# 5

# TUBERCULOSIS IN THE INTENSIVE CARE UNIT

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## INTRODUCTION

Tuberculosis is now recognised to be the leading cause of death associated with a single identifiable infectious pathogen in the world (1). According to estimates of the World Health Organisation, which declared tuberculosis to be a global emergency in 1993, there were nearly 2 billion people in the world infected with this micro-organism, with 8 million new cases of active disease and more than 2 million deaths in 1997 (2). 95% of cases of tuberculosis and 98% of tuberculosis deaths occur in developing countries. Tuberculosis has been estimated to cause 7% of all deaths and 26% of preventable deaths in the developing world (1). Most deaths occur in young adults between the ages of 15 and 40 years, during their most economically productive years (2).

Tuberculosis is a disease of the poor and disadvantaged and is therefore concentrated predominantly in the developing world and in poor areas of major cities in the developed world. Although the greatest numbers of cases occur in certain parts of Southeast Asia, the highest incidence of cases is found in sub-Saharan Africa. Nine of the 10 countries with the highest incidence of tuberculosis are in Africa (3). Countries with the highest burden in sub-Saharan Africa include Nigeria, Kenya, Zimbabwe, Tanzania, Uganda, the Democratic Republic of Congo and South Africa (2). In the African region, the estimated incidence is 259 per 100,000 population, compared with 50 per 100,000 in Europe and America (3). This review focuses on severe tuberculosis infection in the developing world.

## RESURGENCE OF TUBERCULOSIS

Whereas in the 1960s and 1970s tuberculosis appeared to be decreasing, from the mid-1980s tuberculosis began increasing in incidence worldwide. The reasons for this increase were said to occur in three "epidemics". The first epidemic was the association of tuberculosis with general factors such as poverty, malnutrition, a decrease in socio-economic circumstances, homelessness, decline in tuberculosis control programs, poor compliance with treatment regimens, decreased funding for tuberculosis programs, and civil conflict (2,4).

The second epidemic, occurring particularly in Africa, was the association of tuberculosis with human immuno-deficiency virus (HIV) infection (1,2,4). HIV infection is the greatest risk factor for the progression of latent TB infection to active disease (1). The risk of developing tuberculosis in HIV-seropositive patients is between 3-8% annually, with a 50% lifetime risk (2).

Gachot and co-workers were among the first to describe critical illness in HIV-seropositive patients with tuberculosis, which now appears to be increasing worldwide (5,6). They described 12 cases of severe disseminated tuberculosis infection in patients who were HIV-seropositive, 8 of whom had diffuse pulmonary involvement, which was responsible for the development of acute respiratory failure. Seven of these cases required mechanical ventilation. Seven patients in total died.

The association of HIV infection with tuberculosis in adults has been called the "new tuberculosis" since many of these patients present with unusual or atypical features, The interaction between TB and HIV infection is complex (7,8). It does appear that tuberculosis increases viral replication in HIV-infected individuals and HIV-infected patient who develop tuberculosis appear to have a shortened survival (2).

The third epidemic has been that of multidrug resistant (MDR) tuberculosis, occurring especially in countries such as the United States, particularly in association with intravenous drug abuse, but for which conditions do exist throughout the word (9). A particular concern with drug resistant tuberculosis has been the possibility of greater risk of transmission to other individuals, including nosocomial transmission to health care workers (10). The global extent of drug resistant tuberculosis has not been well defined (11). In some countries, such as the former

Soviet Union, Dominican Republic and Argentina, high rates are seen, but data from most of Africa has not obtained (11,12).

# CRITICAL ILLNESS IN ASSOCIATION WITH TUBERCULOSIS

There are a number of conditions that may cause critical illness in patients with tuberculosis (Table 1). Respiratory failure is one of the commonest reasons for intensive care unit admission of patients with tuberculosis. Respiratory failure may be precipitated or complicated by conditions such as pneumothorax, massive haemoptysis, endobronchial obstruction, secondary bacterial infection, and respiratory muscle fatigue (13).

