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What's new in TB?

Background

Australia has among the world's lowest rates of tuberculosis (TB). However, it remains a leading global cause of morbidity and mortality. In Australia, TB remains more common in Indigenous than non-Indigenous Australians, and rates are rising among migrants, reflecting changing immigration patterns and rising rates in their homelands.

Objective

This article reviews recent developments in TB of relevance to Australian general practice and provides an update of advances in the diagnosis and management of TB, and the role of the general practitioners in co-managing people with TB.

Discussion

First hand experience with imported multidrug resistant TB (MDR-TB) is increasing and is anticipated to rise in Australia. The reach of extensively drug resistant TB is also expanding. Although standard guidelines for management of drug susceptible TB remain unchanged, recent progress in the understanding, diagnosis and management of TB has occurred, driven by the need to respond to the challenges of MDR-TB and HIV-TB co-infection.

■ **Appreciation of what's new in tuberculosis (TB) requires a perspective of what's old: *Mycobacterium tuberculosis* (MTB) and other members of the MTB complex (Table 1) have been infecting humans since antiquity.^{1,2} Being therefore consummately adapted to life within the human host,³ MTB infects up to one-third of the global population, is characterised by a dormant phase which confounds diagnosis and control, and in 2006 accounted for an estimated 9.2 million new cases and 1.7 million deaths worldwide.⁴**

Australia largely avoided the late 20th century global TB resurgence, which prompted the declaration of TB as a 'global emergency' by the World Health Organization (WHO) in 1993. The millennium development goals set a target of reducing prevalence and death rates of TB by 50% by 2015. Although many countries are on track to attain these rates, highest burden countries, notably in sub-Saharan Africa where multidrug resistant TB (MDR-TB) and the overlap of TB and HIV epidemics pose crippling challenges, are not.⁴

Against this background, Australia in 2006 reported 1201 TB cases, an incidence of 5.8 per 100 000 population,⁵ with preliminary 2008 figures being similar.⁶ The national strategic plan for TB control recognises the importance of favourable socioeconomic circumstances; successful post-World War II national TB campaigns; specialised, multidisciplinary, free TB services; and effective premigration screening as contributors to Australia's low TB rates.⁷ New challenges faced by Australian practitioners include addressing high rates of TB (~1360/100 000) in Indonesian fishermen entering Northern Territory waters,⁸ and MDR-TB (25% of cases) in Papua New Guinean nationals seeking treatment in the Torres Strait protected zone.⁹ This provides a preview of cases Australian practitioners are likely to be more frequently presented with in coming years as the distribution of MDR-TB continues to expand.

Tuberculosis treatment in Australia is conducted by specialists within centralised, coordinated TB services. Failure to manage TB in this fashion is associated with higher risks of treatment failure and emergence of drug resistance.¹⁰ However, general practitioners have the key responsibilities of recognising at risk people and coordinating care for affected families. In particular, the most vital contribution GPs can make is to avoid TB diagnostic delay by sending sputum specimens



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for specific examination for acid fast bacilli (AFB) and reviewing chest radiograph findings in at risk people with suspicious cough (>2 weeks or 'chronic pneumonia'). This review presents recent developments in TB relevant to Australian general practice. Comprehensive TB management guidelines are provided elsewhere (see *Resources*).

Who is at risk in Australia?

Tuberculosis requires particular consideration in migrants and refugees from high incidence countries. Approximately 85% of new Australian TB cases occur in people born overseas.⁵ Highest global per capita TB rates occur in sub-Saharan Africa,⁴ reflected in high TB notification rates in Australians of sub-Saharan origin.⁵ Commonest countries of origin of people with TB in Australia (consistent with relative sizes of migrant populations) are India, Vietnam, the Philippines, China and Indonesia.⁵ Tuberculosis cases in migrants are usually attributable to reactivation of latent TB infection (LTBI) (often within the first 2 years after migration),¹¹ with smaller contributions from local transmission within migrant communities, and newly acquired infections after visits home.¹² Negative premigration or arrival TB screening does not therefore negate the possibility of subsequent TB.

