Tuberculosis

Dr Denis Spelman, FRACP, FRCPA, MPH and Dr Graeme MacLaren, MB BS, FJFICM, FRACP

Abstract

- Tuberculosis (TB) is a major public health threat, with 32% of the world's population infected with *Mycobacterium tuberculosis* and between 8 and 9 million new cases per year.
- TB is the second-commonest cause of death worldwide, after HIV/AIDS.
- Dual epidemics of TB and HIV/AIDS, in some situations fed by increasing intravenous drug use, impede control efforts.
- Factors resulting in increases in TB cases include HIV, poverty, poor housing, overcrowding, poor access to healthcare and treatment services, and social and health infrastructure disruption.
- Increasing multidrug resistance in mycobacteria poses a threat to effective TB control.
- Isoniazid and rifampicin remain the cornerstones of treatment for drug-sensitive TB.
- With appropriate treatment, more than 95% of patients with drug-sensitive TB can be cured.
- The risk to Australian Defence Force (ADF) personnel of acquiring TB appears to be low, although there are no published figures on the incidence of TB in the ADF.

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OVER THE PAST DECADE, there has been a significant increase in the incidence of tuberculosis (TB) worldwide.[1] TB now poses an enormous public health threat in many high-incidence countries. The increase has been most striking in sub-Saharan Africa, where the HIV/AIDS co-epidemic has played a significant role. Other factors contributing to the rising incidence of TB in developing countries include poverty, malnutrition, poor housing and overcrowding. There may be poor access to, or availability of, healthcare services, including a lack of diagnostic laboratory facilities and a limited number of trained healthcare professionals. These factors may be caused or compounded by increasing social disruption, economic decline, political change and increasing numbers of refugees. Increasing intravenous drug use is also contributing to the dual epidemics of TB and HIV/AIDS.

The rising international incidence of TB may affect members of the Australian Defence Force (ADF) deployed overseas. This article highlights three aspects of TB: global epidemiology, disease presentation and management, and the potential significance of TB to the ADF.

Epidemiology

In 2000, there were between 8 and 9 million new cases of TB, with up to 50% of patients being smear positive (ie, with positive sputum microscopy for mycobacteria).[1] The incidence is highest in Africa, with 290 cases (range, 265–331) per 100 000 population,[2] although the greatest prevalence is in the most populous countries, such as India, Bangladesh and Pakistan. Each year, 6 360 000 new incident cases (80%) occur in the top 22 TB countries.[3] TB is the second- commonest cause of death worldwide.[1] In 1997, there were about 1.87 million deaths, with an average mortality rate of 23%. In some African countries, the mortality rate was as high as 50%.[3]

Thirty-two per cent of the world's population (ie, 1.86 billion people) are infected with *Mycobacterium tuberculosis*. Most of these people have latent *M. tuberculosis* infection.

Australia is fortunate to have a low incidence of TB. In 2002, there were 1028 cases reported, representing an incidence of 5.2 per 100 000 population. The incidences of TB for overseas-born Australians, Indigenous Austral-

Denis Spelman *is Deputy Director of the Infectious Diseases Unit and Head of Microbiology at the Alfred Hospital, Melbourne. He has a longstanding interest in antibiotic use, antibiotic-resistant organisms, and infection control.*

Graeme MacLaren *is an intensive care physician with an interest in infections in critically ill patients. He is currently undertaking advanced training in infectious diseases at the Alfred Hospital, Melbourne.*

Infectious Diseases Unit, Alfred Hospital, Melbourne, VIC.
Denis Spelman, FRACP, FRCPA, MPH Deputy Director, and Head of Microbiology.
Graeme MacLaren, MB BS, FJFICM, FRACP, Registrar.
Correspondence: Dr Denis Spelman, Infectious Diseases Unit, Alfred Hospital, Melbourne, VIC.

ians, and non-Indigenous Australians were 20.2, 8.5 and 1.1 per 100 000 population, respectively.[4] The incidence of TB in the ADF does not appear to have been published in recent years.

