Review Article :

Diagnosis and Management of Tuberculosis in Children

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Abstract:

The global annual incidence of tuberculosis is 9.6 million to which India contributes 2.2million cases. Continued detection of childhood TB to the tune of half a million cases per year indicates ongoing transmission at a higher rate in India, coupled with problems of malnutrition, HIV, poverty, illiteracy, lack of awareness, poor detection rate, noncompliance, apathy, so on and so forth. TB in children is often extra-pulmonary unlike adults. The subtle symptoms and signs, variable presentations make it difficult to diagnose at grass root level in the community due to lack of experience among general practitioners, besides poor facilities for early detection and treatment. The whole gamut of childhood tuberculosis – clinical, diagnostic and therapeutic aspects has been updated in this review.

Key words:

Pediatric tuberculosis, Latent TB, Extra-pulmonary TB, Mantoux test, Gastric aspirate, AFB, GeneXpert, AKT, HIV

Introduction:

Confronted with an alarming situation, the WHO declared TB as global emergency (1993).1/3rd of world's population are infected with My.TB, with an annual burden of 5, 30,000 children which is 6% of the global burden. 74,000 children died from TB in 2012, excluding HIV. TB in children always points to the recent transmission, not controlled as yet. Diagnosis of one child TB indicates 10 times adult cases in community – a tip of the iceberg. Under-5 children are the most vulnerable group. Most conventional tests are of low specificity and low positive predictive value. Still we have inadequate commitments towards the problem, wanting in services, poor detection and management commitments and an over-reliance on BCG, a false sense of security. Epidemiological investigations are of prime importance to establish at risk children as clinical diagnosis often delayed, compounded with late attention to symptoms in children. Low sensitivity of microscopy, slower process of culture and sensitivity, non-specific shadows in chest X-Ray and imprecise tuberculin skin testing compound the problem [1].

Symptoms:

Fever, loss of appetite, weight loss, night sweats, cachexia are known features of wasting diseases like tuberculosis. Diagnostic criteria for Pediatric TB: Specimen (Sputum / Gastric / Nasopharyngeal aspirate) positive for AFB or culture; or 2 or more of the following: (a) Contact history, (b) Cough for more than 2 weeks, (c) Weight loss more than 5% within last 3 months, (d) Reactive Mantaux (Mx), (e) Radiographic finding compatible with TB and (f) response to AKT (Indicated by improvement in weight by >10% in 2 months and decrease in symptoms). The triad of positive Mx, suggestive CxR, and history of contact are most predictive [2]. Specific focus on paediatric TB diagnosis should include all attempts to isolate AFB from GA / sputum / BAL / NPA. The Tuberculin Skin Testing (Mantoux test) to be done using 2 TU and considered positive with induration 10 mm or more after 72 hours. There is no role for sero-diagnosis as well as non-validated in-house PCR.

Bacteriology:

In one study, Induced sputum [3] among under 12 children with 3% saline nebulisation, 8 were found AFB positive out of 29. To obtain gastric aspirate, a feeding tube is left in situ overnight; gastric contents aspirated in morning while child still asleep without disturbing him/her. Yield 75% AFB positivity. Other body fluids,aspirates: Yield less than 50%. BAL in 36 children: 43%. ZN stain: AFB +Ve confirmatory, Culture takes 6-8 weeks, BACTEC MGIT960, fluorescence sequencing 3-14 days whereas GeneXpert on same day with sensitivity report [4].

X'Ray:

Variety of pictures are seen. One study revealed mediastinal lymphadenopathy (27%),adenopathy with consolidation (23%); consolidation with collapse and segmental hyperinflation (17%); miliary TB (11%); cavitary lesions (10%) and pleural effusion (12%).Primary TB as initial infection commonly seen in children. Also more of collapse and consolidation is seen in children. Re-activation or secondary TB is usually seen in adults.

