Approach to Neurotuberculosis
the Great Chameleon

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Disclosures

None

Learning Objectives

- Understanding global TB situation with special emphasis on MDR/XDR TB
- Understanding various CNS presentations of TB
- Learning the latest and recommended investigations
- Understanding the treatment guidelines for CNS TB including MDR/XDR TB

Case history

BJ 25yrs, Female

fever, cough —diagnosed right Pleural effusion secondary to TB started on AKT4 - 1 month

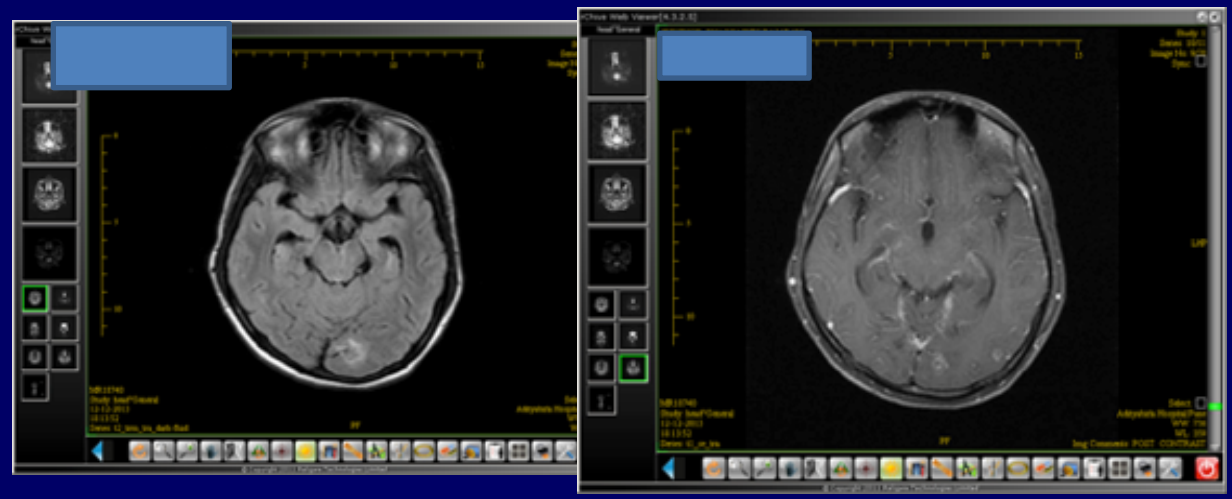
Investigation done there Pleural fluid –No org

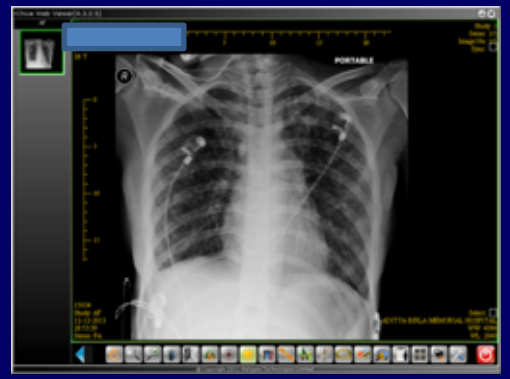
Sputum 3 samples – AFB negative

Developed Altered Sensorium ,CT brain – N

Shifted to our hospital ,Conscious , febrile. Confused, Neck stiffness

Chest Xray military mottling, MRI brain – Left Occipital ring enhancing lesion with meningeal enhancement