Multidrug-resistant TB

Multidrug-resistant TB (MDR-TB) is defined as *M. tuberculosis* with resistance to isoniazid and rifampicin. Many of these isolates possess resistance to other agents as well. MDR-TB has become a major public health threat worldwide. Factors that contribute to the development of drug resistance include inadequate therapy, erratic compliance, and poor infection control practices. In Estonia, Latvia and parts of Russia, more than 10% of cases are MDR-TB.[1] Poor conditions in prisons have contributed to a high incidence of both TB and MDR-TB. It is estimated that in prisons in the former Soviet Union up to a third of patients with TB have MDR-TB.[5] MDR-TB is uncommon in Australia, where 1.9% of isolates were MDR-TB in 2002.[6]

M. tuberculosis resistant to only one first-line agent accounts for more than 30% of *M. tuberculosis* in some countries (eg, 36.9% in Estonia). In Australia, the corresponding figure was 7.7% in 2002.[6]

First-line anti-tuberculosis therapy in adults

Drug	Single daily dose	Major adverse effects	Recommend-ations for use
Isoniazid	300 mg	Hepatitis, peripheral neuropathy	Monitor liver function tests, give concurrent pyridoxine (25 mg daily)
Rifampicin	600 mg	Hepatitis, orange discoloration of body fluids, major drug interactions, flu-like illness	Monitor liver function tests
Pyrazinamide	25 mg/kg (max. 2 g)	Hepatitis, nausea, hyperuricaemia	Monitor liver function tests
Ethambutol	15 mg/kg (max. 2.5 g)	Optic neuritis, rash	Regular checks of visual acuity and colour vision

HIV and TB

HIV is responsible for a significant proportion of the recent increase in TB, with the greatest effect in countries in which there is significant overlap between the HIV and TB risk groups. There are wide variations worldwide: 38% of patients newly diagnosed with TB are also infected with HIV in sub-Saharan Africa, but only 1% in the Western Pacific.[7]

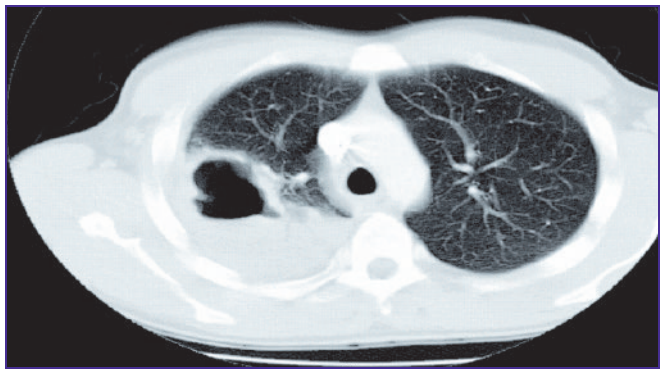
Positive Mantoux test.

Clinical aspects of tuberculosis

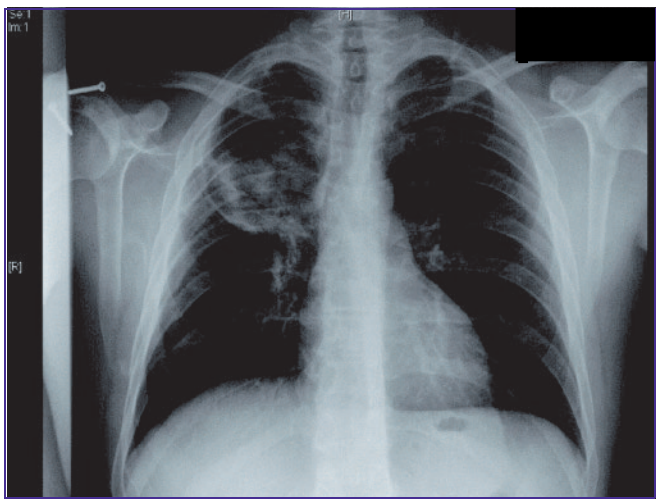
Infection

About 30% of people who are heavily exposed to a patient with active TB will develop primary infection.[8] This occurs when mycobacteria are inhaled in airborne droplets (1–5 µm in diameter) and are taken up by alveolar macrophages. In a small proportion of these patients, the mycobacteria enter the draining lymph nodes and spread into adjacent bronchi, the pleura, or the bloodstream, causing primary progressive TB. This manifests clinically as tuberculous pneumonia, pleural TB, or disseminated TB. However, most patients with primary infection have few or no symptoms, as the mycobacteria are contained by an effective cell-mediated immune response and remain in the lung. These patients have latent TB and are at risk of reactivation of the infection. It is estimated that 5% of patients with latent TB will progress to active disease within 2 years, and an additional 5% will develop active TB at some later stage in life. The risk of progression to active TB is markedly increased by concurrent HIV infection.[8]