Fig. 1: Primary complex. Heavy hilar and para-tracheal shadows, prominent B-V markings extending towards periphery

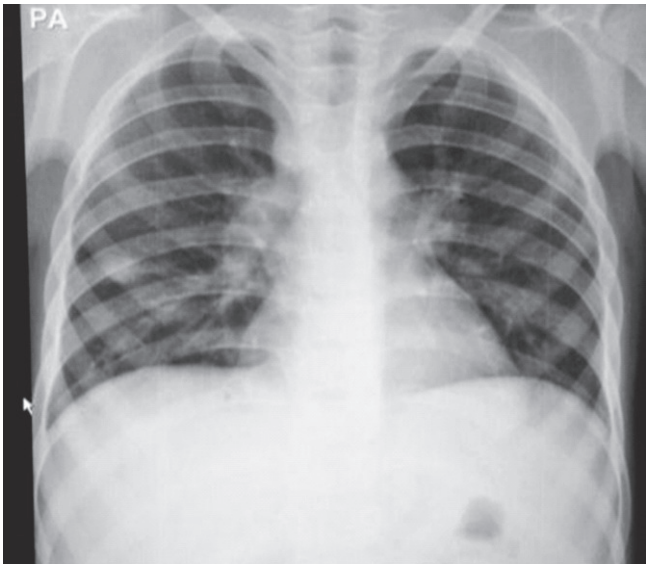
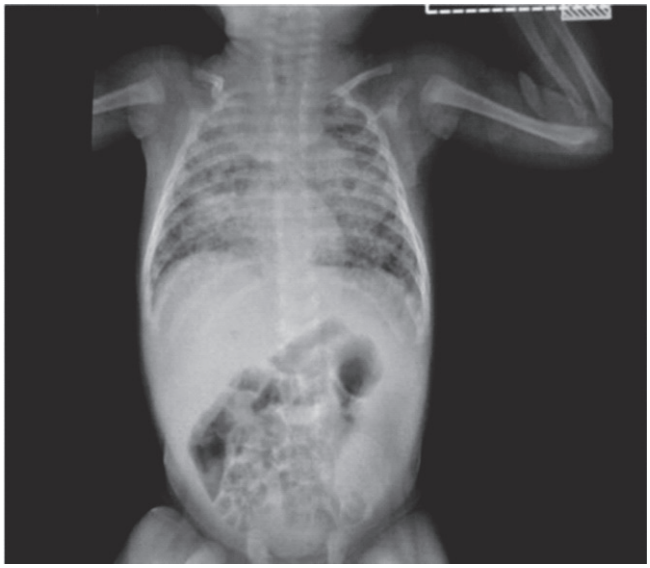


Fig. 2: Miliary & disseminated TB in one month old infant. Lung parenchyma show multiple modularity and interstitial infiltrations. Hepatosplenomegaly, Dilatation of bowel loops evident. Mother open case of pulmonary TB



Extra-pulmonary TB:

Tuberculosis can involve any system. In children, extrapulmonary TB constitutes to the tune of 60 to 80 percent. The scenario is fast changing with advent of HIV/AIDS. The presenting symptomatology would vary depending upon the system involved.

Abdominal TB:

Besides constitutional symptoms, presenting symptoms are variable, often non-specific. While weight loss, nausea, vomiting, diarrhoea predominate in paediatric series, cases of intestinal obstruction, acute pain abdomen mostly reported to surgical facilities [5].

Symptoms	Number	Percentage
Fever	8	18
Weight loss	38	83
Pain in abdomen	42	92
Nausea /Vomiting	10	22
Bowel disturbances	34	75
Constipation /Obstipation	16	35
Diarrhoea	4	9
Constipation alt diarrhoea	14	31
Fullness after food	12	26
Abdomonal distention	12	26
Barborygmi	10	22

Fig. 3: Ulcero-hypertrophic circumferencial lesions on colonoscopy

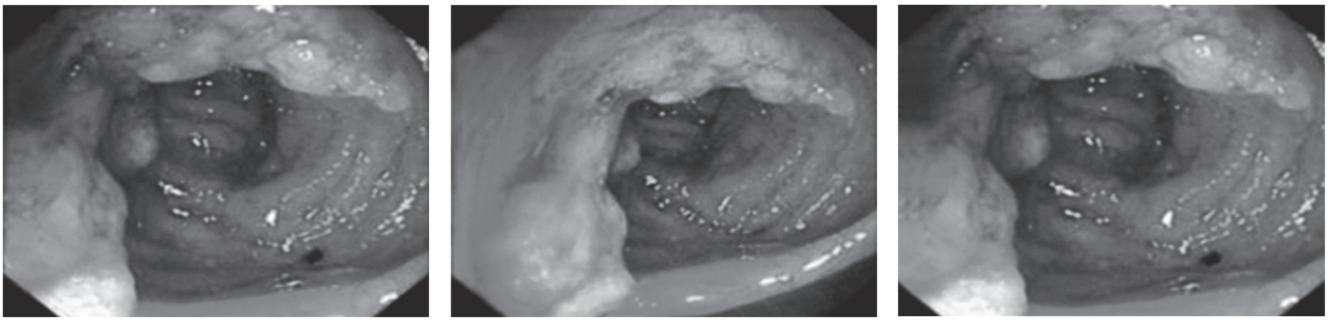
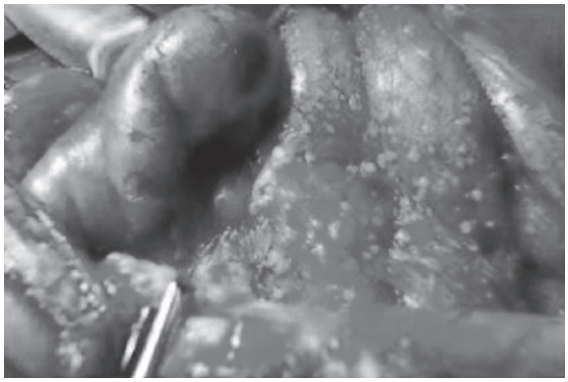


