

Tuberculosis

Introduction

Tuberculosis (TB) is an infectious disease caused by mycobacterium tuberculosis (MTB). TB is a major global public health problem. In 2009, worldwide there were an estimated 9.4 million new cases of active TB, with 1.68 million deaths. One third (32%) of the world's population is estimated to have latent (ie asymptomatic) TB infection. A person with latent TB infection carries a 5-20% lifetime risk of reactivation to active TB.¹

Incidence of TB in the UK declined during the 20th century until the 1980s, since when a steady rise in cases has occurred. TB is once again a major public health problem in the UK, with about 9,000 cases of active TB per year.² Despite the publication of strategy documents and NICE guidelines, the number of cases in the UK has continued to rise.

The two most important challenges for primary care are:

- to diagnose active TB early, to reduce diagnostic delay and prevent spread of infection
- to identify people with latent TB, so that they can receive antibiotic treatment to prevent reactivation of disease

Box 1. TB - Key points

- Incidence of TB in the UK continues to rise
- TB occurs mainly in UK major cities
- Most cases (74%) of TB in the UK occur in people born abroad
- Extrapulmonary TB accounts for almost half the cases of TB in the UK
- Most cases (up to 80%) of active TB arise through reactivation of latent TB infection (not new cross-infection)
- New diagnostic tests (interferon gamma release assays [IGRA]) are an important advance
- Primary care in higher incidence areas can play a key role in screening and case-finding
- Primary care can reduce diagnostic delay

What's new in TB with respect to primary care?

Primary care teams need to know about important new developments in TB and TB care. These include:

- Rising incidence of TB in UK cities
- Changing epidemiology, risk factors and drug resistance

- Importance of diagnosing latent TB
- New diagnostic tests for TB – the interferon gamma release assays (IGRA)
- Increasing role of primary care in diagnosis, screening and management
- New NICE guidance on TB

Rising incidence of TB in UK cities

London is the TB capital of Europe, with a caseload seven times that of the next highest incidence cities, such as Paris and Milan. But TB in the UK is not limited to London, with other cities, notably Birmingham, now being high incidence areas. GPs tend to underestimate the number of new cases of TB that they would expect to see in their practice.³ Incidence in some London boroughs is over 100/100,000 (comparable to rates in high burden countries) – thus a large group practice with a high turnover of patients might see ten new cases of active TB per year.

Changing epidemiology, risk factors and drug resistance

Seventy-four percent of cases of active TB in the UK now occur in people born abroad – a percentage that has risen steadily in the last ten years. TB is twenty-one times more common in non-UK born individuals compared to those born in the UK. Rates of TB are highest in the non-UK born black African, Indian, Pakistani and Bangladeshi populations (incidence rates of 273, 235, 234 and 133/100,000 per year respectively). Studies show that about 80% of new cases of TB in the UK arise by reactivation of latent TB, rather than by cross-infection. This highlights the need to diagnose and treat latent TB – a role in which primary care can take a significant part. It is worth noting that aggressive screening and treatment of latent TB was the key means by which the USA recently got on top of its TB epidemic.

Migration and development of TB.

Screening for active TB at port of entry is a relatively ineffective measure, partly because most cases of active TB in migrants arise by reactivation of latent TB after entry to the UK. The UK does, however, now require pre-entry screening for active TB for people from selected countries planning to stay in the UK for more than six months. Extra-pulmonary TB is more common in migrants.

Vitamin D deficiency is now a recog-

nised risk factor for TB, and trial evidence supports vitamin D supplementation as an important adjunct to TB treatment.⁴

Treatment with Tumour Necrosis Factor alpha (TNF- α) antagonists is now a risk factor for TB. Many people with inflammatory conditions such as rheumatoid arthritis are now treated with TNF- α antagonists. Because TNF- α plays an important role in defence against TB, latent TB can reactivate to active disease in people treated with TNF- α antagonists. Arrangements for screening for TB in such patients are the responsibility of the prescribing consultant.