Pulmonary TB is the most common form of active disease. Presenting symptoms include fatigue, weight loss, cough, haemoptysis, chest pain and shortness of breath. As a result of the HIV epidemic, extrapulmonary TB is now seen more frequently.[9] The manifestations of extrapulmonary TB are protean and include meningitis, pericarditis, peritonitis, lymphadenitis, osteomyelitis, and genitourinary TB. Disseminated (miliary) TB can occur with reactivated TB, as well as with primary progressive disease. It can present in a variety of ways, ranging from pyrexia of unknown origin to septic shock and multiorgan failure. In one series, the diagnosis was only made at autopsy in nearly 20% of patients.[10]



CT scan of HIV-infected patient presenting with cough and sputum after returning from 5 years' residence in Vietnam. Area of consolidation with central cavity. M. tuberculosis *confirmed.*



Chest x-ray of the same patient.

Definitive diagnosis of any form of TB relies on culture of the organism. The diagnosis is rarely made serendipitously, as laboratories do not perform specimen microscopy and culture for *M. tuberculosis* unless specifically requested. Other potential means of diagnosis, such as nucleic-amplification assays, have variable sensitivity and specificity and do not replace culture.[1] Antibiotic susceptibility testing can only be performed after the organism has been cultured, and this is crucial to effective management.

Management

The mortality rate for untreated smear-positive TB is estimated to be between 50% and 80%, and rises to 100% with untreated tuberculous meningitis.[7] With the development of standard multidrug regimens, more than 95% of patients with drug-sensitive tuberculosis can be cured.[1] Tuberculosis is difficult to treat, and treatment should only be undertaken by those with appropriate training and experience. The difficulties are compounded in patients with concurrent HIV infection or in those with MDR-TB, as therapy becomes more complex and the potential harm to the patient from drug interactions and side effects increases.

Four first-line drugs form the basis of current therapy for drug-sensitive *M. tuberculosis*: isoniazid, rifampicin, pyrazinamide and ethambutol. The recommended doses and common side effects are presented in the Box. The standard regimen for active TB is to treat with all four drugs, using isoniazid and rifampicin for 6 months, concurrently with pyrazinamide and ethambutol for the first 2 months of treatment. Ethambutol can be discontinued once the organism is known to be susceptible to both isoniazid and rifampicin. Therapy does not necessarily require daily administration, and regimens have been designed to allow administration two or three times a week.[1,11,12] Directly observed therapy is advocated by many as the standard of care.[1]

Most forms of active TB can be treated with 6 months of medication. Exceptions are tuberculous meningitis, which requires 12 months of therapy, and drug-resistant TB, which requires modification of both the drug regimen and the duration of treatment.[11] Disseminated TB can be treated with 6 months of therapy only after central nervous system disease has been excluded. Latent TB is generally treated with 6 months of isoniazid monotherapy, unless infection with resistant TB is suspected. These patients have follow-up chest x-rays at 6 and 18 months.

There are two indications for second-line agents: patient intolerance to first-line therapy, or MDR-TB. Second-line drugs include streptomycin, amikacin, moxifloxacin, ethoniamide, cycloserine and *p*-aminosalicylic acid. MDR-TB should generally be treated with five agents, incorporating any first-line drugs to which the organism is susceptible, an injectable agent such as amikacin, a fluoroquinolone such as moxifloxacin, and other bacteriostatic second-line agents.[13]

Other issues in the effective management of patients with TB include infection control, the use of adjunctive corticosteroid therapy, and screening for HIV infection. Only patients with pulmonary disease need to be isolated in negative pressure rooms. Once these patients have had three consecutive sputum specimens on separate days showing no mycobacteria on microscopy, isolation can be discontinued. Appropriate masks are required, but gloves and gowns are unnecessary.

Adjunctive corticosteroids are indicated in both tuberculous meningitis and pericarditis, as they have been shown to reduce mortality. For TB meningitis in adults, dexamethasone is recommended at a dose of 12 mg/day in the first 3 weeks, followed by a gradual reduction over another 3 weeks. For TB pericarditis, prednisolone is recommended for 11 weeks (60 mg/day for adults in the first 4 weeks, followed by 30 mg/day for 4 weeks, then 15 mg/day for 2 weeks, then 5 mg/day for 1 week).[12]

Finally, all patients with TB should be tested for HIV, as this may significantly affect patient management. HIV is the most important risk factor for progression to active TB;[1] patients with HIV may potentially benefit from early diagnosis,[14] and therapy for TB needs to be modified if concurrent antiretroviral therapy is being used.

