Tuberculosis

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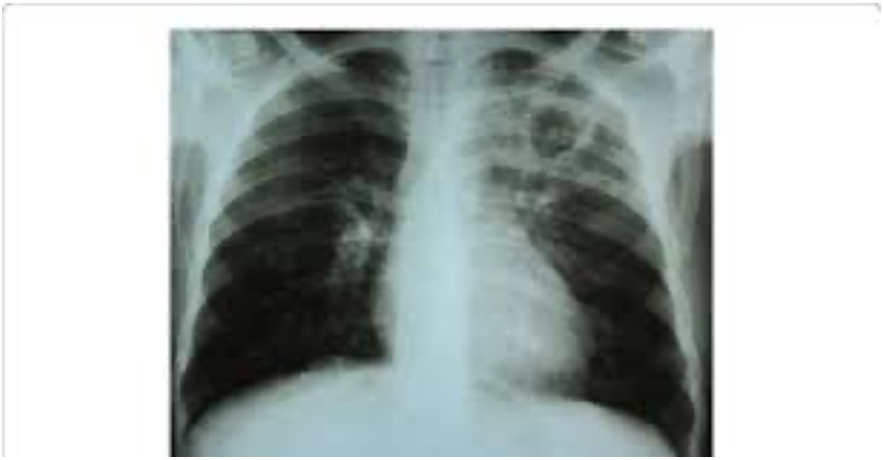
Aban 1403

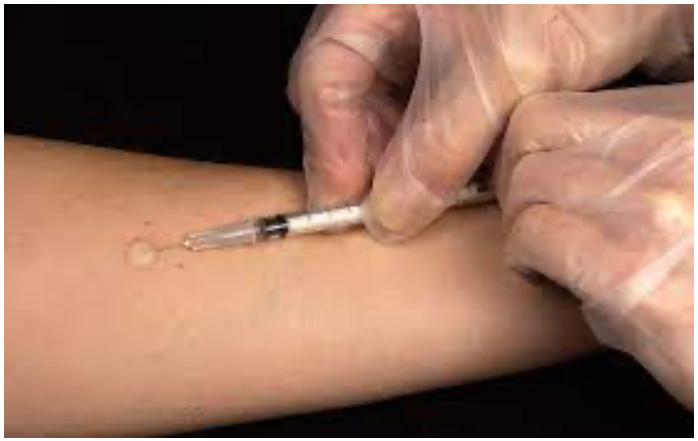
Case presentation:

- A 65-year old man presented with fever and cough for 2 months.
- His symptoms did not resolve despite receiving antibiotics.



Diagnosis:

- Tuberculin skin test(TST):
- Intradermal injection of purified protein derivative (PPD), a crude mixture of different mycobacterial antigens, which stimulates a
  delayed-type hypersensitivity response and causes induration at the injection site within 48–72 hours.



TST:

- This test has relatively low specificity in those with recent bacille Calmette-Guérin (BCG) vaccination and low sensitivity in immunosuppressed individuals (HIV).
- A follow-up clinic visit is required after the placement of the TST, and results must be read within the suggested time frame to be valid.

IGRA:

- IGRAs are in vitro tests that measure release of interferon-gamma (IFN-γ) by T-cells following stimulation by the early secretory antigenic target 6 kDaprotein (ESAT-6) and culture filtrate protein 10 (CFP-10) antigens that are specific to Mtb.
- Unlike the TST, IGRAs are not affected by prior BCG vaccination, or by infection with nontuberculous mycobacteria (NTM).

NEW:

- Newer Mtb antigen-based skin tests (TBSTs) based on specific antigens have been developed, using the same ESAT-6 and CFP-10 antigens.

- All tests use intradermal injection of antigen and, like the TST, are read after 48–72 hours as induration in millimetres, using the method suggested by Mantoux.

Recommendation:

- Mycobacterium tuberculosis antigen-based skin tests (TBSTs) may be used to test for TB infection.

- Based on available evidence, the WHO concluded that the diagnostic accuracy of TBSTs is similar to that of IGRAs and greater than that of the TST.