Indigenous Australians (in some communities more than others) are at higher risk than non-Indigenous Australian born people (6.6 vs. 0.9 per 100 000).⁵ Other commonly identified TB risk factors in Australia are household contact with TB, or residence in a TB high prevalence country for more than 3 months.⁵ Returned travellers uncommonly present with TB.¹³

Human immunodeficiency virus confers the greatest single risk for TB, increasing the chance of latent TB reactivation up to 20-fold.^{14,15} In Australia, HIV-TB co-infection is uncommon, but the reporting of HIV status in people with TB, at 37%, is much lower than recommended.⁵ A new diagnosis of TB must prompt an offer of HIV testing as per local and international recommendations.¹⁶⁻¹⁸ Other forms of immunosuppression also significantly increase the likelihood of LTBI reactivation. In people with LTBI, such as migrants and indigenous people from high TB burden communities, chronic renal failure and high dose corticosteroid use approximately doubles the risk of developing active TB, while TNF- α blockers (eg. infliximab) increase the risk five-fold compared with the comparative population risk of LTBI reactivation.^{19,20}

These at risk groups require screening for LTBI if asymptomatic (see below and *Table 2*), or investigation for active pulmonary or extra pulmonary TB if symptomatic with a clinically relevant syndrome. People with LTBI at risk of progression to active TB, require LTBI

Table 1. Mycobacterium TB and other members of the MTB complex

Mycobacterium genus

- Gram positive, acid fast bacilli. Those pathogenic to humans include mycobacteria of the MTB complex, pathogenic non-tuberculous mycobacteria (NTM) and *M. leprae*
- Tuberculosis causing group – MTB complex:
 - *M. tuberculosis*
 - *M. bovis*
 - *M. africanum*
 - *M. bovis* Bacillus Calmette Guerin (BCG) (attenuated vaccine strain, able to cause disseminated tuberculosis in immunocompromised hosts)
 - Uncommon: *M. microti*, *M. bovis* subspecies *capra*, *M. tuberculosis* subspecies *canettii*, *M. pinnipedii*

treatment (*Table 3*). Detailed screening and LTBI treatment guidelines are provided elsewhere.^{11,21-25}

What's new in TB diagnostics?

Globally, the commonest method for diagnosing TB remains sputum microscopy only; therefore improved access to inexpensive diagnostics is a priority in under resourced settings. There has been promising progress in the development of such tests, including improved microscopy and culture techniques, and rapid molecular methods for detection of rifampicin and isoniazid resistance gene mutations.²⁶ These can provide rifampicin/isoniazid susceptibility results within 1–2 days, compared with approximately 42 days using liquid culture media.²⁷ A reliable point of care test such as antigen detection on blood or sputum would be the 'holy grail' of TB diagnostics; such tests are under investigation²⁸ but not yet commercially available. Nucleic acid amplification tests, including polymerase chain reaction (PCR), have high specificity. Although negative predictive value is low, the possibility of a positive result in smear negative disease can allow more rapid diagnosis while awaiting culture; recently updated Centres for Disease Control (USA) guidelines therefore recommend sputum MTB nucleic acid amplification testing where available and affordable, in cases of suspected, unconfirmed TB, if results would alter management.²⁹

Interferon gamma release assays

Interferon gamma release assays (IGRA), such as QuantiFERON-TB Gold, are potential supplements or alternatives to tuberculin skin testing (TST) for detecting TB exposure. Currently, Australia's National Tuberculosis Advisory Committee discourages use of these tests in clinical settings pending further research into sensitivity, specificity and cost effectiveness (*Table 2*), favouring use of clinical history and TST.^{21,30} Like the TST, IGRA detect T-cell responsiveness to MTB antigens, but this is measured on a blood sample as interferon (IFN)- γ production rather than an in vivo skin reaction, and the antigens used to elicit the response are more specific to MTB than those contained in purified protein derivative. Some diagnostic algorithms incorporate



these tests as adjuncts to,³¹ or replacements of,^{32,33} TST, hence some familiarity with this test is required.

A 'take home message' is that a positive result in either IGRA or TST does not confirm, and a negative test does not exclude, TB exposure.

What's new in TB treatment?

Standard treatment regimens for active and latent disease caused by drug susceptible MTB have not changed in Australia in recent decades (Table 3), however, new developments are discussed below.