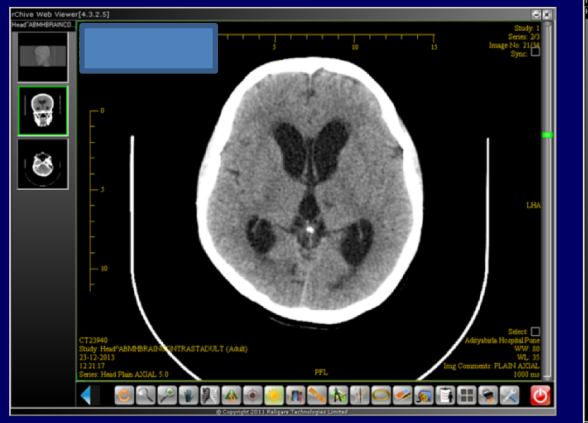


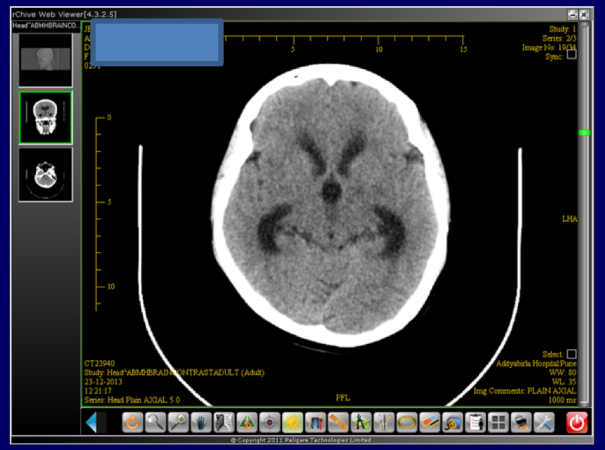


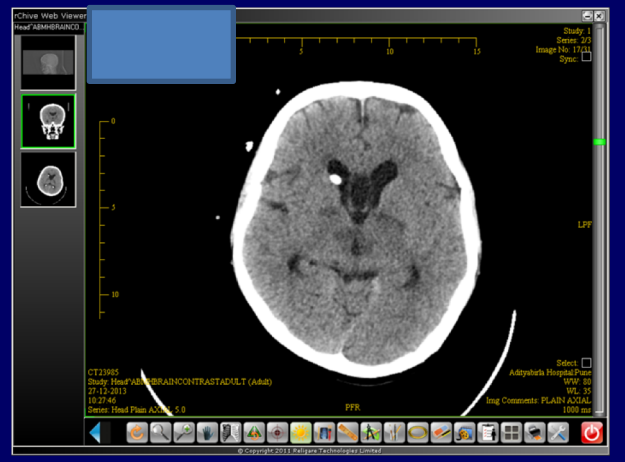
CSF- Protein- 159

- Sugar - <20 (parallel blood sugar 90mg/dl)
- TLC – 190 90% lymphocytes
- ADA- 82, CSF- NO AFB, India Ink- neg, sent for C&S