Cont’

- 1-PLHIV
- 2-children and adolescents aged under 18 years
- 3- people who have been vaccinated with BCG

*** **For all the above-mentioned subpopulations, TBSTs are recommended.**

Use of the TST and IGRAs for the diagnosis of TB disease:

- IGRAs and TST **should not be used** in low- and middle-income countries for the diagnosis of pulmonary or extrapulmonary TB, or for the diagnostic work-up of adults (including people living
with HIV) suspected of active TB in these settings.
-

Strong recommendation

TB infection:

- Either a tuberculin skin test (TST) or interferon-gamma release assays (IGRAs) can be used to test for TB infection.
- **Strong recommendation.**

- The comparison of the TST and IGRAs in the same population does not provide strong evidence that one test should be preferred over the other **for predicting progression** to active TB disease.

A few important points:

- IGRA: sensitivity is reduced in children aged under 2 years and PLHIV.

- When BCG is given at birth, as is the case in most parts of the world, it has a variable, limited impact on TST specificity.

Sputum smear and culture:

- IDSA guideline:
- We recommend that acid-fast bacilli (AFB) smear micros-
  copy be performed in all patients suspected of having pulmonary TB (strong recommendation, moderate-quality evidence).

- Performing 3 AFB smears confirms pulmonary TB with a sensitivity of approximately 70% when culture-confirmed TB disease is the reference standard.

Cont’

- Remarks:
  False-negative results are sufficiently common that a negative AFB smear result does not exclude pulmonary TB.
- Similarly, false-positive results are sufficiently common that a positive AFB smear result does not confirm pulmonary TB.

- Optimal sputum volume is 5–10 mL.

Culture:

- We suggest that both liquid and solid mycobacterial cultures be performed, rather than either culture method alone, for every specimen obtained from an individual with suspected TB disease.

- We suggest performing a diagnostic nucleic acid amplification test (NAAT), rather than not performing a NAAT, on the initial respiratory specimen from patients suspected of having pulmonary TB.

Remarks:

- In AFB smear-positive patients, a negative NAAT makes TB disease unlikely.

- In AFB smear-negative patients with an intermediate to high level of suspicion for disease, a positive NAAT can be used as presumptive evidence of TB disease, but a negative NAAT cannot be used to exclude pulmonary TB.

WHO 2021:

- RECOMMENDATION :

- In adults with signs and symptoms of pulmonary TB, Xpert MTB/RIF should be used as an initial diagnostic test for TB and rifampicin-resistance detection in sputum rather than smear microscopy/culture and phenotypic DST.

Cont’

- Xpert MTB/RIF is an automated PCR test (molecular test) using the GeneXpert platform .

- Xpert MTB/RIF is a single test that can detect both MTBC bacteria and rifampicin resistance within 2 hours of starting the test, with minimal hands-on technical time .

Cont’

- Induced sputum
- Bronchoscopy

- Recommendation : We suggest **sputum induction** rather than flexible bronchoscopic sampling as the initial respiratory sampling method for adults with suspected pulmonary TB who are either unable to expectorate sputum or whose expectorated sputum is AFB smear microscopy negative.

Cont’

- Should post bronchoscopy sputum specimens be collected from adults with suspected pulmonary TB?
- Postbronchoscopy AFB smears have a diagnostic yield of 9%–73% and post bronchoscopy mycobacterial cultures have a yield of 35%–71% according to multiple studies.

- **Remarks**: Post bronchoscopy sputum specimens are used to perform AFB smear microscopy and mycobacterial cultures.

Miliary TB:

- Bronchoscopic sampling in patients with suspected military TB should include bronchial brushings and/or TBB, as the yield from washings is substantially less and the yield from BAL unknown.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So we need to keep our hands down.

DIAGNOSTIC APPROACH: TESTING FOR SUSPECTED EXTRAPULMONARY TB.

- Should cell counts and chemistries be performed on amenable (ie, liquid) specimens collected from sites of suspected extrapulmonary TB?
- Recommendation : We suggest that cell counts and chemistries be performed on amenable fluid specimens collected from sites of suspected extrapulmonary.

- Remarks: Specimens that are amenable to cell counts and chemistries include **pleural, cerebrospinal, ascitic, and joint fluids**.

Cont’

- Should adenosine deaminase (ADA) and free IFN-γ levels be measured on specimens collected from sites of suspected extrapulmonary TB?
- Recommendation : We suggest that ADA levels be measured, on fluid collected from patients with suspected pleural TB, TB meningitis, peritoneal TB, or pericardial TB.
- Recommendation : We suggest that free IFN-γ levels be measured, on fluid collected from patients with suspected pleural TB or peritoneal TB.

