide or ethambutol)

Poly Drug Resistant TB: Resistance against more than one of the first line agents excluding rifampicin and isoniazid.

Rifampicin Resistant TB (RR-TB): Resistance specifically to rifampicin, regardless of resistance to other TB medicines.

Multi Drug Resistant TB (MDR-TB): Resistance to both rifampicin and isoniazid

Extensively Drug Resistant TB(XDR-TB): Further resistance to any of the fluoroquinolones as well as one of the other second line injectable drugs (amikacin, capreomycin or kanamycin)

Other commonly used definitions:

New case of TB: patient naïve to TB medication or has received a course of anti-TB drugs for less than one month.

Previously treated case of TB: A patient previously treated for longer than a month with TB meds. May be due to relapse, reinfection, treatment failure or loss to follow up.\(^1,6,11,20\)

TREATMENT

The different TB drugs have varying effects. Some have bactericidal activity, others are bacteriostatic and some are used for their ability to curb resistance. They may act primarily on differing populations of bacilli within the infected tissue: Some target metabolically active bacilli, others moderately active bacilli, and some on semi-dormant or dormant bacilli.\(^1,7,16\)

The currently accepted treatment for newly acquired drug-susceptible TB is a 6 month course comprising of a 2 month intensive phase and 4 month continuation phase. Isoniazid and Rifampicin form the backbone of these regimens due to their bacteriocidal action. Drugs are generally taken 7 days a week. Directly observed treatment strategy (DOTS) is the accepted standard for the administration of treatment to ensure compliance.\(^7,16\) Fixed-dose preparations help to alleviate the pill burden.\(^1,6,7,16\)

The goal of the intensive phase is to rapidly kill the tubercle bacilli. The standard 4 drug combination of Rifampicin, Isoniazid, Pyrazinamide and Ethambutol (RHZE) is taken for 2 months but patients can improve clinically and become less infectious in as little as 10-14 days. The continuation phase, comprising 2 drugs (Rifampicin and Isoniazid) for 4 months has a sterilizing effect, eliminating the remaining bacilli and preventing subsequent relapse.\(^7,11\)

Treatment success rates of 85% or more are expected for new drug sensitive cases.\(^1\)

Retreatment patient (8 month regimen)

Intensive phase – 5 drugs RHZE + Strep for 2 months, 4 drugs RHZE for 1 month and 3 drugs HRE for 5 months. The retreatment regimen is however being phased out.\(^7\)

Treatment for Extra pulmonary TB

The standard 6 month regimen is equally effective in extra pulmonary cases as in pulmonary TB. The course may be extended to nine months or even a year in some situations, such as in
meningitis, TB affecting the bones/joints and miliary TB. Following the usual two month intensive phase, the continuation phase is protracted to seven months.\textsuperscript{11}

MDR-TB and XDR-TB strains are difficult and expensive to treat, requiring more drugs for longer periods and with lower success rates. Globally the success rate was 48% in 2013. WHO recommendations for the treatment of MDR-TB advocate a course of 20 months centred on second line anti-TB drugs usually chosen on previous exposures and current sensitivities. South African guidelines suggest a 5 drug injectable intensive phase for at least 6 months followed by an 18 month continuation phase of 4 drugs. XDR-TB carries significant mortality: over 90% reported in HIV positive XDR patients in the Tugela Ferry region in KwaZulu-Natal. Preventative measure form a crucial element in the management goals of XDR-TB.\textsuperscript{1,11,16}

Second Line Medications
Second line agents comprise the fluoroquinolone group (e.g. moxifloxacin), aminoglycosides (such as streptomycin or amikacin) and a variety of other medications such as cycloserine, or prothionamide, paraaminosalicylic acid, capreomycin, ethionamide, kanamycin and terizidone. Other drugs that may be considered ‘third line agents’ include thioacetazone, clofazamine, macrolides, linezolid and imipenem.\textsuperscript{16,20}

Adjunctive treatment
Pyridoxine (Vitamin B6) Dose: 25mg daily
To prevent and treat peripheral neuropathy most commonly caused by Isoniazid.\textsuperscript{11}