Fig. 4: Multiple tubercles studded on the surface of visceral peritoneum covering bowel loops.



Tuberculous Meningitis:

Symptoms:

Headache, Anorexia, Nausea, Vomiting, Restlessness, irritability, altered sensorium, Fever, myalgia, tachypnoea, tachycardia, Photo-phobia, neck-rigidity, Stupor, coma,seizures, back-pain.

Seizures: (Focal or generalized)

Due to cerebritis, tuberculoma, meningitis, hydrocephalus, infarction, vasculitis, electrolyte imbalance. Seizure which are difficult to control, often associated with bad prognosis.

Signs:

A. Signs of Meningeal irritation: Nuchal rigidity, Kerning's sign (Flexion of hip at 900 with subsequent pain on extension of leg), Brudzinski sign (Involuntary flexion of knees, Hip follows flexion of Neck while supine). These signs may not be evident in infants.

B. Signs of increased ICT and hydrocephalus: Irritability, headache, vomiting, bulging A.F., widening of cranial sutures, sunset sign, hypertension and bradycardia, apnoea or hyperventilation, stupor, coma, papilledma suggest chronic process, SOL e.g. - brain abscess / sub-dural effusion. Optic atrophy may be encountered.

C. Cranial Nerve Involvement (III, IV, VI, VII): Due to focal inflammation, vasculitis and raised ICT (False localizing signs).

D. Focal neurological deficit

E. Miscellaneous manifestations: Altered Mental Status and decreased sensorium due to raised ICT, hypoxia, lethargy, irritability, stupor, and coma are bad prognosis factors.

Photophobia, cranial nerve involvement, bulging fontanels, separation of sutures and UMN signs are common.

CSF:

- Pressure increased
- Cloudy, cob-web formation
- Cells increased, usually > 10 - 500 / HPF (Lymphocytes)
- Proteins > 40 mg % (Significantly high, can be 100mg% to 5,000 mg%)
- Sugar < 40 mg % (Range 36% - 56%)
- Gram Stain, C /S, AFB, GeneXpert

CT / MRI:

May reveal ring enhanced lesions suggestive of tuberculoma, ventricular dilatations, basal exudates, vasculitis, cerebritis and infarction.

Latent tuberculosis [7]:

After inhalation, most children remain asymptomatic, do not develop active disease, but LTBI; Mx+ve. In-vitro tests measure IFN-y response to T-cell stimulation by My TB Antigens: Protein 10, Antigen target-6.

Untreated infants with LTBI have 40% chance of developing active tuberculosis.

At risk for active TB who deserve treatment are required to be identified on merit for treatment. The risk factors of LTB for progression to active TB are:

1. Age < 5 years, infected recently (< 2 most vulnerable). Have higher risk for progression.
2. Risk of progression decrease through childhood until adulthood when increases again.
3. Infants and children likely to have life threatening TBM, disseminated disease
4. Children have more years at risk to develop disease than adults.
5. Adolescents and young adults, immune compromised, HIV, Malnutrition, associated CRF, diabetes, Silicosis and Mx conversion within last 1-2 years.

Tuberculin test:

My. TB PPD, 1, 2, 5 TU; intradermal,

marked. Read after 72 hrs for induration (mm) measured horizontally.

Interpretation:

- 5 mm +ve in recent contact / HIV / abn CxR
- 10 mm in infants / drug addicts / health workers
- 15 mm in all other, even without any risk factor.

