HANDBOOK OF HIV MEDICINE

- An updated section on the approach to HIV infection in children including paediatric tuberculosis, infant feeding, and clinical paediatric assessment
- The latest updates on HIV medicine and drug management
- New chapters on clinical assessment and adult tuberculosis
- More than 50 full-colour illustrations
- Special focus on the needs of developing countries

THIRD EDITION

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Paediatric tuberculosis

HIV infection increases the risk of tuberculosis (TB). In the absence of antiretroviral therapy HIV-infected infants have a 24-fold higher risk to develop TB disease compared to HIV-uninfected infants in areas of high TB incidence. An increased incidence of congenital TB has also been noted.

Clinical features

Diagnosis of TB in children has always been challenging, but is now more complex because of overlap with other HIV-related lung diseases. Both over- and under-diagnosis are likely, depending on TB incidence and the health worker's experience.

Patient history

It is important to consider the following points when taking a history:

- TB can present at any age, even in neonates.
- Symptoms of pulmonary and extrapulmonary TB (EPTB) are more often acute in HIV-infected children.
- WHO criteria for the diagnosis of TB (cough >2 weeks, failure to thrive, and/or weight loss) are more common in HIV-infected children than in HIV-uninfected children with TB, but other HIV-related conditions can cause similar symptoms.
- Chronic fever is common in HIV-associated TB.
- *A history of contact with an adult TB source case is most important.* This is often the first hint of diagnosis. A history of a known contact is identified in up to 66% of cases.
- The drug susceptibility test results of the source case(s) are essential for the proper management of the childhood contacts.
- Previous antituberculosis treatment in the child or the adult source case is associated with a higher rate of drug resistance.

A history of any of the following may indicate the need for invasive investigations to establish a definite diagnosis:
- absence of an expected response to other treatments (e.g. antibiotics for two weeks);
- previous abnormal chest radiograph findings; or
- persistent lung disease.

**Physical examination**

- Generally, children present with primary pulmonary TB that is more symptomatic than that found in HIV-uninfected children.
- EPTB affects similar sites in both HIV-infected and uninfected children. Peripheral lymph node and central nervous system (CNS) involvement are quite common. Unusual sites, such as the middle ear (causing chronic otorrhoea) need special attention. The increased association of EPTB with HIV infection is not as clear as it is in adults. Note that HIV disease itself results in generalized lymphadenopathy and hepatosplenomegaly.
- There is an increased risk for TB in HIV-infected children without a BCG scar.

**Special investigations**

**Tuberculin skin test**

A Mantoux tuberculin skin test (TST) should be performed. The Mantoux TST consists of an intradermal injection of five tuberculin units (TU) of purified protein derivative (Japanese strain) or two TU of PPD RT23 (Danish strain). Induration is measured transversely in millimetres after 48 to 72 hours. A negative result does not exclude TB. For the HIV-infected child, induration >4 mm denotes a positive result. Repeating a negative TST after nutritional rehabilitation in a severely malnourished child may yield a positive TST. Positive TST results are reported in 40% to 55% of HIV-infected children with TB. Low CD4 counts and progressive HIV disease were associated with negative TST.

**Interferon-gamma Release Assays (IGRAs)**

IGRAs are specific T-cell-based assays developed to identify patients with TB infection. Two types of IGRAs are commercially available: the ELISA-based QuantiFERON-TB Gold In-tube assay (Cellestis Limited, Australia), and the ELISPOT-based T-Spot.TB assay (Oxford Immunotec, UK). These assays have the same sensitivity for identifying TB infection as TST, but they have an increased specificity to TST in high-burden areas of
Most forms of extrapulmonary TB can be treated with the regimens mentioned above for between six to nine months. For patients with TB meningitis, six months of therapy with continuous rifampicin has been shown to be as effective as the traditional nine to 12 regimens. Lastly, adjunctive steroids may be useful in pericardial and meningeal tuberculosis (see Chapter 29: Cardiology and Chapter 35: Neurology).

**Antituberculous therapy and antiretroviral therapy**

Rifampicin-based antituberculous therapy can be given with nucleoside / nucleotide and non-nucleotide reverse transcriptase inhibitor-based ART, and antiretroviral therapy should not be interrupted. However rifampicin interacts with protease inhibitors and dose modification is required (see Chapter 49: Drug-drug interactions).

Antiretroviral therapy (ART) in patients newly diagnosed with TB should be started within two weeks provided the treatment for tuberculosis is being tolerated, social support is in place and adequate antiretroviral training has been given. Patients with a CD4 count >50 cells/µL have the option of starting ART after the first eight weeks of treatment for TB to reduce the risk of mild immune reconstitution disease (See Chapter 50: Immune reconstitution inflammatory syndrome).

Efavirenz is preferable to nevirapine when ART is initiated in tuberculosis patients. Tuberculosis patients who start nevirapine are at increased risk of virological failure as liver enzyme induction caused by rifampicin may cause sub-therapeutic nevirapine levels when given during the first two weeks at a dose of 200 mg daily (if nevirapine is the best option consider initiating treatment at 200 mg twice daily).

**Side-effects of main antituberculous agents**

Isoniazid (H) adverse effects:
- peripheral neuropathy;
- hepatitis (rare);
- generalised skin rash (rare);
- fever;
- joint pains.

*Note: Isoniazid inhibits the metabolism of epileptic drugs such as phenytoin and carbamazepine. Dosages of these drugs may need to be reduced for the duration of treatment.*
Rifampicin (R) adverse effects:
– gastro-intestinal: nausea, anorexia, mild abdominal pain;
– cutaneous reactions: mild flushing and itchiness of the skin;
– hepatitis (uncommon unless concurrent history of liver disease or alcoholism);
– colours urine, sweat and tears orange/pink.
Note: *Rifampicin is an enzyme inducer. Be careful of drug interactions between rifampicin and drugs such as the oral contraceptive pill, warfarin, oral diabetic drugs, digoxin, anti-epileptics. Doses of contraceptive should be increased in patients receiving rifampicin, or other methods of contraception should be used.*

Ethambutol (E) adverse effects:
– progressive loss of vision due to retrobulbar neuritis (colour vision affected first);
– skin rash;
– joint pains;
– peripheral neuropathy.
Note: *Patients should be told to notify a health professional of any changes in vision. Visual disturbance should lead to the immediate discontinuation of ethambutol.*

Pyrazinamide (Z) adverse effects:
– hepatotoxicity;
– arthralgia;
– skin rash on sun exposed areas.
Note: *Patients with liver disease should not receive pyrazinamide.*

Streptomycin (S) adverse events:
– cutaneous hypersensitivity, rash and fever;
– vestibular toxicity causing dizziness, vertigo, unsteadiness, vomiting;
– deafness;
– anaphylaxis;
– renal impairment.
Note: *Avoid streptomycin in patients with pre-existing renal disease or patients >65 years. Streptomycin is contra-indicated in pregnancy and in young children.*
55 Paradoxical TB-IRIS lymphadenitis. The node enlarged and subsequently ruptured after patient started antiretrovirals while on TB treatment.

56 Paradoxical TB-IRIS. The patient developed recurrent cough and fever after starting antiretrovirals while on TB treatment. Chest radiograph shows worsening pulmonary infiltrate with cavitation.

57 Acne IRIS. The patient developed an acne rash two weeks after switching to second line antiretrovirals following virological failure on first-line.