HIV infection predisposes to TB infection. Co-infection is common and anyone with active TB should be tested for HIV. Advanced TB is not infrequently the presenting illness of someone with advanced HIV. The Primary Care team is best placed to identify those at increased risk of both HIV and TB and to offer screening. If new entrants from high TB risk countries are also offered HIV screening (as per NICE guidance) and screened for TB in a timely manner, then numbers of patients presenting with advanced disease (both TB and HIV) should reduce.

Drug resistance complicates treatment. Almost one in ten cases of active TB in London are resistant to isoniazid. 1.3% of cases in the UK are multi-drug resistant (MDR-TB, defined as at least resistant to both isoniazid and rifampicin). Four cases of extensively drug resistant TB (XDR-TB) occurred in 2010.²

New diagnostic tests for TB

The tuberculin skin test (TST) is the oldest screening test in medicine. Drawbacks of the TST include poor sensitivity and specificity, especially in people immunised with BCG, and the need for the patient to return to have the test read. Interferon gamma release assays (IGRA) overcome both these problems. These tests work on the principle that white blood cells (T lymphocytes) of a person infected with MTB will release interferon gamma when stimulated by antigens unique to MTB (CFP-10 and ESAT-6). Neither the BCG bacillus nor non-tuberculous mycobacteria have these antigens, hence BCG immunisation and infection with non-tuberculous mycobacteria do not lead to a positive IGRA test. The place of IGRAs is under constant review, but stud-

ies are showing their usefulness in screening for latent TB.⁵

Box 2. Risk factors for TB

Common risk factors that should prompt consideration of TB infection:

- HIV infection
- Low socioeconomic status, especially homelessness
- Migration from country with high prevalence of TB
- Intravenous drug use
- Recent incarceration in prison
- Poor nutritional status
- Vitamin D deficiency
- Anti-TNF treatments for inflammatory conditions

Diagnosing active TB – reducing diagnostic delay

Patients diagnosed with active TB often complain that their GP missed the diagnosis. Whilst patients with TB symptoms may delay presenting to health care (roughly 4 weeks) for various reasons – stigma of TB, poor access to healthcare – studies show that, once they attend, opportunities for an early diagnosis are often missed (for example, patients may be treated with repeated courses of antibiotics for a chest infection). Maintaining a high index of suspicion for TB is key.

Diagnostic delays are common in:

- White British born young adults, where no one has thought of the diagnosis and treated with antibiotics and asthma drugs for months. These patients are typically very infectious and lead to secondary cases of active and latent TB.
- Pregnant women in at risk groups and with symptoms – GPs (and Obstetricians) are very reluctant to request chest x rays. Sputum smear positive pulmonary TB in pregnancy often presents very late when other children and babies have been infected.
- Those with an insidious onset of back pain or abdominal problems (usually from Indian sub-continent) where there are both GP and secondary care delays. The most devastating are those with spinal TB when delay can lead to paralysis.

TB can infect almost any organ in the body. Extra-pulmonary TB is common, especially in migrants. The classic symptoms of active TB remain unchanged:

- Fatigue
- Weight loss
- Anorexia
- Lymphadenopathy
- Cough
- Breathlessness
- Night sweats
- Fever
- Haemoptysis

Diagnostic delay could be reduced by GPs and practice nurses by doing three things for people with these symptoms:

- 1) send sputum frequently and early for microscopy and culture for AFBs (acid fast bacilli),
- 2) request chest X rays early in those not responding to antibiotics,
- 3) request ESR/CRP/inflammatory markers and full blood counts in those with TB symptoms.

Each case of active TB should (like cancer) be seen as a critical incident, with a review of diagnostic delay.

Screening and case-finding for TB in primary care

NICE guidelines recommend that Primary Care Teams screen patients for TB, especially in areas of high TB incidence (areas with over 40 cases/100,000 population would seem a reasonable threshold).⁶ Simple verbal screening of those registering in primary care can identify individuals who need further testing.⁷ Three questions are appropriate, with a positive reply to any prompting action:

- Do you have any symptoms of TB? (investigate)
- Have you migrated to the UK in the last 5 years from a country with high TB prevalence? (screen for latent TB)
- Are you a TB contact - ie living with a person with active TB? (refer to TB team for contact tracing)

TST or IGRA for screening for latent TB in primary care?