Same interpretation if has had BCG.

BCG test is no longer used for diagnosis of TB. In-vitro assessment of gamma-interferon production or testing for CMI may replace Mx test in future.

IGRA:

Preferred in BCG recipients and children aged more than 5 years:

1. T-SPOT.TB measures number of lymphocyte / monocytes producing IFN-y
2. QuantiFERON-TB measures whole blood IFN-y. Do not contain Agn of My. Bovis & My. Avium from Environment. Hence Higher specificity as compared to Mx TST.
3. Only one patient encounter Vs. twice with Mx (Mx preferred in < 5 year olds)

Indications for undertaking advanced tests:

1. for diagnosis of PTB: Xpert MTB/RIF should be used as an initial test for suspected cases and MDR TB with HIV (Depending on resources).
2. for diagnosis of extra-PTB: Xpert MTB/RIF is preferred to conventional microscopy and CSF culture in suspected TBM.
3. Xpert/RIF are considered as an alternative test for non-respiratory specimens.
4. Lymph-node biopsy, FNAC and BAL for AFB resorted to for tissue diagnosis.

Rational approach in cases of children:

1. Liquid BACTEC-MGIT960 C/S and molecular based My.TB NAAT for early diagnosis
2. Combined AFB + Culture, clinical exam; algorithm based approach reliable.
3. High index of suspicion in the appropriate clinical setting is the key

Certain important definitions [8] on treatment out-come must be understood:

1. Cured: Bact +ve at initiation, proved to be smear/ culture - ve in last month of treatment
2. Treatment completed: Completed treatment but My.TB positivity report in last month N/A
3. Treatment failure: Positive for My. TB for 5 months on therapy.
4. Lost to follow-up: Did not receive ATT or has interruption for 2 months or more.
5. Drug resistant (Mono): To at least 1st line drug
6. Poly-resistance: To > 2 drugs other than INH, RIF
7. MDR TB: Resistant to INH and RIF
8. XDR TB: Resistant to any one of fluoroquinolone, one 2nd line injectable and INH, RIF
9. Primary drug resistance: Resistance in patient who never took ATT in past
10. Acquired resistance: in view of previous treatment, may be infection with resistant TB

Drug therapy [1, 9] according to Revised Categories (2013):

I. New case (Smear +ve / -ve PTB / extra-pulmonary): = 6 months therapy

Intensive phase: 2 H3R3Z3E3 = 2 months

Maintenance phase: 4 H3R3 = 4 months

II. Re-treatment (Relapse, fail to respond or lost to follow-up) for 8 months

Intensive phase: 2 H3R3Z3E3S3 + 1 H3R3Z3E = 3 months

Maintenance phase: 5 H3R3E3 = 5 months

Daily dosing is preferred in paediatric practice which is also being tried in 5 different states under RNTCP. Intermittent therapy in maintenance phase for HIV uninfected under DOTS (Supervised) is reasonable. However, daily dosing advocated for initial 2 weeks (5).

Supplimentation of 5 to 10 mg Pyridoxine has been recommended by WHO [10], although there is no such recommendation under RNTCP within DOTS.