Cont’

- Neither the ADA level nor the IFN-γ level provide a definitive diagnosis of extrapulmonary TB disease; rather, they provide supportive evidence that must be interpreted in the entire clinical context.

Cont’

- We suggest that AFB smear microscopy be performed, on specimens collected from sites of suspected extrapulmonary TB.

- However, a negative result may not be used to exclude TB because false-negative results are exceedingly common.

- We recommend that mycobacterial cultures be performed on specimens collected from sites of suspected extrapulmonary TB.

Cont’

- We suggest that NAAT be performed, on specimens collected from sites of suspected extrapulmonary TB.

- **The recommendation is conditional**
- At this time there are no FDA-approved NAATs for use with extrapulmonary specimens.

Biopsy:

- Histologic examination


I'M FEELING GOOD

Results:

- AFB: +
- CBC:
- WBC:5400
- Hb: 9.6
- HIV Ab: negative
- LFT: normal
- Bun , Cr: normal

Treatment:

- Recommendation1:
- New patients with pulmonary TB should receive a regimen containing 6 months of rifampicin: 2HRZE/4HR.

- The recommendation also applies to extrapulmonary TB – except TB of the **central nervous system, bone or joint** for which some expert groups suggest longer therapy.

Recommendation2:

- Wherever feasible, the optimal dosing frequency for new patients with pulmonary TB is **daily** throughout the course of treatment.

- Thrice weekly throughout therapy : drug resistance.

- “Daily” is considered to mean at least **five times** per week.

Recommendation3:

- The use of fixed-dose combination(FDC) tablets is recommended over separate drug formulations in treatment of patients with drug-susceptible TB .

FDC tablet:

- INH: 75 mg
- Rifampin: 150 mg
- PZA: 400 mg
- EMB: 275 mg
- 40-52 kg: 3 t
- 52-70Kg: 4t
- Over 70 kg: according to age

FDC tablet:

- Subgroup consideration.
- The reduced pill burden as a result of using FDCs may be especially valuable in patients with co-morbidities (notably HIV infection) .

- Patients with some specific medical conditions (e.g. intolerance to certain TB drugs, liver or renal function impairment) are likely to require individual medication dose adjustment which can be done only with **separate drug formulations.**

Recommendation4:

- In new pulmonary TB patients treated with the regimen containing rifampicin throughout treatment, if a positive sputum smear is found at completion of the intensive phase**, the extension of the intensive phase is not recommended .**
- **2017 guidelines**

Recommendation5:

- People aged 12 years or older with drug-susceptible pulmonary TB, may receive a 4-month regimen of isoniazid, rifapentine, moxifloxacin and pyrazinamide.

Recommendation 6:

- In children and adolescents between 3 months and 16 years of age with **non-severe TB** (without suspicion or evidence of MDR/RR-TB), a **4-month treatment regimen** (2HRZ(E)/2HR) should be used (strong recommendation, moderate certainty of evidence) – **new recommendation.**

Non-severe TB:

- Non-severe TB is defined as: Peripheral lymph node TB; intrathoracic lymph node TB without airway obstruction; uncomplicated TB pleural effusion or paucibacillary, non-cavitary disease, confined to one lobe of the lungs, and without a miliary pattern.

- The use of **ethambutol** in the first two months of treatment is recommended in settings with a high prevalence of HIV, or of isoniazid resistance.

Recommendation7:

- It is recommended that TB patients who are living with **HIV** should receive at least the same duration of daily TB treatment as HIV-negative TB patients.

- ART should be started as soon as possible within two weeks of initiating TB treatment, regardless of CD4 cell count, among people living with HIV.

Adjuvant steroids:

- Tuberculous meningitis:
- Dexamethasone or prednisolone tapered over 6–8 weeks should be used.

- Tuberculous pericarditis

MONITORING TREATMENT RESPONSE AND DRUG TOXICITY

- Bacteriologic evaluation through commercial liquid-culture systems (or—when liquid-culture capacity is not yet available—through smear microscopy) is essential in monitoring the response to TB treatment.

- The patient's weight should be monitored regularly and the drug dosage adjusted with any significant weight change.

CONT'

- Patients with pulmonary disease should have their sputum examined monthly until cultures become negative to allow early detection of treatment failure.