- Na -121







6 week later CSF culture : Mycobacterium Tuberculosis Complex

Sensitivity-

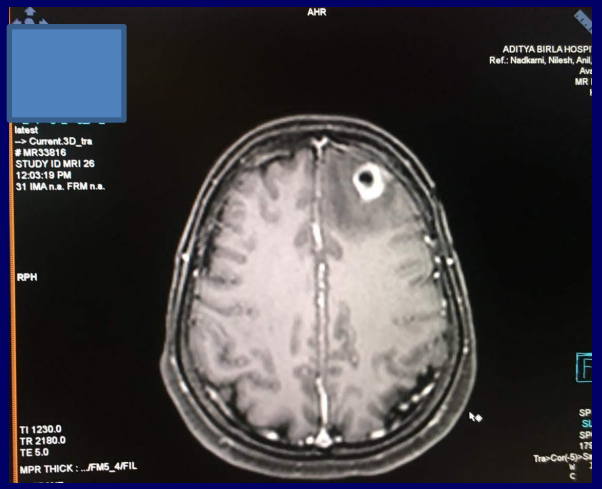
Ethambutol- Resistant

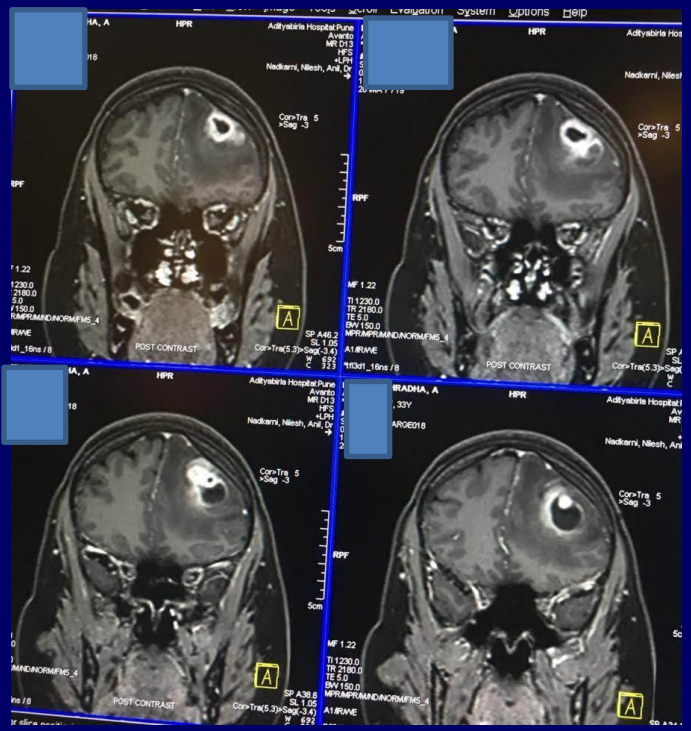
Pyrizinamide- Resistant

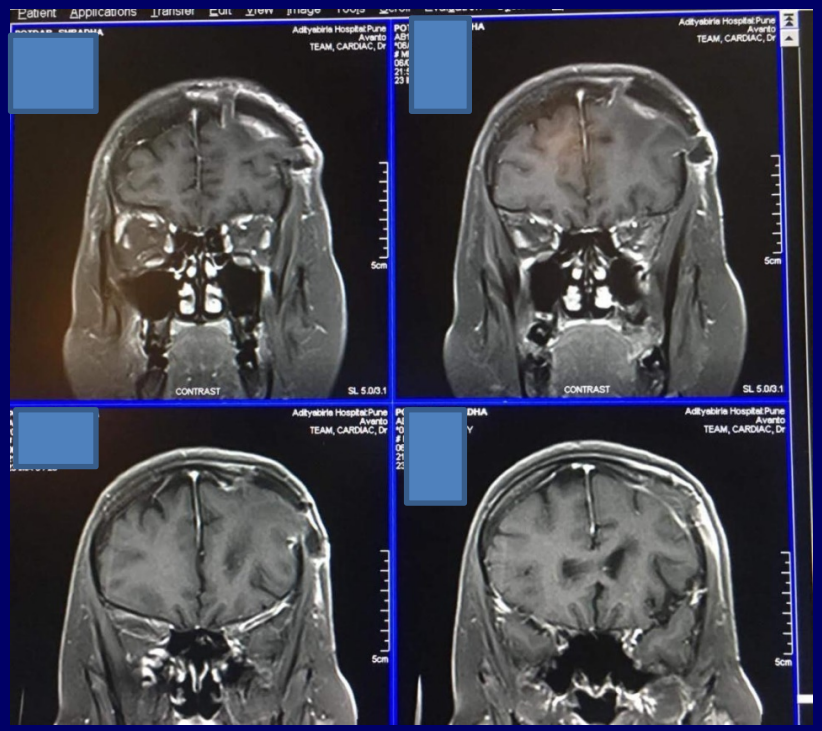
Rifampicin - Resistant