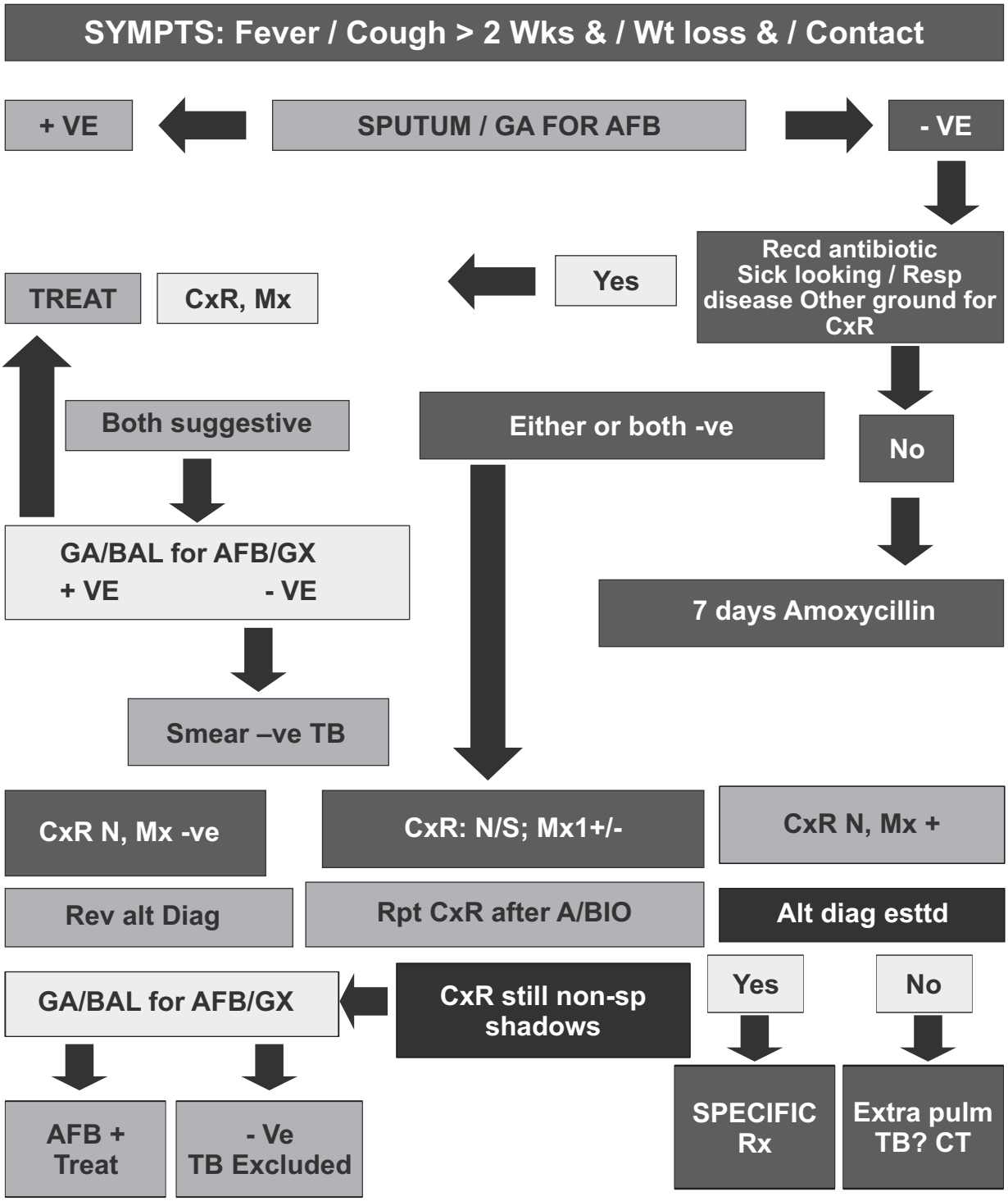
Table 2: First line Anti-TB drugs and their doses for children

Drugs	**Dose** (National Guideline)	**Dose** (WHO Guideline)
INH	10 mg/kg	10(10-15)mg/kg
RIFAMPICIN	10-12 mg/kg	15(10-20)mg/kg
ETHAMBUTOL	20-25mg/kg	25(15-25)mg/kg
PYRAZINAMIDE	30-35 mg/kg	35(30-40)mg/kg
STREPTOMYCIN	15 mg/kg	15-25 mg/kg

Difficulties in treating Paediatric TB cases under DOTS:

1. DOTS regimen is not preferred for seriously sick children, TBM, HIV, intestinal TB, hepatitis where supervised daily dosing in hospital is desirable. WHO recommends daily regimen in areas of high HIV prevalence (If more than 5% among adults; and more than 1% among pregnant ladies).
2. If there are persistent symptoms and signs, extend the intensive phase by 1 month and maintenance by 3 months. Also in disseminated TB, CNS, LN, bone TB.
3. Conventionally, the Clinicians' Choice have been: For TBM & LN: 1 Year and for Bone TB: 1 ½ years.
4. Studies on short-term chemotherapy were originally conducted for pulmonary tuberculosis among adults. Subsequently the results were extrapolated to extra-pulmonary forms and children.
5. Very few studies are available on children with long-term follow-up, especially on extrapulmonary TB.
6. There are certain other genuine difficulties peculiar to children in DOTS. TB in children is generally pauci-bacillary in nature with a higher proportion as extra-pulmonary TB.
7. Training of doctors and staff in specimen collection from children remains much needed.
8. Pediatric formulations, particularly liquid preparations and appropriate dosage forms (Being resolved) are not available under DOTS.
9. Regarding duration of therapy, particularly extra-pulmonary types, STC is not preferred.
10. Notification, treatment with due attention, sincerity and seriousness by family as well as by practitioners with standard regimen are important.