Steroids
Adjunctive therapy with corticosteroids is advocated for some forms of extra-pulmonary tuberculosis. Corticosteroids as adjuvant therapy may attenuate the inflammatory response, which may reduce tissue damage and constitutional effects. The general consensus for corticosteroid use among international guidelines is in the context of a) Tuberculous meningitis, where steroids may improve survival and reduce disability and b) tuberculous pericardial effusion, with reported benefit being reduction in0 the severity and rate of fluid re-accumulation. The largest study of steroids in TBM employed a tapering dose of dexamethasone over the course of 0 to 8 weeks. Starting doses were 0.3 to 0.4 mg/kg/day. British guidelines recommend prednisolone (or equivalent)commenced at 20 to 40 mg daily tapered gradually over 2-4 weeks. There are no direct comparative studies on dosing or the type of steroid to be used in TBM. Some evidence may exist for the use of steroids in tuberculous pleural effusions, with faster resolution of effusions reported at 4 weeks, but overall no differences in residual fluid at 8 weeks or mortality were found. Many case reports of corticosteroid use for pulmonary disease were published in the 1950s to 1960s and proposed faster clinical and radiological resolution, especially in severe disease, but this failed to translate into mortality benefit or circumventing long-term lung damage. A 2008 retrospective study suggested improved survival with its use in pulmonary TB, however a 2012 meta-analysis reported a non-significant trend in the same context. However, such effects have yet to be evaluated in prospective studies and consensus is lacking. In general, corticosteroid use is considered for selected patients with severe forms of pulmonary tuberculosis, usually for those who develop ARDS.\textsuperscript{11,16,19}

Drug Side Effects:
Rifampicin:
Anorexia, nausea, abdominal pain, hepatotoxicity, thrombocytopenia, discoloration of urine. Hepatic enzyme induction\textsuperscript{6,11,16}
Isoniazid:
Peripheral neuropathy, hepatotoxicity, nephrotoxicity and hypersensitivity reaction. It may result in increased toxicity of carbamazepine, phenytoin. It decreases blood levels of oral contraceptives, warfarin, sulfonylureas, and methadone. 6,9

Pyrazinamide:
May decrease effects of allopurinol, colchicine, and probenecid. May cause hypersensitivity reaction 16

Ethambutol: Optic neuritis, nephrotoxicity. 6,16

Streptomycin: Nephrotoxicity, peripheral neuritis, and ototoxicity, vertigo 11,16

Capreomycin: Ototoxicity, Nephrotoxicity, electrolyte abnormalities

Quinolones: Myalgia, Arthralgia

PAS and Ethionamide: GIT symptoms, Hypothyroidism

Cycloserine/Terizidone: Seizures, psychosis, depression and suicidal ideation

Clofazamine: skin discoloration

Linezolid: bone marrow suppression, peripheral neuropathy

Hepatotoxicity is a complication common to Isoniazid, rifampicin and pyrazinamide. Hepatotoxicity arises most commonly in the initial 2 months of therapy but can occur later.11,12 It may be more likely in the elderly, the malnourished, alcoholics, or in the presence of HIV or viral hepatic co-infection. It is important to be aware that miliary TB may itself cause deranged liver function in which case treatment is the answer.16

Symptomatic hepatitis (transaminases often >5X ULN) has a mortality of almost 5%. Elective surgery should be avoided during this period. International guidelines vary slightly but recommend immediate halting of tuberculosis drugs if transaminases exceed three to five times the upper limit of normal or if the bilirubin rises, with careful re-introduction under specialist care. In cases such as meningitis where stopping treatment completely carries high risk, a combination of relatively non-hepatotoxic drugs, such as an aminoglycoside, Ethambutol and a fluoroquinolone could be given. 6,11,16

The treatment of TB in patients with pre-existent liver disease is not clear, and suggestions include the standard regime with closer monitoring, or a combination of Ethambutol, a fluoroquinolone and an aminoglycoside for up to 2 years. 16

Nephrotoxicity
Pyrazinamide and Ethambutol may require dose adjustments once glomerular filtration rate drops below 30 ml/minute/1.73 m². Similar caution should be taken with aminoglycosides and cycloserine. No guidelines are available for use while receiving renal replacement therapy, and consultation between intensivists, pharmacy, ID specialists, nephrologists and drug level monitoring is advisable. 16

Pregnancy
Other than streptomycin and possible teratogenicity with ethionamide, the majority of TB drugs are safe for use in pregnancy and all are considered safe as in the lactating mother. 11
ANAESTHETIC IMPLICATIONS

The TB patient may present to theatre for a number of indications. They may present for related or unrelated elective or emergency surgery. TB related surgery includes lymph node biopsies, bronchoscopies, mediastinoscopies, laparotomies/laparoscopy, thoracic surgery, pericardectomy or neurosurgical procedures.