New drugs for TB

The drought in new TB drug discovery appears to be breaking, with about 30 new agents in the developmental pipeline.^{34,35} A metronidazole related antibiotic, PA-824, has been found to be successful against MTB in vitro and in mouse models³⁶ and is now in phase 2 human trials. Novel agents targeting specific MTB genes are under investigation.³⁷ Quinolones, with a well established place in the treatment of MDR-TB, are under investigation for their potential to shorten treatment durations in drug sensitive TB.³⁸ Of critical importance is the need to limit misuse of new drugs, eg. use of quinolones as monotherapy in TB misdiagnosed as pneumonia is associated with development of resistance and delayed TB diagnosis.³⁹

HIV-TB co-infection management

Traditionally, delayed commencement of antiretroviral treatment (ART) was recommended in HIV-TB co-infection due to overlapping drug toxicities, drug interactions, and the potential for paradoxical worsening of TB pathology due to immune restoration inflammatory syndrome.⁴⁰ However, it is becoming clearer that benefits of early ART outweigh these risks, and that despite rifampicin induced increased clearance of non-nucleoside reverse transcriptase drugs (efavirenz/nevirapine), serum levels of these drugs can remain adequately efficacious to permit their use.⁴¹ Current guidelines recommend starting ART within 2–8 weeks of TB treatment initiation if CD4 <200, and after 8 weeks if CD4 200–350, preferably using an efavirenz based regimen.^{17,40,41}

The importance of TB screening in people with HIV (eg. using a combination of symptom check, sputum microscopy, TST), and isoniazid preventive therapy if LTBI is identified, are increasingly recognised as critical and underutilised public health measures.⁴²

MDR-TB management

Multidrug resistant TB was initially recognised to result from poor treatment programs with low adherence, leading to selection of drug resistance mutations in infecting MTB strains.⁴³ However, it

Table 2. Advantages and disadvantages of interferon gamma release assays^{29,57–62}

IGRA disadvantages compared with tuberculin skin testing
Currently less collective experience with IGRA exists, and there are uncertainties in how to interpret results, eg. when there is discordance between IGRA and TST, discordance between different IGRA types, and when serial IGRA results change (reversion/conversion)
Requires blood taking, which in infants (a common target group for screening) is more difficult, and often not done by rural/remote health workers and registered nurses
Loss of patient educational opportunities which are provided when TB nurse performs and reads TST
IGRA possibly less sensitive
IGRA test kit more expensive than PPD
Reversions from positive to negative can occur over time and are difficult to interpret (but usually only occur when the initial reading was low-positive)
Requires laboratory reagents and staff not generally available in resource limited settings, thereby restricting accessibility in remote settings
Indeterminate results can occur, eg. due to failures of controls, inadequate cell separation, cross contamination
Greater incidence of discordance between IGRA and TST in children (usually TST positive, IGRA negative)
IGRA advantages compared with TST
IGRA only target antigens present in MTB 'region of difference 1' (RDI1) such as CFP10 and ESAT6, which are not shared by other mycobacteria except <i>M. kansasii</i> , <i>M. marinum</i> and <i>M. szulgai</i> , thereby increasing the specificity of the test
Unaffected by prior BCG vaccination, for same reason as above (RDI antigens not present in <i>M. bovis</i> BCG)
Only requires one clinic attendance if negative
Disadvantages of both IGRA and TST
Unable to distinguish active from latent disease
False negatives occur especially in immunosuppression
No gold standard for LTBI diagnosis, therefore the true sensitivity and specificity of both tests cannot be accurately evaluated
A niche for IGRA use?
QTF-G may be strategically used in settings such as previously BCG vaccinated TB contacts with a positive skin test, and BCG vaccinated health care workers in low TB incidence countries who require repeat testing
TST = tuberculin skin test using purified protein derivative (PPD) (also known as Mantoux test)



