Tuberculosis

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Irish Thoracic Society

Symptoms & signs:

- Cough
- Dyspnoea
- Fevers
- Night sweats
- Weight loss
- Haemoptysis (Rasmussen's aneurysm)
- 50-70% is pulmonary TB – may affect any organ system

Epidemiology:

- More than 1.7 billion people (about 25 percent of the world population) are estimated to be infected with *M. tuberculosis*
- According to the World Health Organization (WHO), in 2018, 10 million individuals became ill with TB and 1.5 million died
- The highest rates (100 per 100,000 or higher) are observed in sub-Saharan Africa, India, and the islands of Southeast Asia and Micronesia.
- Estimated 540,000-660,000 cases of MDR/Rifampicin-resistant-TB emerged in 2016 – most cases from China, India, and the Russian Federation.

Risk Factors

HIV infection — Among HIV-infected individuals, the risk of developing TB disease is 9 - 16 times that of HIV-uninfected individuals (roughly 10%/year V 10% lifetime risk in HIV -ve)
Immunosuppression – anti-TNFα agents, solid organ or haematological transplants.
Glucocorticoids – Patients receiving a daily dose of ≥15 mg of prednisone (or its equivalent) for ≥1 month are at increased risk for TB
Diabetes
Poor nutritional status
Vitamin D deficiency
Chronic renal failure

Investigations

Sputum smear microscopy (Ziehl-Neelsen staining) -sensitivity and positive predictive value of AFB smear microscopy are approximately 45 to 80 percent and 50 to 80 percent. In HIV-infected patients, the sensitivity of sputum smear is diminished because pulmonary cavities occur less frequently and the organism burden is lower in the setting of HIV infection. Acid-fast bacteria visualized on a slide may represent *M. tuberculosis* or nontuberculous mycobacteria (NTM), so species identification requires culture and/or molecular techniques. Sputum smear status is used to monitor response to treatment, guide infection control practices, and guide contact investigations.

Mycobacterial solid and liquid cultures are considered the diagnostic gold standard by WHO. The sensitivity and specificity of sputum culture are about 80 and 98 percent, respectively. Culture is required for drug susceptibility testing and for species identification.

Molecular techniques – line probe assay technology, based on PCR and reverse hybridisation methods. Gene Xpert MTB/RIF -used for rapid diagnosis of TB (approx. 1 hour 45 mins). Also tests for mutations associated with rifampicin resistance (*rpoB* gene). Another line probe assay, the GenoType MTBDR*sl* 2.0 was developed for the detection of *M. tuberculosis* and simultaneous detection of resistance-conferring mutations of fluoroquinolones (FLQ) (*gyrA* and *gyrB* genes) and second-line injectable drugs (SLID) (*rrs* and *eis* genes).

Tuberculin skin test (TST) – measures cutaneous reaction elicited by the intradermal injection of a mixture of antigens from *M. tuberculosis* cultures.

Interferon-gamma release assay (IGRA) – measures in vitro the release of cytokines from lymphocytes incubated with two specific antigens present in M. tuberculosis but absent in M. bovis and in most nontuberculous mycobacteria. IGRA equally sensitive to TST, more specific and avoids false positive skin reactions.

Latent TB:

- Latent TB – no signs or symptoms of disease – only immunological markers of prior contact
- It is estimated that 10% of infected individuals develop TB disease, half of them within 2 years after infection and 90% never develop the disease.
- Higher risk of later reactivation in immunosuppressed individuals and children.
- Tests for LTBI are indirect and rely on reaction between sensitized lymphocytes and antigens from *Mycobacterium tuberculosis* – TST and IGRA.

LTBI Treatment Options:

Treatment	Duration
Isoniazid (INH)	6 months
Rifampicin (RIF)	4 months
INH + RIF	3 months
Rifapentine + INH	Once weekly x 3 months

Types of drug-resistant TB

Mono-resistance	Resistance to one first-line anti-TB drug only
Poly-resistance	resistance to more than one first-line anti-TB drug, other than both isoniazid and rifampicin
Multi-drug resistance (MDR-TB)	resistance to at least both isoniazid and rifampicin
Extensive drug resistance (XDR)	resistance to any fluoroquinolone, and at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin), in addition to multidrug resistance
Rifampicin resistance (RR)	resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin, in the form of mono-resistance, poly-resistance, MDR or XDR.

Treatment -based on drug susceptibility testing and resistance patterns

TB regimens consist of an intensive phase and then a continuation phase

Duration of TB regimen –

- pan-sensitive TB 6/12
- cavitary disease 9/12
- Extrapulmonary disease – treatment usually the same except in CNS, bone and joint involvement– 12 months recommended
- MDR/XDR TB – historically 18-24 months, new shorter regimens (the Bangladesh regimen) available 9 -12 months, but selection based on drug susceptibility testing.

Pan-sensitive TB - Rifampicin/Isoniazid/Pyrazinamide/Ethambutol – all 4 drugs for intensive phase (2/12) and then Rif/INH for continuation phase (4/12)

MDR-TB –

ATS/CDC/ERS/IDSA Guidelines intensive phase of 5 or more drugs (based on DST) for 5 – 7 months after conversion of cultures to negative followed by a continuation phase of 4 drugs to complete total duration of 15 to 21 months after culture conversion. Fluoroquinolone (Levofloxacin or Moxifloxacin), Bedaquilline, Linezolid, Clofazimine, Cycloserine – other options in guidelines such as Amikacin, Delamanid, Ethionamide, PAS.

WHO MDR regimen –intensive phase of 5 drugs, administered for 18 – 24 months. Drugs grouped A, B and C.

Nix TB trial – Bedaquilline, Pretomanid, Linezolid – a 6 month regimen for MDR and XDR TB.

Corticosteroid therapy (dexamethasone or prednisolone) during the first 6 – 8 weeks for TB meningitis (reduces early mortality), TB pericarditis, renal TB (prevents ureteric stenosis) and in spinal TB with cord compression (may prevent cord compression) is advocated.