The important considerations for the anaesthetist are:

• The overall condition of the patient and the effects of the disease on systemic and organ specific function.
• Current medication and the possible drug interactions.
• Appropriate infection control measures to prevent transmission of tuberculosis to healthcare personnel and fellow patients.  

Patient Condition:
The many systemic implications of TB disease itself need to be borne in mind as well as the possibility of associated conditions such as HIV. Universal precautions should be taken when in doubt. Patients may be chronically ill, malnourished and frequently anaemic.  

Of major concern to anaesthetists would be the effects on the respiratory system. Fibrotic, bronchiectatic and cavitatory changes can distort the airway and impair gaseous exchange. Collapse and consolidated regions can aggravate V/Q mismatching and bullous lesions risk pneumothoraces under positive pressure. Suppurative lung disease risks contamination of unaffected lung segments. Patients with TB may have an ineffective cough as a result of malnutrition and weakness and an inability to clear secretions and are therefore prone to superimposed pneumonia. Chronic lung disease as a result of long-standing tuberculosis can result in pulmonary hypertension and cor pulmonale.  

A full review the patient’s medical history, examination and relevant biochemical and radiological investigations are needed to evaluate any suspected degree of organ dysfunction. Pulmonary function tests and arterial blood gas analysis are often performed as indicated. Conducting a thorough medication history is essential. Antituberculosis agents should be taken on the day of surgery. 

Drug interactions
Drug interactions are largely a consequence of pharmacokinetic alterations resulting from induction of hepatic enzymes. These may be compounded by concurrent HAART, specifically protease inhibitors. Rifampicin is the drug most often implicated in these interactions. It is a powerful inducer of the cytochrome P450 enzyme system, particularly the 3A4 subgroup. It may decrease effects of digoxin, methadone, fluconazole, oral anti diabetic drugs, oral anticoagulants, phenytoin, and verapamil.  

This isoenzyme is also present and hence upregulated in the small intestine therefore a more profound effect is noted in oral medications rather than parenteral. Isoniazid is an enzyme inhibitor, though acts preferentially on other isoenzymes to rifampicin so they do not simply negate each other.
Effects on commonly used anaesthetic drugs:

<table>
<thead>
<tr>
<th>Induction Agents</th>
<th>TB drugs should not impact on single induction doses. However upregulated metabolism may increase the potential for awareness in total intravenous anaesthesia.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local Anaesthetics</td>
<td>TB therapy is unlikely to decrease efficacy. Increased metabolism may reduce the chance of local anaesthetic systemic toxicity.</td>
</tr>
<tr>
<td>Volatile anaesthetics</td>
<td>Theoretical increased risk of halothane hepatitis. (CYP2E1 induction may increase metabolism to trifluoroacetic acid). The newer agents are preferable due to their lessor hepatic metabolism.</td>
</tr>
<tr>
<td>Suxamethonium</td>
<td>Unaffected except if hepatic dysfunction reduces pseudocholinesterase levels</td>
</tr>
<tr>
<td>Non depolarisers</td>
<td>Negligible effect on Atracurium\textsuperscript{2} cisatracurium and pancuronium (renal excretion). Vecuronium and rocuronium may be shortened by enzyme induction. Streptomycin can prolong the duration of non-depolarising relaxants.</td>
</tr>
<tr>
<td>Analgesics</td>
<td>Diminished analgesic effect of codeine and oral morphine has been reported following pretreatment with rifampicin. Codeine is preferentially metabolised to inactive norcodeine and has a reduced overall effect. Fentanyl and alfentanil may both be expected to have reduced efficacy and duration secondary to CYP450 3A4 induction. Tramadol is unaffected. Diclofenac effect is reduced with rifampicin, ibuprofen is unchanged.</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Reduced plasma concentration</td>
</tr>
</tbody>
</table>

Limited studies look specifically at interactions between anaesthetic agents and TB treatment. Most available information is extrapolated from studies on the effects of other known CYP450 inducers or inhibitors. Anaesthetic technique including drug choices is ultimately guided by patient variables, the intended procedure and the extent of the disease. Loco-regional anaesthesia is frequently the more attractive option in patients with severe lung pathology. However, this may not always be possible. Drugs and dosages should be tailored to the anticipated drug interaction, titrated and monitored appropriately. Careful documentation of peripheral neuropathy should be undertaken before carrying out regional nerve blocks. Hepatotoxic drugs should be avoided in cases of liver dysfunction.\textsuperscript{5}