Isoniazid --- Resistant

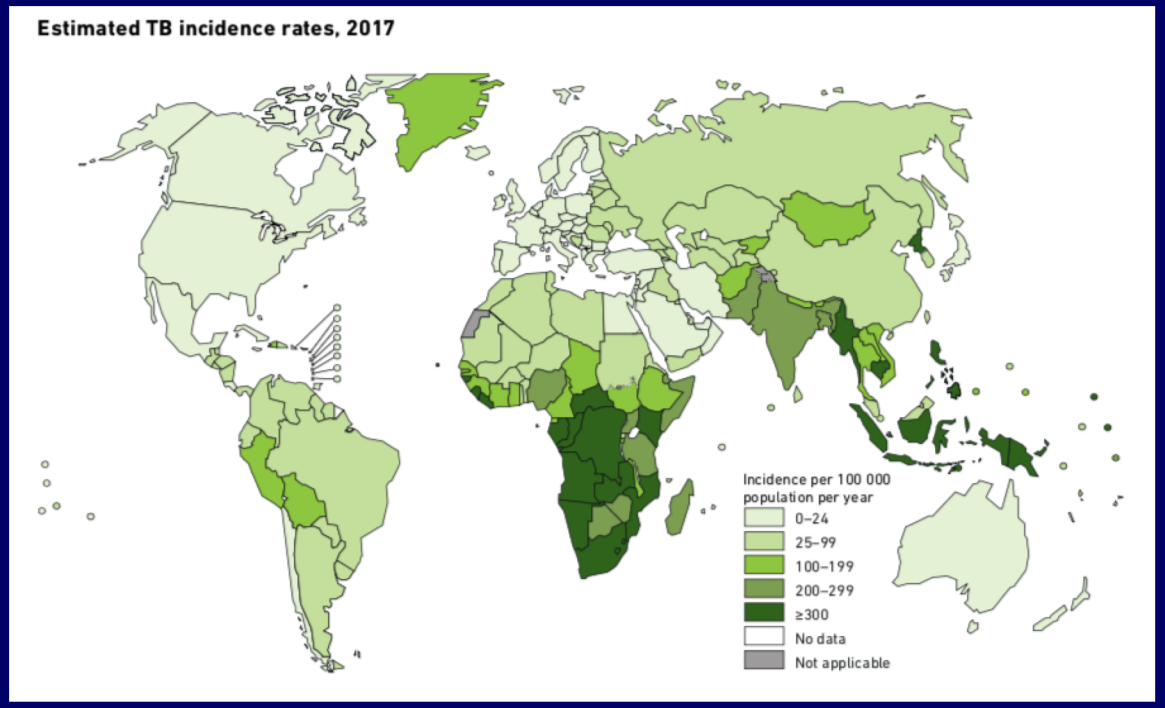
31 years old lady admitted with seizures ,
Mri brain showed left frontal thick ring enhancing lesion with perifocal edema.
CXR normal. Lab normal .
CSF not done . Started on AKT4 with tapering dose of steroids