FIG. 7. ALGORHYTHM FOR DIAGNOSIS AND MANAGEMENT OF TUBERCULOSIS IN CHILDREN



Chemoprophylaxis:

Serves 2 goals: reduce reservoir, protect young from active disease.

INH prophylaxis - 9 months reduce risk by 90% (6 months by 26-90%; 3, 6,12 months by 31,63, 93%) (Cochrane DB syst rev.2000(2) Z:CD001363). RNTCP recommends INH 10mg / Kg OD for 6 months (For 9 months in US). Recently, a 12 dose combination therapy of Rifapentine + INH over 3 months duration has been tried [11].

Indications:

Symptomatic children below 6 months, babies with sputum +ve contacts (Irrespective of Mx); First rule out active TB.

All HIV +ve who were exposed to sputum +ve TB case; or having Mx > 5mm

Mx +ve children on immunosuppression and Neonate born to sputum AFB +ve mother.

Managing Drug induced hepatitis [12]:

Indicated by appetite loss, nausea, vomiting, icterus. May result in acute liver failure (ALF)

in 2-39% cases. Rule out other causes of ALF. Out of 5, three drugs (INH, RIF, RBN,

PZM) induce liver enzymes. ALT > 1.5 times rise is usual; Upto 3 times of upper limit of normal range doesn't warrant discontinuing AKT. Withheld only if ALT rise > 5 times of ULN. In severe disease (TBM, miliary): SM, OFL, EMB. LFT every 3rd day. If ALT < 3 timesof ULN, restart AKT. Start Rifampicin at lowdose, increase after 3 days. Add INH, dose subsequently hiked. S2E2H2 + E10H10 if RIF induced hepatotoxicity. E9R9Z9 in case INH induced hepatotoxicity. H9R9 if PZM not used in initial induction phase.

Newer Anti-TB drugs:

Most are in Ph-III / IV clinical trials. Expected to be more potent, reduce duration, inhibit new targets to be suitable for MDR TB; must be compatible with existing AKT and ART drugs, having no antagonism. Exploring newer uses of existing anti-micobials: Fluoroquinolones, Rifamycins, Riminophenazines, Clofazimines, meropenem / imipenem plus Clavunate combinations, Oxazolidinones (PA 824), SQ 109, Sutezolid (PNU 100480).

Approved for use: (Both included in WHO essential drug list, 2015)

1. Bedaquiniline (Diarylquinoline derivative). Being provided by RNTCP to XDR TB on close monitoring and on limited trial basis. 2. Dalamanid (OPC 67683)

Vaccines:

At present, BCG is the only vaccine available for prevention of TB. However, the existing data indicates that it prevents only 5% of the vaccinated individuals from TB associated fatalities. Though BCG is the most widely administered of all vaccines, TB still continues to scourge human life. It was found to be protective against the meningeal TB in young children. Nevertheless, its efficacy in preventing adult pulmonary TB which is responsible for the major burden of morbidity and mortality varies dramatically. In carefully conducted studies throughout the world, BCG efficacy varies from 0% in Chinglepet, India to 80% in the UK. Of late, several vaccines are under trial. They are for pre-exposure and postexposure varieties. Recombinant BCG (rBCG), live attenuated, hybrid sub-unit, protein adjuvented, vector delivery dependent and booster vaccines are under active clinical trial.

Conclusion:

After Small-pox and polio, the world aims at eradicating tuberculosis by 2035. It is a herculean task no doubt, although not impossible. It's success depends on intensive and sustained case detection, besides cent percent drug compliance at all levels to stamp outthe reservoir of infection. Chest physicians usually manage TB patients. Their availability is scarce. Physicians and general practitioners usually avoid handling TB cases for obvious reasons, taking excuses like lack of

training and logistics. The childhood TB, mostly extrapulmonary and LTB, are handled by pediatricians. Their number and presence are very limited in rural India, looking at 42% of our population being children. Hence intensive campaign is required not only to train all our medical students, interns and general practitioners, but also initiate a mass movement at the grass root level, the way we could involve our school and college teachers, students, village panchayats, Government officials, Armed Forces in case of Polio for ensuring success. Training modules need to be developed on priority for expeditious implementation on voluntary and PPP mode inaddition to concerted efforts at Government establishments and all medical colleges. Otherwise the 'Stop TB by 2035' is likely to remain as a distant dream.

Sources of support: None

Declaration on competing interests: None

Funding: None

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