INFECTION CONTROL

The possibility of spreading tuberculosis to other patients and to theatre staff is an ever present concern. The extent of the risk rests on the setting, occupational category, burden of TB in the community, patient profiles, and efficacy of TB infection control processes. In 1993, healthcare personnel accounted for 3.2% of tuberculosis cases. In 2010, 23 XDR-TB and 208 MDR-TB cases among healthcare staff were reported in KZN. It is imperative that anaesthetists take measures to protect themselves, their patients and fellow healthcare workers (HCWs).\textsuperscript{6, 10, 13, 18}

Anaesthetists are at particular risk from airborne pathogens bearing in mind the close proximity to the patient’s airway as well as their participation in procedures that might induce aerosol or coughing. These include laryngoscopy, tracheal intubation, bronchoscopy, suctioning of the airways and positive pressure ventilation.\textsuperscript{6, 13, 21}
In 2005, the American Society of Anesthesiologists (ASA) published recommendations addressing the perioperative precautions applicable to those with active tuberculosis. 3,22

1. Elective surgical procedures should be postponed where possible until the patient is deemed non-infectious. This was defined as having completed at least 2-3 weeks with symptom improvement and 3 consecutive negative sputa. Where postponing is not feasible, surgery should take place in a surgical suite with recommended ventilatory controls. Cases should be planned for the end of the day to maximize the time available for removal of airborne contamination. 2,6,13,21

2. Patients should be transported straight to theatre wearing well-fitting surgical masks or N95 masks to prevent respiratory secretions from entering the air. They should not be kept in a central holding area where potential transmission other patients could take place. 6,9

3. The doors of the OT should be closed, and numbers of personnel and traffic into and out of theatre minimised. Infectious hazard signs should be positioned prominently to alert unwitting staff. 2,13,21

4. The anaesthesiologist and other theatre staff should wear N95 or compatible face masks. These masks should be fit-tested for each worker using an aerosolized substance to ensure adequate face seal. Standard surgical masks are not suitable due to lack of seal and their ability to filter particles in the tubercle bacilli range is less than 50%. 10,21,22

5. Exhausted air should be diverted away from the hospital. 22

6. High-efficiency particulate air (HEPA) filters should be placed between the Y-piece on the breathing circuit and the patient's airway or on the expiratory limb of the circuit to prevent contamination of anaesthesia equipment or discharge of tubercle bacilli into the ambient air and the scavenging system. It should be able to prevent passage of particles 0.3 μm or larger. Further specifications require filter efficiency greater than 95% (i.e., penetration <5%) at the highest capable flow rates of the ventilator. Use of a dedicated anaesthesia machine and ventilator is recommended by some. 2,6,13,22 To date there are no documented cases of TB transmission via an anaesthesia machine. 15

7. Suspected or confirmed infectious patients should ideally undergo recovery in isolation. A negative pressure (i.e., air flow is channelled from the outer adjacent space [e.g., the corridor] into the room) isolation room is a single-occupancy unit designed to prevent spread of airborne droplets. Air from the room is preferably exhausted to the outside, but can be recirculated if filtered through a HEPA filter. A minimum of six air changes per hour(ACH) is recommended for these rooms. 9,10,12,13

If no isolation room is available, recovery in the OT or an ICU isolation room is recommended. The N95® mask can be reapplied to the patient post-operatively once active airway management is no longer needed. Airflow resistance may be increased up to 120% by doing this and so is best avoided in the hypoxic or distressed patient and should be removed if these develop. Oxygen can be supplemented by placing a large venturi-type face mask over the N95® mask. 6,22

ASA Recommendation for Equipment

For equipment which will come into contact with mucous membranes but not normally breach body surfaces, it is sufficient that these be decontaminated but not strictly sterile. These items include laryngoscope blades, face masks, oral and nasal airways, breathing circuits and connectors, self-inflating resuscitation bags and oesophageal/nasopharyngeal/rectal temperature monitors. Condensate within the breathing tubes should be evacuated when it accumulates and disposed. Decontamination prior to reuse is achieved by thorough cleaning with a high-level disinfectant effective against tuberculous bacilli. 6,10,22