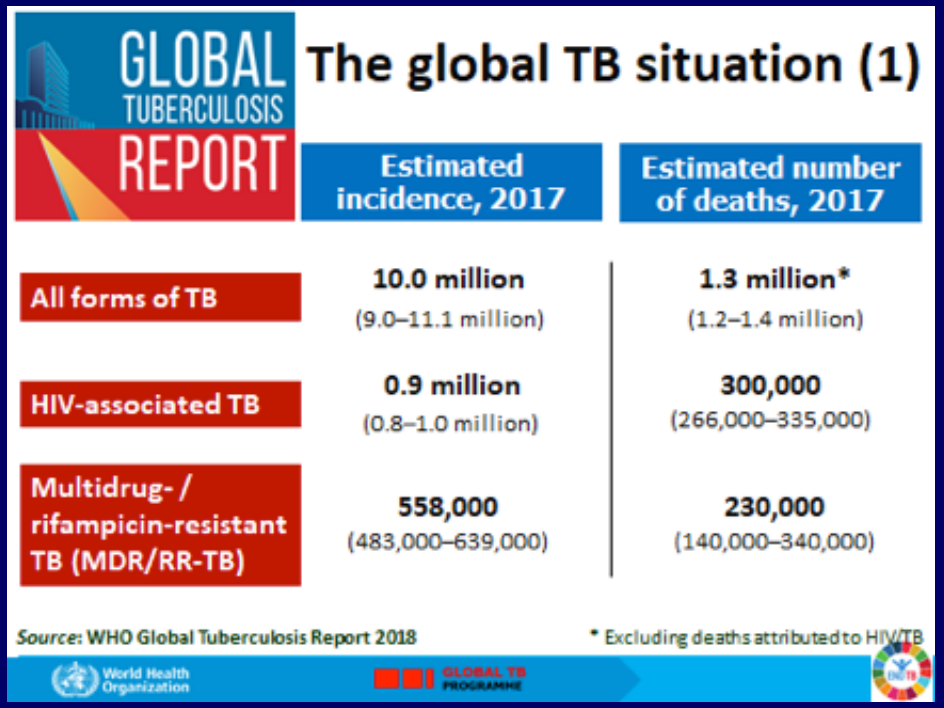






Case shared By Dr Rakesh Ranjan Consultant Neurosurgeon Aditya Birla Hospital Pune India





Incidence of TB in the UAE is considered low at 0.79 per 100,000 inhabitants compared to other countries, down from 4.2 per 100,000 in 2000, according to the Global Tuberculosis Report.

- CNS tuberculosis occurs in up to 10% and has protean clinical manifestations. The burden is directly proportional to the prevalence of TB

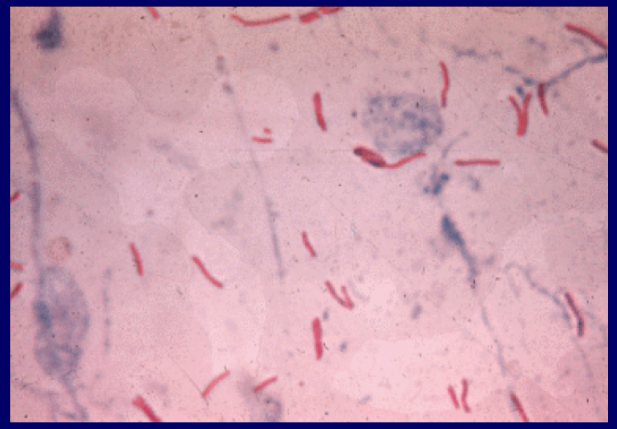
Tuberculous meningitis is the most devastating form of extra-pulmonary tuberculosis with 30% mortality and disabling neurological sequelae in > 25% survivors.

Causative organism

- CNS tuberculosis is caused by the human strain of Myobacterium tuberculosis.
- However in immunocompromised patients, atypical mycobacteria are an important cause of infection.
- They are now called non-tuberculous mycobacteria which include:

  Mycobacterium avium

  Mycobacterium intracellulare



Pathophysiology

- CNS tuberculosis is secondary to disease elsewhere in the body and reach the brain by hematogenous route.

- Initial small tuberculous lesions (Rich foci) develop in meninges, subpial or subependymal surface of the brain or the spinal cord, and may remain dormant for years.

- Reactivation may be due to endogenous factors: Innate immunological and non immunological defenses ,level of function of cell mediated immunity.
- Release of M tuberculosis results in a T lymphocyte dependent necrotising granulomatous inflammatory response.

