Tuberculosis

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Tuberculosis (TB) disease declined in incidence over the course of the 20th century but this trend has now reversed in the UK and elsewhere (Fig 1). The number of cases in Britain has risen by nearly a third since 2000.[1] Migration, socio-economic deprivation, HIV co-infection and the greater use of immunosuppressive agents and biological therapies in healthcare have all contributed to this increase. Underlying the global increase is the ability of the *Mycobacterium tuberculosis* (MTB) complex to remain in an apparently clinically inactive state for many years before symptomatic disease develops.[2] Almost one-third of the world's population are thought to have latent TB infection (LTBI), providing an enormous reservoir for disease. TB control requires strategies that can detect active and latent disease promptly and treat them appropriately. This review will discuss new advances in this area.

Epidemiology

Forty per cent of the almost 8,500 new cases of TB in the UK in 2006 occurred in London.[1] However, nearly three-quarters of those with active TB were born abroad so it is inevitable that the rest of the country will inevitably see an increase as migrant populations move beyond London.[1] To complicate matters further, recent work from the Health Protection Agency indicates that many people born abroad develop active disease only after several years in the UK.[3] This appears to arise mainly from pre-existing clinically dormant LTBI progressing to active disease.

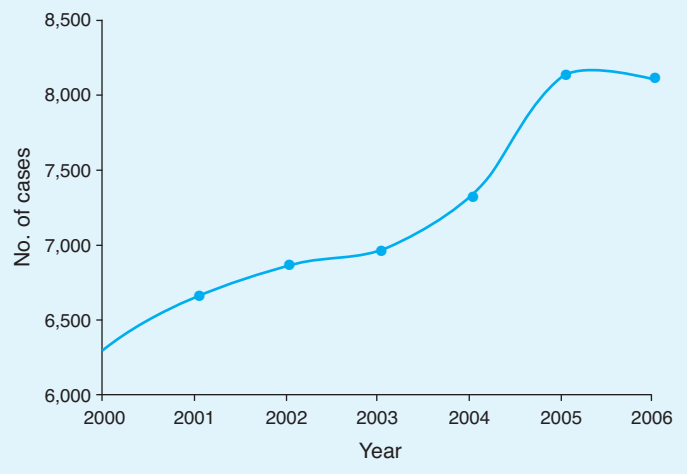

Fig 1. The rising incidence of new cases of tuberculosis in England and Wales from 2000 to 2006.[1]

Key Points

- **Tuberculosis (TB) is becoming more common in the UK and should be considered, especially in high-risk groups**
- **HIV and immunomodulatory drugs interact with TB to make disease more likely, though harder to diagnose and treat**
- **New immune-based tests (interferon-gamma release assay tests) are available for use in diagnosing latent TB infection**
- **Drug resistance is an increasing problem and should be considered when treating TB**
- **Drug treatment of active TB in the UK is currently for a minimum of six months, initially with four drugs**

KEY WORDS: drug resistance, immunosuppression, interferon-gamma release assay tests, latent tuberculosis infection, tuberculosis

Latent tuberculosis infection and tuberculosis

In most people a host immune response is enough to prevent symptoms ever developing. In those in whom it does develop it usually occurs within two years of initial infection, but in a proportion of cases MTB appears to resist clearance for many years. Progression to active disease may then occur naturally, though it is frequently precipitated by states of debilitation or immunosuppression. Individuals in endemic areas can be infected with new strains of MTB which may be difficult to distinguish from apparent reactivation of LTBI.[4]

Diagnosis

Latent tuberculosis infection

Tuberculin skin test. By definition, MTB cannot be cultured from an individual with LTBI, so diagnosis relies on excluding disease yet detecting a host immune response to the organism. The most common immune-based test for LTBI is the century-old tuberculin skin test (TST). In the UK this is a Mantoux-type intradermal injection which relies on detecting cutaneous delayed-type hypersensitivity to tuberculin purified protein derivative (PPD) at 48–72 hours. This test has a number of disadvantages, not least of which is that subjects who have had BCG immunisation are likely to have a positive TST due to cross-reacting antigens (Table 1). Although it is still often used, it is not a particularly sensitive or specific test for the diagnosis of LTBI.

Interferon-gamma release assay. In recent years, advances in immunology have led to the development of a new *ex vivo* test, the interferon-gamma (IFN-γ) release assay (IGRA).[5] This detects the strong T helper type 1 (cell-mediated immune) responses, including IFN-γ, evoked by MTB in host cells. The current IGRA tests contain a variety of MTB antigens not present in BCG (lost when the organism was serially passaged to remove its virulence) and are thus more specific than TST. They are also largely blood-based and provide results within 24 hours.