Routine bacterial culture monitoring and sterilization/disinfection of the internal components of the anesthesia machine (e.g., gas outlets, gas valves, pressure regulators, flow meters and vaporizers) is not indicated or realistically feasible. Periodic cleaning and disinfection of
unidirectional valves and soda lime canisters may be considered. Cleaning and disinfection of the anaesthetic machine if undertaken should be conducted as per manufacturer guidelines. If there is a possibility of anesthesia machine contamination, formaldehyde gas can be used for sterilization.\textsuperscript{16,22}

Lensed equipment, including flexible fiberoptic endoscopes should be disinfected according to manufacturer's instructions. Suction and other working channels must be irrigated promptly after use and carefully cleaned of organic debris prior to decontamination/sterilization.\textsuperscript{22}

The CDC guidelines, issued in 1994 and most recently updated in 2005, also include a comprehensive program for the prevention of TB in health care settings. It advocates a TB infection control approach based on a three-tier complimentary set of controls, involving administrative, environmental/engineering, and respiratory protection.\textsuperscript{10,13}

Administrative Measures
Administrative measures often involve collaboration with the local state health department and include educational awareness programs, TB risk assessments, screening programs and protocols to ensure prompt identification and treatment of patients with TB; undertaking proper sterilization or decontamination of equipment; and promotion of respiratory hygiene and cough etiquette.\textsuperscript{10,13,21}

Environmental Controls
The second tier is the use of environmental or engineering controls to avoid spread by reducing the counts of infectious droplet nuclei in ambient air. This is achieved through dilution or removal of infectious particles via the effective use of ventilation, high efficiency particulate air filtration or ultraviolet germicidal irradiation (UVGI).\textsuperscript{13,16}

Ventilation in the OT should be designed so as to minimize contaminated air seepage into surrounding areas while providing sterile surgical conditions. Most current operating rooms are designed to be positive pressure relative to the neighbouring areas in order to prevent contaminants from being drawn into the surgical field. This is sometimes combined with a negative pressure anteroom. In an OT that has no anteroom, the doors must be kept closed, and traffic in and out of OT minimized. The use of additional air-cleaning technologies should be considered to augment the effective ACH.\textsuperscript{12,22}

Ultraviolet germicidal irradiation utilises electromagnetic radiation of wavelengths between the blue region of the visible spectrum and the radiograph region. (range: 100–280 nm). UVGI is effective at inactivating M. tuberculosis under experimental conditions and has a germicidal efficiency equivalent to 17 air changes per hour. Changes in air mixing and relative humidity as well as UVGI intensity and lamp configuration all affect the efficacy of UVGI. Its use is somewhat controversial due to their expense and potential for ultraviolet irradiation injuries.\textsuperscript{10,13,16}

Respiratory-Protection Controls
This promotes the preventative use of respiratory protective equipment in such circumstances that present a heightened risk for transmission. N95 masks or personal respirators where available can be employed.\textsuperscript{11,13}

Recommendations for Skin Testing Programs for HCWs
It is recommended that anaesthesia personnel have a baseline skin test and chest x-ray and thereafter intermittent skin testing. If testing shows initial skin test positivity or new conversion on subsequent testing, an evaluation for active TB should be taken which will involve follow-up chest imaging and clinical review.
Frequency of TB screening as suggested by the CDC should be based on magnitude of exposure, which is a composite of the TB burden within the population served by the health care facility and the exposures specific to different occupational groups. Risk is considered very low if no patients with active TB were admitted to an area during the past year and in this setting periodic screening is not necessary.

For low risk of exposure (<6 patients with active TB encountered in past year), annual screening is recommended. For moderate risk (>6 patients per year) screening should occur every 6 months to a year. High-risk HCWs (recent cases of transmission at institution) should be screened every three months and measures taken to improve the tuberculosis control plan of the health care facility. 

Tuberculosis as described by CDC for HCWs at risk of progression to disease with a positive skin test is INH for 6-9 months. These programmes are hindered by the confounding effects of previous BCG immunisation and inconsistent adherence to INH therapy.

TUBERCULOSIS IN ICU

It is estimated that 1-3% of TB patients require ICU. Tuberculosis may present to the ICU setting for a variety of reasons and although usually related to lung pathology it may present acutely in almost any organ system and mimic other infectious or non-infectious processes adding to diagnostic and therapeutic dilemmas. Timely diagnosis is key to instituting appropriate therapy in management of critically ill TB patients, as delays to starting therapy are associated with worsening morbidity and mortality. This however is sometimes difficult due to atypical presentations that obscure clinical diagnosis and difficulties in obtaining samples for mycobacterial analysis. It is recommended that for patients in which a high index of suspicion exists for tuberculosis empiric therapy be commenced before the results of diagnostic tests are available.