- Thick gelatinous exudate around the sylvian fissures, basal cisterns, brainstem and cerebellum causing
  - Hydrocephalous
  - Adhesive arachnoiditis
  - Obliterative vasculitis

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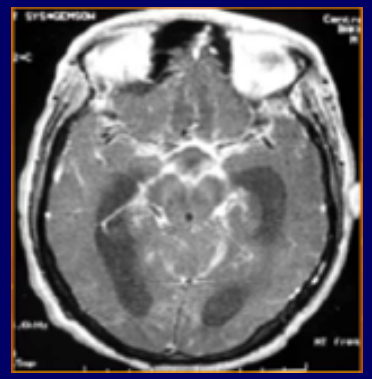
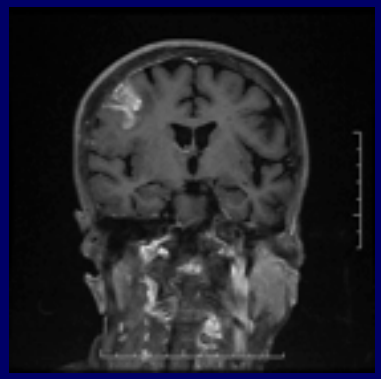
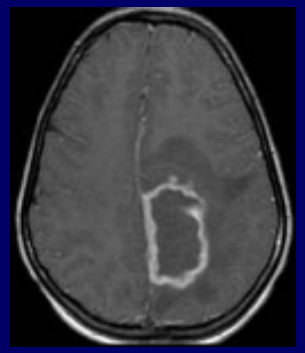
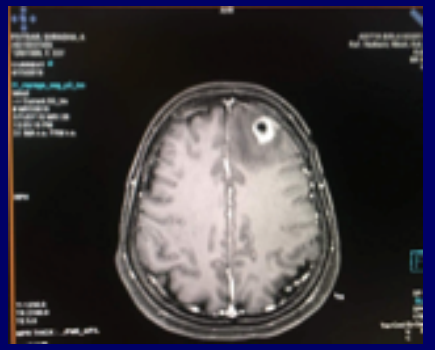
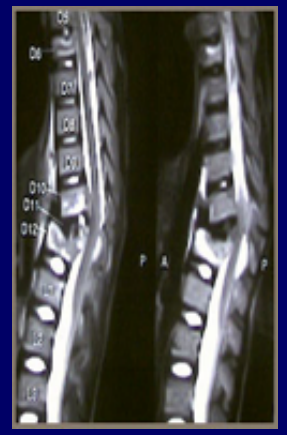
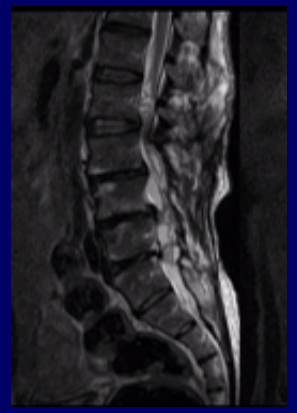
Classification and presentation

- Intracranial
  - Tuberculous meningitis
  - Tuberculoma
  - Tuberculous abscess
  - Tuberculous encephalopathy
  - Tuberculous vasculopathy

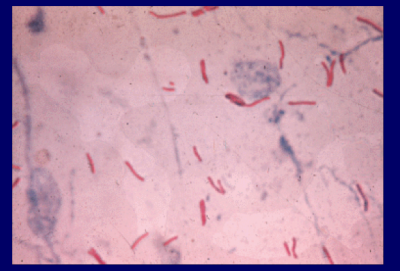
- Spinal
  - Pott's spine and Pott's paraplegia
  - Tuberculous arachnoiditis
  - Spinal tuberculoma
  - Spinal meningitis