Tuberculosis may remain undiagnosed in patients presenting with unusual features, such as in HIV-seropositive patients and in the setting of respiratory failure (14-20). Delay in diagnosis or failure to diagnose tuberculosis is an important factor responsible for the ongoing mortality of patients, in some cases tuberculosis has only been diagnosed at post-mortem. It therefore remains essential to be aware of the continuing occurrence of tuberculosis in patients and to consider this diagnosis in critically ill cases, especially those presenting in respiratory failure. It may be appropriate in some critically ill cases who are unfit to have further invasive diagnostic testing, or in patients pending the outcome of further investigations, to institute a trial of anti-tuberculosis therapy, with careful follow up (5,6).

*Table 1.* Major causes of critical illness in patients with tuberculosis
- Acute respiratory failure
- Tuberculous pericarditis
- Tuberculous meningitis
- Tuberculous adrenocortical insufficiency
- Side effects of anti-tuberculosis chemotherapy

## Respiratory failure

Respiratory failure in patients with tuberculosis, although relatively uncommon, has been described with regularity over a number of years in both adults and children (13,21-39). The most commonly described entity is that of acute respiratory distress syndrome occurring in association with miliary tuberculosis (13,24-30,32,34,37,39).

The occasional development of an ARDS in patients with tuberculosis is said to depend on the dose and type of bacillary antigen entering the blood stream, as well as on the state of the host's immune response, and particularly the presence of what was previously called delayed hypersensitivity (13,34,37). In miliary tuberculosis (as apposed to localised pulmonary tuberculosis) bacilli and bacillary antigens enter the bloodstream from a large area of the lungs. Whereas small bacillary loads tend to prime a "protective" (predominantly Thl response), large bacillary loads tend to prime a "destructive" (predominantly Th2 response) (40-42). The factors contributing to the Th1/Th2 shift in tuberculosis infection are being increasingly recognised (40-42).

While ARDS has been described as the cause of respiratory failure in these cases, this diagnosis is often made simply on clinical grounds and is usually not confirmed by either invasive techniques, such as Swan Ganz catheter monitoring, or histology (33). Although disseminated intravascular coagulation (DIC) has been described in a number of patients with miliary tuberculosis, both with and without ARDS (24,25,28,32,34), it appears that this is a complication of the ARDS and not the cause of respiratory failure (13). Nevertheless in miliary tuberculosis it is associated with a poorer prognosis (13,33). The syndrome of antidiuretic hormone secretion (SIADH) has also been said to be a contributory factor to ARDS, by causing increased interstitial and alveolar oedema (23,38).

ARDS has been also described to occur in patients with tuberculous pneumonia and even fibrocavitatory tuberculosis (22,23,31). Some of these cases also had complicating DIC, as has been described in miliary tuberculosis (31). Another cause of respiratory failure in patients with bronchogenic tuberculosis is said to be ventilation/perfusion (V/Q) mismatching due to the presence of large amounts of caseous material in the small airways, with distal collapse of the airways and alveolar spaces, leading to hypoxia and respiratory failure (13).

The mortality of patients with tuberculosis requiring ventilation remains high (37). Where this has been studied, the APACHE II score has consistently predicted a mortality lower than that observed (58), and the mortality in ventilated cases with respiratory failure associated with tuberculosis is higher than that in patients with respiratory failure associated with non-tuberculous pneumonia. Part of this increased mortality may relate to delay in diagnosis of tuberculosis, with subsequent delay in initiation of therapy (37).