Most studies of critically ill TB patients focus on pulmonary TB. By far the most common reason for referral is respiratory failure. This may be due solely to TB or compounded by superimposed pneumonia, pleural effusions, spontaneous pneumothorax or other manifestations of extra pulmonary disease. The reported incidence of ARDS varies across studies from 12.1% to as high as 60%. Reported mortality for patients admitted with active TB and respiratory failure requiring mechanical ventilation is poor, with in-hospital mortalities of 26 to 81% reported.

Administration of effective anti-tuberculosis treatment is itself complicated by drug toxicity, erratic enteral absorption and pharmacokinetics (altered volume of distribution, clearance and protein binding in ICU patients), drug interactions and organ dysfunction, such as hepatic and renal impairment. The true incidence of sub therapeutic levels of anti-TB drugs in ICU patients is not known and therapeutic drug monitoring is not always practical, especially in resource constrained settings. Parenteral administration in critically ill patients for the initial 72 hours has been suggested if available. Parenteral preparations are available for Rifampicin, Isoniazid, fluoroquinolones and aminoglycosides.

Superimposed bacterial infection can complicate TB related ICU admissions and additional antibacterial therapy should be considered early. The most commonly isolated nosocomial pathogens are Pseudomonas aeruginosa, Acinetobacter baumannii, Acinetobacter spp., Staphylococcus aureus, and Stenotrophomonas maltophilia.

In the setting of HIV, diagnostic difficulties, drug interactions, timing of ART and the risk of IRIS must be considered as well as EPTB, and mixed infection.
Reasons for Admission

The incidence of respiratory failure necessitating mechanical ventilation (MV) in hospitalised pulmonary TB patients is about 1.5% to 5.0%. Aggravating factors such as bacterial pneumonia, chronic obstructive pulmonary disease, immunosuppression and malignancy may be present in about 72% of ICU related cases. Acute respiratory failure (ARF) caused by TB has been associated with mortality rates between 25.9% and 81%, in contrast to respiratory failure due to severe nontuberculous pneumonia (25%).

Rates of co-existing extra-pulmonary TB can be up to 19 to 22%. In one study, common complications included nosocomial pneumonia (67.2%), pneumothorax (13.8%), ARDS (12.1%), acute renal failure (12.1%) and multi-organ failure (MOF -3.4%). Patients with miliary TB were more likely to develop ARDS and more likely to die of MOF.

Though rare disseminated TB can infrequently result in septic shock, originally termed Landouzy septicaemia after the original description. Most often described in the context of HIV, and lately associated with use of biologics in rheumatological disease, it can still develop in the absence of obvious predisposing factors. Adrenal insufficiency may be another consequence of disseminated disease, and should be considered in the context of refractory hypotension or hyponatraemia.

CNS TB

Neurological decline due to tuberculosis meningitis (TBM) is a less common but significant reason for ICU referral. Patients may exhibit seizures or focal neurological deficits as the result of expanding cerebral tuberculomas or a tuberculous brain abscess necessitating neurosurgical intervention as well as medical therapy. Tuberculous meningitis and disseminated tuberculosis represent acute, aggressive forms of TB and are most often fatal. If suspected, empirical therapy should be instituted unless an alternative diagnosis is clear.

In addition to bearing a high mortality, TBM poses two further challenges for the intensivist relevant to neurocritical care - hyponatraemia and hydrocephalus. Hyponatraemia has been independently associated with a worse outcome. The pathogenic mechanisms may involve the syndrome of inappropriate anti-diuretic hormone or cerebral salt wasting. No specific guidelines exist for its management, but fluid restriction, hypertonic saline, fludrocortisone and demeclocycline may have a place following careful consideration of the fluid status of the patient.

Hydrocephalus is not uncommon and may be detected radiologically in about 77% of cases. Tuberculous exudates in the basal cisterns usually result in a communicating hydrocephalus though non-communicating hydrocephalus can occur as a tuberculoma or cerebral oedema obstructs CSF flow. Neurosurgical intervention in the form of a shunt procedure or an endoscopic third ventriculostomy is then required. Other principles of neurocritical care are also applicable to TBM.