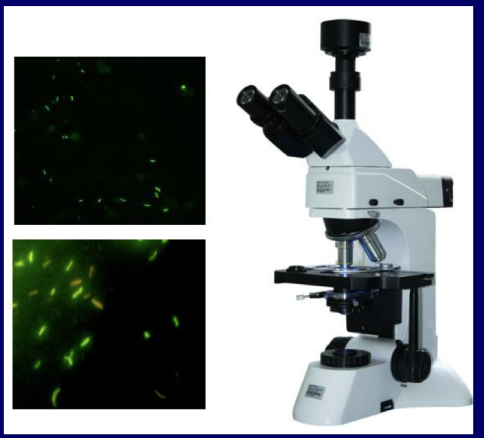



Cerebrospinal fluid examination

- Predominantly lymphocytic pleocytosis, increased proteins , low CSF/ blood glucose ratio.
- WBC count can be normal in presence of depressed CMI (elderly and HIV positive individuals).
- Smear is +ve in 10%, can be increased by examining large volume of CSF.
- Culture is +ve in 25-70%. Repeat CSF frequently shows a falling glucose level, a rising protein concentration and a shift to mononuclear predominance.CSF cell counts decrease by 50% during the first month but may not become normal for a year.
- CSF glucose becomes normal in 1 to 2 months and protein becomes normal by 12 months or longer.
- CSF cultures should be sterile by the first month, but PCR results may remain positive for a month
- Gene expert -centrifugation of larger CSF volumes (median: 6 mL, interquartile range: 4–10 mL) resulted in 72% (13/18) sensitivity, which was equivalent to culture (71%, 12/17) .

DIAGNOSTIC PLATFORM	TEST NAME	TURNAROUND TIME	DESCRIPTION AND COMMENTS
Smear microscopy	Conventional light microscopy – Ziehl-Neelsen	2 hours	Less sensitive than fluorescent/LED microscopy.
	Conventional fluorescence microscopy		Requires a quartz-halogen or high-pressure mercury vapour lamp. Sensitivity is improved over light microscopy, observation time is reduced. Expensive.
	Light emitting diode (LED) fluorescence microscopy		LED microscopes improve sensitivity by 10% over conventional light microscopy. Observation time is similar to conventional fluorescence microscopy. LED conversion kits for light microscopes are available.
Solid culture	Lowenstein–Jensen	3 weeks smear positive 4–8 weeks smear negative	Egg-based medium, inexpensive.
	Middlebrook and Cohn 7H10		Agar based medium. Less prone to contamination than Lowenstein–Jensen but more expensive.
Automated liquid culture		8 days smear positive 2–6 weeks smear negative	Liquid culture systems. Fully automated systems that use either fluorimetric or colourimetric detection.

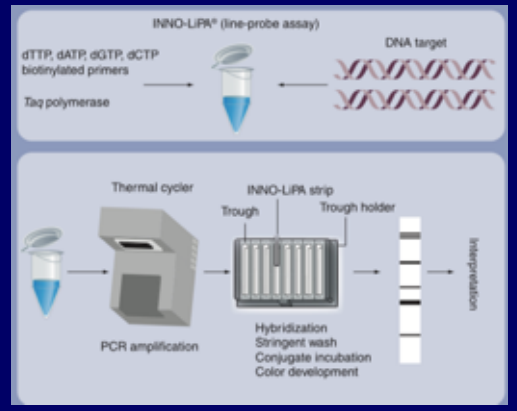




DIAGNOSTIC PLATFORM	TEST NAME	TURNAROUND TIME	DESCRIPTION AND COMMENTS
Non-commercial WHO endorsed culture and DST techniques	Media-based microscopic observation drug susceptibility (MODS)	2–21 days direct 3–4 weeks indirect	MODS is a manual liquid technique that uses basic laboratory equipment (including an inverted microscope). Colonies are observed through the bottom of a sealed plastic container. Allows for H and R DST. MODS requires additional staff skills and a containment laboratory.
	Nitrate reductase assay (NRA)	6–9 days direct 7–11 weeks indirect	NRA is a colourimetric test using solid media. Allows for H and R DST. TB cells are cultured for 10 days and Greiss reagent is added, which indicates the presence of growing cells.
	Colourimetric redox indicator (CRI)	3–5 weeks	CRI is an indirect colourimetric test using liquid media. TB cell are cultured in the presence of a dye. Allows for H and R DST.
Molecular testing	Line probe assay (LPA)	1–2 day (direct on smear positive specimen only)	Two LPA have been developed to detect *M. tuberculosis* resistant to R and H either directly or indirectly. DNA targets are amplified by PCR and hybridized to immobilized oligonucleotide targets. Results are visualized colourimetrically. If it is a smear negative specimen, culture must be grown first.
	Xpert MTB/RIF	2 hours	A fully automated test working in a dedicated platform performing detection of MTB and R resistance, using real-time PCR. Results are available in less than two hours.