Tuberculosis and the military

Acquisition risk

There are few reports of TB in the military. The reports that do exist suggest the risk of acquiring TB in the armed forces is low. However, these reports are generally from Western countries. It is also unclear whether the acquisition of TB predominantly occurs before enlistment or while on active duty.

In the US Navy, extensive skin testing (Mantoux testing) using purified protein derivative (PPD, or tuberculin) is performed. From 1980 to 1986, more than two million skin tests were performed on Navy and Marine Corps personnel on active duty. A low proportion (0.97%) were positive.[15]

A case–control study of troops who underwent skin test conversion while deployed to Guantanamo Bay, Cuba, showed that the two independent predictors of PPD conversion were working near coughing migrants, and being born outside the US. Surprisingly, contact with people with known TB appeared to be protective. This may be explained by the fact that these TB patients were mostly in hospital and already receiving therapy.[16]

Between 1980 and 1996, there were 936 US Army personnel with active tuberculosis requiring hospitalisation, and the number significantly decreased during this period. The incidence in soldiers was 29% of that in the general population (for people aged 25–44 years),[17] reinforcing the view that this military population is at low risk.

In contrast, a study of TB cases in the Greek armed forces revealed 4628 patients hospitalised with TB between 1965 and 1993.[18] The incidence gradually increased between 1965 and 1980, but then decreased following introduction of bacille Calmette–Guérin (BCG) vaccination. In 1993, the incidences in the Greek Army, Navy and Air Force were 18, 25, and 15 per 100 000, respectively. These figures were significantly higher than in the civilian population.

Recent conflicts in which the ADF served have been in countries with high rates of TB. Afghanistan is 18th in the top 22 high-burden countries, with a published incidence of 333 cases per 100 000 population.[2] In East Timor, the incidence of smear-positive TB was estimated at 250 per 100 000 population. In Iraq, there were 25 251 cases in 2000. Despite such potential exposure, the ADF has experienced "a very low incidence of TB disease in recent years".[19]

Prevention

TB control programs may include screening through skin testing, treatment of latent TB infection, follow-up for people at risk, the use of BCG vaccination, and aggressive treatment of those with TB.

BCG is used as a routine childhood vaccine in some countries with high incidence of TB. It was routinely used in Australia until 1984, and was stopped as the incidence of TB continued to decline. It is still recommended for some high-risk groups, such as Aboriginal neonates in areas of high incidence.[20]

BCG is not used for ADF personnel, and its role in the prevention and control of TB remains controversial. The basis for concerns regarding BCG revolve around its variable efficacy in adult populations, as well as the infrequent, but potentially serious, adverse reactions, and the loss of the Mantoux skin test as a diagnostic tool.[1] Although the exact incidence of TB in the ADF has not been published, BCG use for all ADF personnel is not indicated if the incidence is genuinely very low. However, there is a need for ongoing surveillance for new cases in the ADF, as well as monitoring of TB rates in countries of deployment. The role of BCG vaccination in the ADF may need to be reconsidered in the future if the rates of MDR-TB continue to rise and no other vaccines are developed.

Screening

Mantoux testing is used as a part of TB control and prevention efforts in many settings, including the military.[16,21] ADF policy is to screen all personnel on entry into the ADF.[19] Screening is repeated after deployment to and removal from a high-incidence country when deployment has been for at least 3 months, if there has been a known exposure to an infectious patient, or a high-risk exposure for TB. The risk of exposure is probably greatest in ADF members who are healthcare workers, as they may have repeated and prolonged exposure to patients with TB.

Patients with induration of $\geqslant 15$ mm on the Mantoux test are considered positive and should be referred for specialist review and management of latent TB infection. Interpretation of Mantoux results can be confounded by past BCG vaccination and exposure to mycobacteria other than *M. tuberculosis*. In this situation, a newly available blood test may be helpful in interpreting a positive or equivocal Mantoux test. In this test, PPD and antigens specific for *M. tuberculosis* (but not BCG) are added to the patient's blood and the release of interferon gamma from mononuclear cells is measured. This test may offer a significant advantage over Mantoux testing for people who have had the BCG vaccine.[22]

Conclusion

TB remains one of the most important infectious diseases worldwide, but there is good evidence that it can be controlled. For example, the implementation of an effective directly observed therapy program in Peru led to an 80% reduction in TB mortality within 3 years.[7] However, these control efforts may be confounded by the HIV/AIDS epidemic.

The risk to the ADF from TB appears to be low, although the data are somewhat meagre. This risk may increase as the incidence of MDR-TB continues to rise. Policy concerning TB and the ADF will need to be reviewed on a regular basis.

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