Predictors of mortality:

Several factors have been identified across the literature as potential predictors of mortality among critically ill TB patients. These include disseminated disease, usually in the context of HIV infection, acute respiratory distress syndrome (ARDS), sepsis (usually associated Gram-negative) and multiple organ failure (MOF). Multilobar involvement on radiology, hypoalbuminaemia, high apache scores, acute kidney injury and need for mechanical ventilation have also been used in the prognostic evaluation of such patients. It has been suggested that APACHE II scores at ICU admission might underestimate the mortality rate among tuberculosis patients requiring MV.
Lee et al. showed the SOFA score to be a good prognosticator in miliary TB related ARDS.\textsuperscript{25} Ki et al found the presence of shock and advanced age to be associated with worse outcome.\textsuperscript{26} Several studies also ascribed poor outcomes to late ICU admission and delay to treatment (>1 month).\textsuperscript{27,28,29}

Influence of HIV on outcome:
In a study of 58 pts with confirmed TB admitted to ICU between 1990 and 2001 the in-hospital mortality was 15 of 58 (25.9%). Only 7% of the enrolled patients were HIV positive, but it did not have a bearing on mortality.\textsuperscript{1}

Silva et al., in a 2 year retrospective study in Brazil, aimed to describe the characteristics of TB patients requiring ICU, and predictors of in-hospital mortality in a developing country with intermediate-to-high TB endemicity. Of the 67 adult pts enrolled, 62 (92.5%) had acute respiratory failure requiring ventilation. 24 (35.8%) patients had pulmonary disease only, 21 (31.3%) had extra pulmonary disease only, and 22 (32.8%) had coexistent pulmonary and extra pulmonary disease. A prior history of TB was present in 6 patients. Comorbid diseases were present in 58 (86.6%) patients, with co-infection with HIV being the most frequent (68.7%). The median CD4 count of these patients was 83 (range: 34 - 145), and only 6 (13.0%) were receiving HAART on admission. Demographic and clinical characteristics were comparable between the survivors and non survivors. An in-hospital mortality of 66% was reported. No association was found between diagnosis of HIV and mortality (p = 0.999), regardless of level of immunosuppression and use of ART.\textsuperscript{4}

A French retrospective single centre study of 53 pts over a 10 year period included smokers(64%), alcohol users(42%), drug users(12%) and HIV infected(23%) patients. Three independent factors found to be associated with mortality: a miliary pattern on chest x-ray, need for mechanical ventilation and need for vasopressors. In this study HIV patients (CD4 <200) were more likely to have EPTB (50%) but mortality was comparable.\textsuperscript{5}

**Biosafety**

As in other healthcare settings, tuberculosis transmission control measures in the intensive care units are comprised of a)administrative measures—early screening, diagnosis, treatment and isolation of suspected cases, education of personnel; b) environmental (or engineering) control measures—negative pressure isolation rooms, adequate ventilation, HEPA filters, UVGI; and c) respiratory protection measures—use of N95 masks by the staff. High volume ICUs caring for patients with potential or confirmed TB should have at least one isolation room. Closed system endotracheal suctioning should be used.\textsuperscript{13,19,23}

**Diagnosis of TB in the ICU**

Investigations include sputum samples/endotracheal aspirates (preferably on different days), for AFB microscopy and culture. Nucleic acid amplification tests if available can be employed bearing in mind a positive result could merely indicate incidental latent TB in a patient with another reason for ICU admission. A study by a UCT Critical Care Research Group of 81 patients, 52(66%) of which were HIV-infected, showed a sensitivity of around 88% with the Xpert MTB/RIF as well as a 35% relative increase in the pick up rate when applied to smear negative cases.\textsuperscript{16,18}

If sputum cannot be acquired, options include bronchial lavage (sensitivity 87%) and gastric aspirates. There is little evidence for the utility of gastric aspirates in the diagnosis of TB in adults, and particularly in the ICU setting. A positive culture rate in patients with pulmonary TB is reported at about 5%. Low specificity in some studies may be due to atypical mycobacteria in gastric aspirates.\textsuperscript{16}
Histological samples taken at bronchoscopy or transbronchial biopsy may improve diagnostic yield and assist in rapid diagnosis, however is not without risk in the mechanically ventilated patient. Related complications include bleeding and pneumothorax. Bronchoscopy through a non-invasive ventilation mask has been described to facilitate sampling in hypoxic non-intubated patients. Other invasive options in sputum negative patients include pleural biopsy and mediastinoscopy.¹⁶,²³