Table 3. Anti-TB agents and treatment strategies

Anti-TB agents, WHO classification ⁶³		Drug
Group 1	First line oral antituberculosis agents	Isoniazid, rifampicin, ethambutol, pyrazinamide, rifabutin
Group 2	Injectable antituberculosis agents	Streptomycin, kanamycin, amikacin, capreomycin
Group 3	Fluoroquinolones	Moxifloxacin, levofloxacin, ofloxacin
Group 4	Second line oral bacteriostatic antituberculosis agents	Ethionamide, prothionamide, cycloserine, terizidone, para-aminosalicylic acid
Group 5	Antituberculosis agents with unclear efficacy	Clofazimine, amoxicillin/clavulanate, linezolid, thioacetazone, imipenem/cilastin, high dose isoniazid, clarithromycin
Standard first line TB treatment		
Rifampicin, isoniazid*, pyrazinamide, ethambutol daily or thrice weekly for 2 month 'intensive phase' then rifampicin and isoniazid daily or thrice weekly for 4 month 'continuation phase'. Dosing (see reference 23)		
Standard LTBI treatment**		
Isoniazid* daily 9 months ^{23–25}		
MDR-TB treatment strategies		
Two phase regimen using at least five drugs to which the infecting isolate is sensitive. Drugs include remaining first line drugs to which the organism is sensitive (ethambutol and/or pyrazinamide) plus a quinolone (descending order of potency against MTB: moxifloxacin = gatifloxacin > levofloxacin > ofloxacin = ciprofloxacin) plus an injectable agent from Group 2 above, plus others as required. High dose isoniazid may retain efficacy against MDR isolates with low level isoniazid resistance ^{64,65}		
Phase 1: includes injectable agent, minimum 6 month duration and at least 4 months past culture conversion		
Phase 2: after cessation of the injectable agent, continued for at least 18 months after culture conversion ^{63,66}		
LTBI treatment where infecting strain is thought to be MDR-TB		
No Level 1 evidence. Two drug regimen tailored to the sensitivity profile of the MTB isolated from the contact may be efficacious, eg. pyrazinamide + ethambutol or a quinolone 6–12 months; ⁶⁵ alternatively, a monitoring approach may be appropriate, especially in children		
* Vitamin B6 (pyridoxine) 25 mg/day routinely accompanies isoniazid to reduce the incidence of peripheral neuropathy		
** Combination therapy is needed in active but not latent TB, as active TB is characterised by high bacillary numbers, hence the number of bacilli with spontaneously arising resistance mutations at baseline, which can be selected out by inadequate regimens, is much greater than in LTBI ⁶⁷		

is increasingly found to be a primary transmitted organism in high MDR burden areas, emphasising the vital importance of infection control.^{9,44,45} Multidrug resistant TB treatment regimens (*Table 3*) are prolonged, costly, and associated with significant side effects and adherence difficulties. However, well functioning programs, especially those incorporating the WHO recommendations of ≥ 18 months treatment duration after culture conversion and directly observed therapy throughout, report cure rates of $>60\%$.⁴⁶ Similar success rates have recently been reported for extensively drug resistant TB (XDR-TB) in some programs.⁴⁷ (Note: XDR-TB = resistant to rifampicin, isoniazid, any fluoroquinolone and at least one second line injectable agent such as amikacin, capreomycin or kanamycin). This has overturned the spectre of 'untreatable TB' which has surrounded XDR-TB,⁴⁸ and comprehensive new recommendations for combating XDR-TB are available.⁴⁹

How can GPs care for patients with TB?

Although speciality TB treatment units have the responsibility for reporting and treating TB, managing medication adverse events and ensuring adequate contact tracing (see *Resources*), GPs are at the forefront of having to suspect TB and LTBI, and integrate TB care with other medical needs of the affected individual and their family.

Avoid diagnostic delay

By considering pulmonary TB in people with symptoms (eg. cough $>2-3$ weeks, fever ≥ 3 weeks, loss of $>10\%$ body weight) and epidemiological risk factors, GPs have the valuable opportunity to avoid diagnostic delay. Delayed diagnosis aggravates the individual's morbidity, increases public health risk, and complicates the subsequent contact tracing required.

Key actions to making a timely diagnosis are:

- request AFB examination on sputum in addition to standard microscopy/culture
- improve yield by requesting morning sputum specimens, and arranging 2–3 collections, and
- assiduous follow up of chest radiography.

As a negative smear does not exclude pulmonary TB, clinical suspicion in a person from a TB endemic country warrants referral to TB services (see *Resources*), regardless of AFB sputum smear result.