- With the recommended 6-month standard first-line regimen, >80% of drug-susceptible TB patients will have negative sputum cultures at the end of the second month of treatment.
- By the end of the third month, the sputum of virtually all patients should be culture negative.

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- In some patients, especially those with extensive cavitary disease and large numbers of organisms, AFB smear conversion may lag behind culture conversion as a result of the expectoration and microscopic visualization of dead bacilli.
- Therefore, as capacity is built, smear microscopy should be progressively abandoned as a monitoring tool in favor of liquid culture.
- As noted above, patients with cavitary disease in whom sputum culture conversion does not occur by 2 months require immediate testing or retesting for drug resistance.

CONT’

- When a patient’s sputum cultures or smears remain positive at ≥3 months despite good adherence, treatment failure caused by drug resistance is likely.

- The pattern of drug resistance should guide the choice of the best treatment option.

CONT'

- A sputum specimen should be collected at the end of treatment to document cure.
- In settings where mycobacterial cultures are not yet available, monitoring by AFB smear examination should be undertaken at 2, 5, and 6 months.
- Bacteriologic monitoring of patients with extrapulmonary TB is more difficult and often is not feasible.
- In these cases, the response to treatment must be assessed clinically with the help of medical imaging

CONT'

- Monitoring of the response to chemotherapy by nucleic acid amplification technology, such as the Xpert MTB/RIF assay, is not suitable because these tests can produce positive results due to nonviable bacilli.
- Likewise, serial chest radiographs are not recommended because radiographic changes may lag behind bacteriologic response and are not highly sensitive. After the completion of treatment, neither sputum examination nor CXR is recommended for routine follow-up purposes.
- However, a chest radiograph obtained at the end of treatment may be useful for comparative purposes should the patient develop symptoms of recurrent TB months or years later.

DRUG TOXICITY:

- The most common adverse reaction of significance among people treated for drug-susceptible TB is hepatitis.

- Patients should be carefully educated about the signs and symptoms of drug-induced hepatitis (e.g., dark urine, loss of appetite, nausea) and should be instructed to discontinue treatment promptly and see their health care provider if these manifestations occur.

HEPATITIS:

- Although biochemical monitoring is not routinely recommended, all adult patients should undergo baseline assessment of liver function (e.g., measurement of serum levels of hepatic aminotransferases and bilirubin).
- Older patients, those with concomitant diseases, those with a history of hepatic disease (especially hepatitis C), and those using alcohol daily should be monitored especially closely (i.e., monthly), with repeated measurements of aminotransferases, during the initial phase of treatment.
- Up to 20% of patients have small increases (up to three times the upper limit of normal) in serum levels of aspartate aminotransferase that are not accompanied by symptoms and are of no consequence.

CONT’

- Suspension of treatment should be considered for patients with symptomatic hepatitis, especially when accompanied by at least a three-fold increase in serum levels of AST and/or ALT, and for patients without symptoms of hepatic injury who have marked (at least five-fold) elevations in serum levels of AST and/or ALT.
- Drugs should be reintroduced one at a time after liver function has returned to normal.

CONT’

- Hypersensitivity reactions usually require the discontinuation of all drugs and rechallenge to determine which agent is the culprit.
- Because of the variety of regimens available, it usually is not necessary—although it is possible—to desensitize patients.
- Hyperuricemia and arthralgia caused by pyrazinamide can usually be managed by the administration of acetylsalicylic acid; however, pyrazinamide treatment should be stopped if the patient develops gouty arthritis.

Renal failure:

- Isoniazid, rifampin, and pyrazinamide may be given in the usual doses in cases of mild to moderate renal failure, but the dosages of isoniazid and pyrazinamide should be reduced for all patients with severe renal failure except those undergoing hemodialysis.

Liver failure:

- Patients with severe hepatic disease may be treated with ethambutol, streptomycin, and possibly another drug (e.g., a fluoroquinolone); if required, isoniazid and rifampin may be administered under close supervision.
- The use of pyrazinamide by patients with liver failure should be avoided.

- Silicotuberculosis necessitates the extension of therapy by at least 2 months

Pregnancy:

- 9 months of treatment with isoniazid and rifampin supplemented by ethambutol for the first 2 months.
- WHO
- Streptomycin is contraindicated because it is known to cause eighth-cranial-nerve damage in the fetus.
- The thioamides, bedaquiline, and delamanid should also be avoided in the treatment of pregnant women with MDR-TB.
- Treatment for TB is not a contraindication to breast- feeding.