A negative CXR can almost safely rule out TB (unless in the setting of HIV). However, it should be remembered that endobronchial lesions and early apical lesions may not be picked up and inactivity of disease cannot be judged definitively on CXR alone. A literature review by Silva looking at studies up to 2011, reported the most common radiological findings to be reticular/nodular infiltrates and consolidation, and cavitation in 27-50% of cases. Most studies fail to identify radiological changes specific for TB. In view of the aforementioned facts, the role of chest X-ray in the clinical diagnosis of pulmonary tuberculosis in ICU patients remains uncertain, and it is possible that chest X-ray does not contribute as much as thought.¹⁶,¹⁹,²³

Non-pulmonary samples
Extra pulmonary TB is a common presentation to the intensive care unit. It is often associated with HIV and may present independently or concurrent with pulmonary TB. Samples taken are generally paucibacillary compared to those in pulmonary disease and microbiological confirmation is often reliant on more invasive diagnostic methods such as pleural biopsies and lymph node aspiration. Adjunctive tests like adenosine deaminase may have a role in supporting the diagnosis. Whilst culture is still the standard, PCR technologies are starting to play an important role in establishing early diagnosis. The role of NAATs on nonrespiratory samples is still in its infancy and few guidelines exist but meta-analysis has shown CSF testing to have comparable sensitivity (56%) and specificity (98%) to microscopy. Urine culture may play a role in disseminated disease, with a sensitivity of 25 to 69%, while the urine microscopy is of limited value due to high rates of non tuberculous mycobacteria.¹⁶

The role of TB blood cultures seems to have most value in the setting of disseminated TB in those with advanced HIV immunosuppression. The positive yield diminishes significantly as CD4 counts rise above 300 cells/μl. Its usefulness in non-HIV immunosuppression has not been determined. The role of IGRA in ICU patients is not recommended as a high false negative rate is common. There is continuing research into developing new generation IGRA and T-cell-based diagnostic models that circumvent some of the present shortfalls of IGRA.¹⁶
TB RESEARCH AND DEVELOPMENT

After many years, novel TB drugs are in development and new combination regimens are being tested in clinical trials. Presently, 10 new or repurposed anti-TB drugs are in the final stages of clinical development, hopefully to add to the current armamentarium.

In the past 24 months, two new agents have been approved for the management of MDR-TB: bedaquiline and delamanid. Another agent, Rifapentine (a rifamycin with a greater half-life compared to Rifampicin) is in the process of Phase II and Phase III evaluation.

Two alternative regimens for drug sensitive TB are being assessed in Phase II clinical studies: 3,4 REMox – Rifampicin, moxifloxacin, Pyrazinamide, and Ethambutol; and PaMZ – Pa824, moxifloxacin, and Pyrazinamide. If proven effective, it is probable that at minimum one of these regimens will be adopted and implemented in parallel to standard therapy. 1

Research continues on new TB vaccines, currently in Phase I or Phase II trials, with the hope of overcoming some of the limitations of the BCG vaccine (now almost a 100 years old). For now, however, a reliable preventative vaccine that is effective in adults remains elusive.

Several new diagnostic technologies are under evaluation or are currently available for the simultaneous detection of a large number of resistance-conferring mutations. However most of these instruments are still only feasible as reference laboratory investigations, demanding expensive infrastructure and trained staff. These include microarray-based multiplexing diagnostic platforms, the loop-mediated isothermal amplification (LAMP) platform and the MTBDR sl assay aimed primarily at detection of resistance to second line agents.

The ideal test would provide quick detection in both pulmonary and extra pulmonary TB on a variety of specimens (e.g., urine, blood, oral mucosal transudates, saliva) and one that is good in smear-negative pulmonary TB and childhood. 1

CONCLUSION

Tuberculosis is a common disease in South Africa and much of the world, forming a deadly liaison with HIV. It has substantial implications for the anaesthetist, with complex clinical presentations, the potential for drug toxicity and interactions and potential for transmission of tuberculosis to other patients and theatre staff. 6,16 The patient with TB presents many challenges to the perioperative team and but a solid knowledge base can make for informed choices, pre-emptive measures and allow for the provision of a safe perioperative experience for all involved.
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