Drug susceptibility testing

- **Phenotypic DST (conventional DST)**
- **Genotypic DST**



Summary table of accuracy

Drug	Genes	Accuracy	Comment
INH	katG, inhA , mabA (fabG1) ahpC-oxyR	Se: 84% / Sp: 98%	All mutations (including not confidence-graded)
RIF	rpoB	Se: 96% / Sp: 99%	
FQ	gyrA, gyrB	Se: 89% / Sp: 100%	
PZA	pncA	Se: 83% / Sp: 98%	
AMK	eis, rrs	Se: 79% / Sp: 100%	

World Health Organization

Patterns of drug resistance

- 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.
- Multidrug resistance (MDR): 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): It includes any resistance to rifampicin, in the form of mono-resistance, poly-resistance, MDR or XDR

WHO recommended drug groups

GROUP NAME	ANTI-TB AGENT
Group 1. First-line oral agents	Isoniazid Rifampicin Ethambutol Pyrazinamide Rifabutin[a] Rifapentine[a]
Group 2. Injectable anti-TB drugs (injectable agents or parental agents)	Streptomycin[b] Kanamycin Amikacin Capreomycin
Group 3. Fluoroquinolones (FQs)[d]	Levofloxacin Moxifloxacin Gatifloxacin[c]
Group 4. Oral bacteriostatic second-line anti-TB drugs	Ethionamide Prothionamide Cycloserine Terizidone[e] Para-aminosalicylic acid Para-aminosalicylate sodium

GROUP NAME	ANTI-TB AGENT
Group 5. Anti-TB drugs with limited data on efficacy and/or long term safety in the treatment of drug-resistant TB (This group includes new anti-TB agents)	Bedaquiline Delamanid Linezolid Clofazimine Amoxicillin/ clavulanate Imipenem/cilastatin[f] Meropenem[f] High-dose isoniazid Thioacetazone[g] Clarithromycin[g]

Treatment of drug sensitive CNS TB

- CNS tuberculosis is categorized under TB treatment category I by WHO.
- Initial phase therapy (2 mths) with isoniazid, rifampicin, pyrazinamide and streptomycin or ethambutol followed by continuation phase (7 mths) with isoniazid and rifampicin.
- The BTS and IDSA/ATS recommend 9-12 months of ATT. Therapy should be extended to 18 months in patients who do not tolerate pyrazinamide.

General principles of treatment of MDR TB

- The intensive phase (i.e. the initial part of treatment during which a Group 2 injectable agent is used) lasts at least eight months
- MDR regimens should include at least pyrazinamide, a fluoroquinolone, an injectable anti-TB drug, ethionamide (or prothionamide) and either cycloserine or PAS (para- aminosalycylic acid) if cycloserine cannot be use
- The total length of treatment is expected to be at least 20 months in most patients not previously treated for MDR-TB .
- Antiretroviral therapy (ART) is recommended for all patients with HIV and drug-resistant TB, irrespective of CD4 cell-count, as early as possible (within the first eight weeks) following initiation of the anti-TB treatment
- Adjuvent use of corticosteroids has been shown not to increase mortality when the patient is on an effective regimen.& can be beneficial in conditions like severe central nervous system or pericardial involvement

Key take home messages

- Early diagnosis requires a high index of suspicion.

- Knowledge of newer diagnostics and awareness of MDR /XDR TB

Helps in better management of the case

- CT or MRI showing basal meningeal enhancement with any degree of hydrocephalus is strongly suggestive of TBM.

- Clinical outcome depends greatly on the stage of disease and correct treatment initiated.

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