Tuberculin skin testing (TST) can work in primary care but requires nurses or health care assistants to be technically competent and patients to return for reading. NICE proposes a two-stage test (ie using TST, then IGRA), which is cumbersome. Recent studies show the feasibility of using IGRA testing alone. IGRA testing is becoming available in primary care and the simplicity of this one-test approach may lead to its adoption in high incidence areas. The threshold for testing migrants is a matter of debate.⁵

IGRA tests are currently not recommended for screening for active TB.

Treating active and latent TB infection

Active and latent TB are currently treated and managed by secondary care TB teams. Monitoring of compliance with therapy is expensive so commissioning may shift monitoring (such as DOT – Directly Observed Therapy) to the community or primary care. Treatment for latent TB comprises either six months of isoniazid or three months of rifampicin and isoniazid. Uncomplicated active TB is treated with a six-month, four-drug initial regimen (six months of isoniazid and rifampicin supplemented in the first two

months with pyrazinamide and ethambutol).

Side-effects of TB medication

Primary care professionals should be aware of the side effects of TB medication. Major side-effects include rashes (any TB medication), vomiting and jaundice (rifampicin and isoniazid); dizziness and deafness (streptomycin); visual impairment (ethambutol); and rarely shock, purpura, or acute renal failure (rifampicin). Minor side-effects include (harmless) red colouration of the urine (rifampicin).

Check the BNF for significant drug interactions if prescribing any drug to a patient on TB drugs, but maybe specifically mentioning contraception (including implants).

What role for primary care?

Primary care can play a key role in controlling the UK's TB epidemic. Box 3 provides a summary:

Box 3. Summary of role of primary care in TB care

- Ensure easy access to care for higher risk groups (homeless, migrants, recently imprisoned, drug-users)
- Maximise uptake of BCG for eligible children
- Screen and case-find for TB (in high incidence areas)
- Ensure early diagnosis and rapid referral of people with active TB
- Carry out critical incident review for each new case of active TB
- Keep a TB register for active and latent TB; ensure hospital-prescribed drugs are listed on medication screens
- Reinforce adherence for patients on treatment; be aware of potential toxicity of TB medication
- Know your local TB Service contact details and telephone for advice as to how best to refer
- Update your TB knowledge (RCGP online learning has two new TB modules: <http://www.elearning.rcgp.org.uk/course/info.php?id=107>)

Support agencies for health professionals, patients and carers

TB Alert (<http://www.tbalert.org>), the UK's TB charity. The Health Protection Agency (<http://www.hpa.org.uk/>), information on current epidemiology, testing, FAQs for patients. Migrant Health Guide (<http://www.hpa.org.uk/web/HPAweb&Page&MigrantHealthHome/Page/1271066169944>), set up by the HPA, excellent information for health professionals and patients.

References

1. Maartens G, Wilkinson RJ. Tuberculosis. *Lancet* 2007;**370**:2030-43.
2. Tuberculosis in the UK: 2012 report. London: Health Protection Agency, 2012.
3. TB ALERT (unpublished survey) 2011.
4. Martineau AR, Timms PM, Bothamley GH *et al*. High-dose vitamin D3 during intensive-phase antimicrobial treatment of pulmonary tuberculosis: a double-blind randomised controlled trial. *Lancet* 2011;**377**(9761):242-50.
5. Pareek M, Watson JP, Ormerod LP *et al*. Screening of immigrants in the UK for imported latent tuberculosis: a multicentre cohort study and cost-effectiveness analysis. *Lancet Infect Dis* 2011;**11**(6):435-44.
6. NICE Clinical Guideline 117 – Tuberculosis. March 2011.
7. Griffiths C, Sturdy P, Brewin P *et al*. Educational outreach to promote screening for tuberculosis in primary care: a cluster randomised controlled trial. *Lancet* 2007;**369**:1528-34.