There are no formal randomized studies of anti-tuberculosis therapy in critically ill patients on which recommendations for chemotherapy can be based. Nevertheless it usually recommended that 4 standard drugs be given, namely rifampicin, isoniazid, pyrazinamide and ethambutol. Drugs that are available in some countries for parenteral use include rifampicin, isoniazid, and streptomycin, and these may be considered in cases where there are serious concerns of gastrointestinal absorption (13). The use of corticosteroids in patients with tuberculosis is discussed in detail elsewhere (43-45). However, most authors recommend the use of these agents to all patients with acute respiratory failure, provided the patients are initiated on effective anti-tuberculosis therapy (13,32). Similar recommendations are made for patients with HIV-associated tuberculosis in the ICU, particularly if they are extremely ill, severely hypoxic, or have involvement of the meninges or pericardium (6).

## Pericarditis

Pericardial involvement by tuberculosis in not uncommon (46). It occurs most commonly due the rupture of a caseous lymph node into the pericardial space. Less often in may occur as part of haematogenous dissemination (13). Occasionally it occurs from contiguous spread from a lung lesion (46). Significant complications of pericardial involvement include the development of cardiac tamponade or constrictive pericarditis (13).

Symptoms are very variable (46). While patients may present with fever and chest pain, the onset may be much more subtle or the presentation be related to the cardiac consequences of the effusion. Cardiac tamponade may occur with either a small rapidly developing effusion or with a large effusion that accumulates slowly over a longer period of time (13). While initially cardiac compression occurs due to fluid alone, later an effusive constrictive process may follow. This has been said to be the most common clinical presentation in South Africa, and is associated with increased pericardial pressure due to due to pericardial effusion in the presence of visceral pericardial constriction (46). This may be a stage in the development of classical constrictive pericarditis (46).

While the diagnosis of the presence of a pericardial effusion is often relatively straightforward on clinical examination and cardiac ultrasound, elucidation of the cause of the effusion (such as being due to tuberculosis) is not easy (13). Fluid obtained from pericardiocentesis is similar to that of pleural fluid – an exudate with a predominance of lymphocytes (13). A positive acid-fast smear is very uncommon and culture is positive in 25-

50% of cases (13). In a study from South Africa, tubercle bacilli were cultured from 59% of 189 pericardial effusions (46). Elevated levels of adenosine deaminase (ADA) in pericardial fluid were found to be helpful in assisting in the diagnosis of tuberculosis in a study from South Africa (46). Pericardial biopsy has also been recommended for diagnosis (13).

Cardiac tamponade due to a pericardial effusion requires urgent therapeutic and diagnostic pericardiocentesis (13). All patients should be treated with anti-tuberculosis drugs as used for pulmonary tuberculosis. A study from South Africa indicated that adjunctive prednisolone reduces the risk of death from pericarditis, reduces the need for repeat pericardiocentesis, but does not change the need for pericardiectomy for constriction (46,47). The addition of prednisone/prednisolone in dosages of 60 – 80 mg/day is therefore usually recommended, unless contraindicated, to be tapered over 6 months (13). Patients not requiring pericardiectomy initially should be followed up with serial echocardiography and managed appropriately. Constrictive pericarditis due to tuberculosis requires anti-tuberculosis therapy, as for pericardial effusion, together with pericardiectomy for persistent constriction (46) Constrictive pericarditis with cardiac decompensation requires an urgent pericardiectomy (13).

## Meningitis

Meningeal involvement is probably one of the most serious complications of tuberculosis and the most common cause of death from this infection, particularly in children (48). The increasing incidence of tuberculosis in association with the HIV epidemic appears to be associated with an increased incidence of tuberculous meningitis in adults (49,50). Meningitis occurs as a consequence of the rupture of a subarachnoid focus (Rich's focus that developed following previous haematogenous dissemination (50)), into the subarachnoid space (13). The major impact of the dense inflammatory exudate is on the basal meninges (so-called "basal meningitis")(13, 50). Cranial nerve involvement is quite common and with the inflammatory arteritis, vascular occlusion with cerebral infarction occurs commonly. Blockage of the basal cisterns by the inflammatory exudates may result in obstructive hydrocephalus. Most cases are referred to an intensive care unit for deteriorating neurological status (49).