■ TB PREVENTIVE TREATMENT (TPT)

- Chemoprophylaxis or preventive chemotherapy, and previously referred to as treatment of latent TB infection is a fundamental intervention in TB control and elimination strategies.
- Infection can be tested using TST or IGRA, although these tests just measure host immune response to TB antigens.
- Unfortunately, at present, there is no gold-standard diagnostic test that can confirm true infection (as opposed to immunologic memory of previous exposure) or predict which infected individuals will develop active TB.

Cont’

- As a result, decisions to treat infection should include consideration of the risk of progression in an individual.
- For skin testing, five tuberculin units of polysorbate-stabilized PPD should be injected intradermally into the volar surface of the forearm (i.e., the Mantoux method).
- Reactions are read at 48–72 h as the transverse diameter (in millimeters) of induration; the diameter of erythema is not considered.

Tuberculin Reaction Size and Cutoff for Tuberculosis (TB) Preventive Treatment

PPD ≥5

- HIV-infected persons
- Recent contacts of a patient with TB
- Organ transplant recipients
- Persons with fibrotic lesions consistent with old TB on chest radiography
- Persons who are immunosuppressed—e.g., due to the use of glucocorticoids or tumor necrosis factor α inhibitors
- Persons with high-risk medical conditions(SILICOSIS, ESRD managed by hemodialysys).

CONT’

PPD≥10

- Recent immigrants (≤5 years) from high-prevalence countries
- Injection drug users
- Mycobacteriology laboratory personnel; residents and employees of high-risk congregate setting(correctional facilities, nursing homes, homeless shelters, and hospitals and other health care facilities).
- Children <5 years of age; children and adolescents exposed to adults in high-risk categories.

Recommended Regimens and Drug Dosages for Tuberculosis Preventive Treatment

- Isoniazid alone for 6 or 9 months
- Rifampin alone for 4 months
- Isoniazid plus rifampin for 3 months
- Rifapentine plus isoniazid for 3 months
- Rifapentine plus isoniazid for 1 month

CONT’

- A 6- to 9-month course of isoniazid reduces the risk of active TB in infected people by up to 90%.

- In the absence of reinfection, the protective effect is believed to be lifelong.
- The rifampin-containing regimens should be considered for persons who are likely to have been infected with an isoniazid-resistant strain.

CONT’

- A clinical trial showed that a regimen of isoniazid (900 mg) and rifapentine (900 mg), given once weekly for 12 weeks, is as effective as the standard 9-month isoniazid regimen.

- This regimen was associated with higher rates of treatment completion (82% vs 69%) and less hepatotoxicity (0.4% vs 2.7%) than isoniazid alone, although the rate of permanent discontinuation due to an adverse event was higher (4.9% vs 3.7%).

CONT'

- Recently, an open- label, randomized, phase 3 noninferiority trial has shown that among HIV-infected persons, a 1-month regimen of daily rifapentine plus isoniazid was noninferior to the 9-month daily isoniazid regimen and ensured a higher treatment completion.

- As a result, the WHO has included a 1-month regimen composed of daily isoniazid (300 mg) and rifapentine (600 mg) among the available options for people aged 13 years or more.

TPT:

- TPT among persons likely to have been infected by a multidrug- resistant strain is a challenge because no clinical trial results are available to guide treatment.
- Drug selection should be based on the drug susceptibility profile of the index case.
- One regimen recommended by the WHO is daily levofloxacin (750−1000 mg daily among adults) for 6 months.

CONT’

- Currently, no evidence shows that large-scale use of TPT leads to significant development of drug resistance.

- However, before TPT begins, it is mandatory to carefully exclude active TB in order to prevent undertreatment and promote development of drug resistance.

PRINCIPLES OF TB CONTROL

- Respiratory isolation of persons with suspected TB until they are proven to be noninfectious (at least by sputum AFB smear negativity),
- proper ventilation in rooms of patients with infectious TB,
- use of ultraviolet irradiation in areas of increased risk of TB transmission,
- correct use of personal protective equipment,
- and periodic screening of personnel who may come into contact with known or unsuspected cases of TB.


Health