Infection control

General practices require a policy for ensuring adequate respiratory precautions for people with suspected or confirmed infectious pulmonary TB attending their practice, or whom they care for in nursing homes, prisons or other institutions, including avoidance of communal areas and use of face masks.^{22,24}



Avoid drug interactions

Rifampicin is a potent inhibitor of cytochrome P450 isoenzymes, especially CYP3A4 and CYP2C8/9, and therefore great attention to other medications metabolised by these enzymes, especially anticonvulsants, oral contraceptives and warfarin, is required.

Nutrition

Malnutrition contributes to TB risk and complicates active TB.⁵⁰ Specific micronutrients with immunological functions such as vitamin D may be of particular importance,^{51,52} but trial outcomes examining use of these agents as supplements in TB treatment are pending. Food scarcity is obviously less problematic in Australia than in high TB burden countries, but nutritional optimisation and replacement of deficient nutrients in individuals with TB is in keeping with current WHO recommendations.⁵³

Smoking cessation

Active and passive smoking are associated with elevated TB risk and worse outcomes from TB infection.⁵⁴ Smoking cessation is therefore an important potential intervention area, although the impact of quitting after diagnosis on individual patient outcomes remains to be determined.

Psychological support and adherence help

Psychological and practical supports are key requirements of TB care. Tuberculosis remains deeply stigmatised in many societies, and confinement in respiratory isolation can be traumatising.⁵⁵ A diagnosis of TB can therefore require management of negative psychological effects. The prolonged duration of therapy requires assiduous measures to promote adherence. The most widely used of these is the WHO sanctioned 'DOTS' (directly observed therapy – short course). Other adherence promoting measures include addressing financial costs of leave from work by assisting in accessing short term disability pensions, addressing any problematic beliefs about TB including those to do with law and migration status, and providing ongoing education about the need to continue treatment even after symptom resolution.⁵⁶

Conclusion

Important new developments in TB diagnosis and treatment have occurred in recent years. These include the availability of new diagnostic tests, updated guidelines on managing HIV-TB co-infection, new data showing better prognoses for people with MDR-TB/XDR-TB, and renewed emphasis on the importance of infection control. Australia remains in the fortunate position of having very low TB rates by global standards, low drug resistance (although increasing cases are projected), infrequent cases of HIV co-infection, and access to MTB culture and susceptibility testing. Maintaining this position despite the high global burden of TB requires ongoing timely TB screening, a low threshold for considering the diagnosis of active TB in people at risk, and psychosocial support to assist adherence to treatment.

Resources

Australian state and territory TB contacts

- Australian Capital Territory Tuberculosis Service, c/o Thoracic Unit, The Canberra Hospital. Telephone 02 6244 2066
- New South Wales Tuberculosis Program, NSW Department of Health. Telephone 02 9391 9277
- Northern Territory Tuberculosis Unit, Centre for Disease Control. Telephone 08 8922 8804
- Queensland Tuberculosis Control Centre. Telephone 07 3896 3939
- South Australian Tuberculosis Services, Royal Adelaide Hospital Chest Clinic. Telephone 08 8222 4867
- Tasmanian Tuberculosis Services, Southern Region – Respiratory Unit, Royal Hobart Hospital, phone 03 6222 7353; Northern Region – Respiratory Unit, Launceston General Hospital, telephone 03 6348 7708; North-Western Region – Chest Clinic, Community Nursing, telephone 03 6421 7700
- Victorian Tuberculosis Control Section, Department of Human Services. Telephone 03 9096 5110 or 1300 651 160
- Western Australian Tuberculosis Control Program, Perth Chest Clinic. Telephone 08 9219 3222.

Guidelines and resources

- Australian National Tuberculosis Advisory Committee (NTAC). Available at www.health.gov.au/internet/main/publishing.nsf/Content/cdna-ntac-about.htm
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- Stop TB Partnership. Available at www.stoptb.org/.

Fact sheets for patients

- www.health.vic.gov.au/ideas/diseases/tb_facts
- www.health.nt.gov.au/Centre_for_Disease_Control/Publications/CDC_Factsheets/index.aspx.

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