The diagnosis of tuberculous meningitis is not always straightforward. When typical signs of meningitis are present, the diagnosis may be suspected. However, early clinical signs may be very non-specific (50).

The cornerstone of the diagnosis is the CSF examination, which characteristically shows a raised protein level, a low glucose level, and an increased cell count with a predominance of lymphocytes (13,50). Acid-fast bacilli are seen only in a minority of cases.

Therapy for meningitis, with or without concomitant HIV infection is similar, using the standard drugs. Several of the standard anti-tuberculosis drugs, such as rifampicin, pyrazinamide and isoniazid penetrate reasonably well into the CSF and are recommended as part of therapy. Corticosteroids are often recommended as part of adjunctive therapy, particularly in cases with confusion or altered level of consciousness, focal neurological signs, or hemiplegia (13,50-52). Studies have confirmed the benefit on survival and intellectual outcome of children with tuberculous meningitis, with enhanced resolution of the basal exudates, but no effect on intracranial pressure or incidence of basal ganglion infarction (53).

The mortality rate of tuberculous meningitis remains high and patients are often left with permanent neurological sequelae (49,54,55). The main clinical prognostic features are delay in onset of treatment and neurological status at presentation (49,52).

## Adrenocortical Insufficiency
Classic Addison's disease occurs in patients with inactive tuberculosis in whom the adrenal gland tissue has been replaced by granulomas, which are often calcified. In these cases, reactivation of tuberculosis may result in symptoms of both tuberculosis and adrenal insufficiency (13). Sometimes adrenocortical insufficiency does arise as a consequence of miliary tuberculosis in cases in which the adrenal glands are significantly involved (13,56) Rifampicin therapy has been noted to precipitate Addison's disease in patients with borderline adrenal function, as a consequence of increased metabolism of corticosteroids (57). It is important to be aware that a diagnosis of adrenocortical insufficiency may be made even in the presence of apparently normal random levels of cortisol measurements in the blood. Therapy includes hormone replacement, as well as anti-tuberculosis treatment in cases with active infection.

## Drug toxicity (57-63)
Adverse drug reactions to anti-tuberculosis drugs are an important cause of additional morbidity, and sometimes mortality, in patients with tuberculosis. It is important to try and differentiate effects due to

disseminated tuberculosis from side effects due to drugs used for treatment. Serious hepatotoxicity is relatively uncommon, but is probably one of the most important adverse drug reactions causing critical illness in patients on treatment, which may be precipitated by several of the commonly used anti-tuberculosis agents. Other potentially serious consequences of drug therapy include effects on the haematological system (thrombocytopenia, neutropenia and aplastic anaemia), the neurological system (seizures), the endocrine system (precipitation of Addison's disease by rifampicin), renal dysfunction, and multiple potentially harmful drug interactions. Anaphylaxis is a very uncommon side effect occasionally described with some of the anti-tuberculosis drugs and drug overdoses with any of the agents may also sometimes be fatal.

## THE FUTURE OF TUBERCULOSIS TREATMENT AND PREVENTION

Despite the fact that modern short course treatment is highly effective and cost effective, tuberculosis stills remains a leading cause of disease and suffering (64). It has been nearly 30 years since the introduction of novel compounds for tuberculosis treatment (65). There are a number of compelling reasons why new agents are desperately required, including the need for treatment with fewer drugs, shorter courses, improved MDR control and the treatment of latent infection (65). Deciphering the biology of *Mycobacterium tuberculosis,* through knowledge of its complete genome sequence, enhances this possibility (66). Also of importance is the tuberculosis vaccine, yet despite clear benefits against disseminated childhood infection, its efficacy against adult pulmonary disease has varied widely (67, 68). Developing a novel tuberculosis vaccine represents a daunting task, but is absolutely essential (67, 68).

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