The National Institute for Health and Clinical Excellence has incorporated these tests into their 2006 guidelines, recommending an IGRA test on all those with a positive TST who are potentially exposed to TB but are asymptomatic.[6] The TST may soon be abandoned completely in certain situations, such as large-scale case-finding in populations with previous BCG immunisation.

There are two commercially available IGRA assays:

- T-Spot TB test, which uses an ELISpot platform
- Quantiferon-TB Gold (ELISA methodology).

The availability of access to one or other of these is likely to determine the choice of test used in an individual healthcare setting. Both appear to work reasonably well in field conditions. Although the former is probably rather more sensitive,[5] the ELISA test is somewhat simpler in operational terms in that samples can be stored for longer, and hence 'batched', to allow cost savings on what is otherwise a relatively expensive test.

Tuberculosis disease

Most effort is spent on the early detection of pulmonary (and hence infectious) TB disease, but almost half the cases in the UK are extrapulmonary. A recent report found that none of the classic triad of symptoms (fever, weight loss and sweats) was present in a quarter of unselected UK TB cases.[7] The same study showed that the inflammatory markers C-reactive protein and erythrocyte sedimentation rate were often normal pretreatment. Hence, once considered, a TB diagnosis should not be discarded too quickly.

Microscopic smear test. The traditional rapid diagnostic approach is a microscopic smear using either Ziehl-Neelsen or fluorescent stains to detect mycobacteria. This approach is mainly performed on sputum. Although simple, quick and cheap, it cannot distinguish MTB from other mycobacteria, is highly operator-dependent and has an overall sensitivity of only 30–80%.[8]

Cultures. Although up to 40% of all notified active TB cases are culture-negative, the gold standard test remains culture from a body fluid or tissue. A positive culture enables drug sensitivities to be determined. The traditional method using solid media can take weeks to give a result, but the recent introduction of liquid culture broths with automated detection has reduced this to days. This is an important advance as a delayed diagnosis can lead to patients being prescribed drugs that are ineffective yet potentially toxic.

A novel and inexpensive method of culture, microscopic observation drug sensitivity, has recently been reported to give results within a few days which are both sensitive and specific.[9]

Nucleic acid probes. At the opposite end of the technological scale, nucleic acid probes are now used in developed countries to detect mycobacteria, providing genotypic data regarding drug resistance within a few hours.

Table 1. Problems with the tuberculin skin test (TST).

Problem	Notes
Variability	Training required for reading the test Subjectivity and operator bias occur
Location	Available clinic room required
Repeat visits	Subjects must return for results to be read (ca 30% do not)
Lack of reproducibility	Response may vary according to PPD manufacturer and batch
False-positive results	More than 10% of positive TST are false-positives due to previous BCG vaccination
Cross-reactivity	Non-tuberculous mycobacteria cause a positive TST in 30%
Boosting	TST responses are boosted by repeat testing, especially if vaccinated with BCG in the past, limiting the reproducibility of results
Active TB	TST is insensitive in active TB (20–40% TST-negative)
Anergy	50% of those with HIV and TB are TST-negative Reduced TST responses may occur in sarcoidosis and conditions or drugs causing immunosuppression

PPD = purified protein derivative; TB = tuberculosis.

Tuberculosis in patients with HIV and those on immunomodulating drugs

It is entirely predictable that any condition which perturbs protective host immunity to MTB will lead to an increase in cases of active disease. The extent to which this occurs depends on the degree of disruption of the host's immune system and the number of people affected by such a condition. Rates of TB infection are therefore high in those countries in which HIV is prevalent. The risk of progression from LTBI to active TB disease in those with HIV is estimated to be about 5–10% per year – similar to the *lifetime* risk of TB progression in an HIV-negative individual.[10] The altered immune response in TB/HIV coinfection has several clinical consequences (Table 2).

T-cell suppressing therapies such as anti-tumour necrosis factor-alpha drugs may also impair host immune response

to TB. These therapies are now established in the treatment of Crohn's disease, rheumatoid arthritis, ankylosing spondylitis and psoriasis. The risk of active TB is increased approximately fourfold when using these drugs. Presentation of TB usually occurs within the first three months of treatment,[11] and most cases have followed treatment with infliximab. The British Thoracic Society has produced guidance to help physicians assess the risk of a patient on these drugs developing active TB.[12]

Treatment of tuberculosis

M. tuberculosis is a slow-growing, intracellular organism so treatment requires the use of multiple drugs for a prolonged period of time. The recommended treatment standard in the UK is a minimum of six months' rifampicin and isoniazid together with pyrazinamide and ethambutol for the first two months or until drug susceptibilities are known ('quadruple therapy').[6] TB in some sites (eg cerebral or meningeal TB) requires even longer treatment for cure and corticosteroids may need to be added to the regimen.[13]

Drug resistance

Given the length, complexity and adverse event profile of drug treatments, patient adherence can be difficult to maintain.[7] Together with the relatively high cost of drugs, poor prescribing patterns and minimal global drug control, this has led to widespread drug resistance.[14] Although some resistance patterns are not of great clinical significance, multidrug and extensively drug resistant (XDR) organisms (Table 3) have a major impact on treatment costs and outcome. During a recent South African outbreak of XDR TB, the case fatality rate approached 100%.[15] To date, there have been only a handful of XDR cases reported in the UK but, given increasing global numbers, this is likely to rise.

Drug resistance will be controlled only if clinicians consider the possibility of a drug resistant organism early in treatment. Individual patient assessment may be helpful, for example whether the patient has risk factors such as:

- previous TB treatment
- acquisition of the disease in a high prevalence area, and/or
- a history of non-adherence.

Targeted use of rapid diagnostic tests, such as new molecular tests using line probe assays or bacteriophage assays, and careful clinical monitoring and segregation of suspected cases can all help.[16]

Other approaches

Packages of individualised care including 'directly observed therapy' and the use of combination pills containing two or even three medications are useful. Recently, several potent drugs have been developed that should hopefully lead to more effective, yet shorter regimens.[17] These include quinolones such as moxifloxacin, the nitroimidazopyran PA-824, diarylquinoline TMC207 (R207910) and long-acting rifamycins (eg rifapentine).[18]

HIV coinfection

Treating TB in those with HIV coinfection is complex. There are numerous potential interactions between the drugs used for the two diseases. Consequently,

Table 2. The impact of HIV on tuberculosis (TB).

Feature or test	Effect of HIV
Clinical presentation	Often atypical: more systemic features, non-pulmonary disease and widespread dissemination
Chest radiograph	Often atypical: lacks characteristic cavitation More pulmonary infiltrates, mediastinal lymph nodes and pleural effusions
Sputum smear for AFB	More likely to be paucibacillary or negative
Sputum culture	More likely to be negative
Nucleic acid amplification tests	Sensitivity reduced by ca 30%
Tuberculin skin test	20–40% false-negatives
Rapid immune-based tests: T-spot TB Quantiferon-TB Gold	 Sensitivity reduced by ca 20% (especially if low blood CD4)
Histology of tissue sample	Fewer granulomas Fewer AFB in biopsy
TB treatment response	Increased mortality at low blood CD4 counts
'Paradoxical reaction' on TB treatment	More common (x 2) More systemic symptoms

AFB = acid-fast bacilli.

Table 3. Drug resistance in tuberculosis.

Resistance severity	Definition	UK incidence (2006) (%)[1]
Mono-resistance	Resistance to a single first-line agent (INH resistance is most common). Rifampicin resistance is more common in those with HIV	7.7
Multidrug resistance (MDR)	Resistance to both INH and rifampicin	1.1
Extensively drug resistant (XDR)	Multidrug resistance + fluoroquinolone resistance + resistance to at least 1 of 3 second-line injectable agents (capreomycin, kanamycin, amikacin)	ca 0

INH = isoniazid.

standard TB therapy will often need to be modified in order to maintain the efficacy of the antiretroviral agents given for the HIV infection. Immune reconstitution inflammatory syndrome (IRIS) occurs in almost one-third of patients being treated for both conditions.[19] At its simplest, IRIS is similar to a 'paradoxical reaction' where there is acute clinical deterioration during a treatment which was previously effective. It is strongly recommended that the management of these dually-infected patients be undertaken at centres with the necessary skill mix.

Conclusions

TB is a global problem that will not go away. Its control requires all doctors, particularly physicians, to maintain a high index of clinical suspicion. Despite the availability of new methodologies, the diagnosis of active and latent TB remains challenging. Both the interaction with HIV and increased rates of TB drug resistance add further complexity. Current standard therapy is with four drugs initially for at least six months. There is hope that shorter, effective treatments will be available soon.

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