Management of Tuberculosis in Children

Basic Training Module

Based on Indian Academy of Pediatrics-RNTCP Consensus Guidelines 2015

Outline

- Module 1 Defining the Magnitude of the Problem
- Module 2 Natural History of Disease
- Module 3 Pulm TB Diagnostics Part 1 (Symptoms, Radiology, TST)
- Module 4 TB Diagnostics Part 2 (Microbiology, etc)
- Module 5 Pulm TB diagnostic algorithm case based
- Module 6 Lymphnode TB diagnostics
- Module 7 Pleural TB diagnostics
- Module 8 Abdominal TB diagnostics
- Module 9 Neuro TB diagnostics
- Module 10 Bone and Joint TB
- Module 11 Treatment of TB
- Module 12 Monitoring of treatment – Defining response and non response
- Module 13 Management of adverse effects
- Module 14 Drug Resistant (DR) TB
- Module 15 Special conditions HIV TB
- Module 16 Special conditions Neonate of a mother with TB
- Module 17 Prevention of TB

Module 1:

Understanding the Magnitude of the Problem

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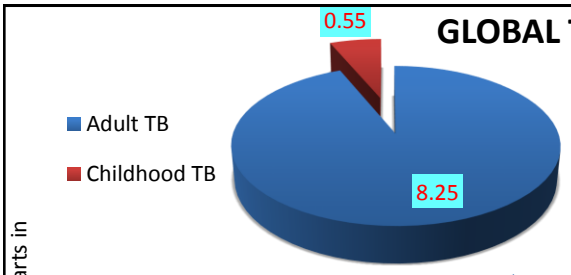
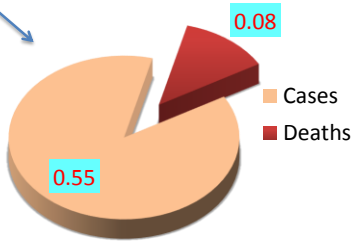
GLOBAL TB BURDEN

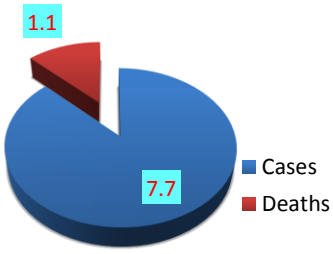


- **Most commonly child TB is pulmonary TB**
- **But the proportion of EPTB is higher as compared to adults**

Childhood TB



All number in charts in millions



Upto 200 children die of TB every day!

Global TB Burden

** WHO Global TB Report 2014*

Roadmap for childhood tuberculosis - WHO 2013

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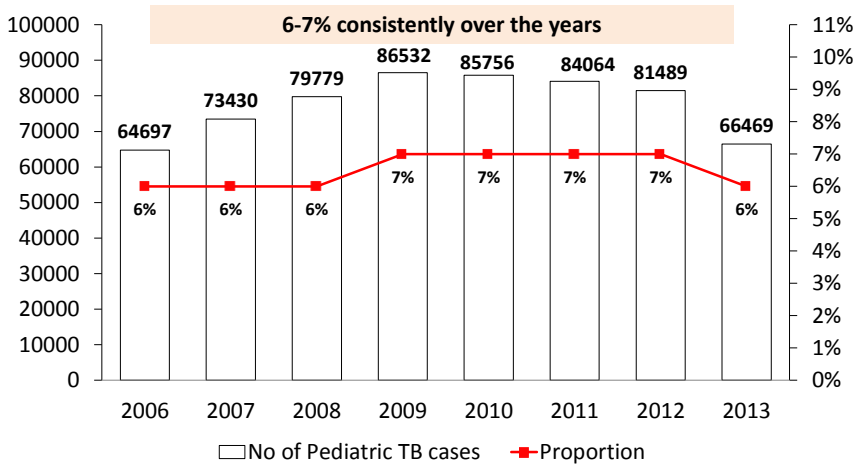
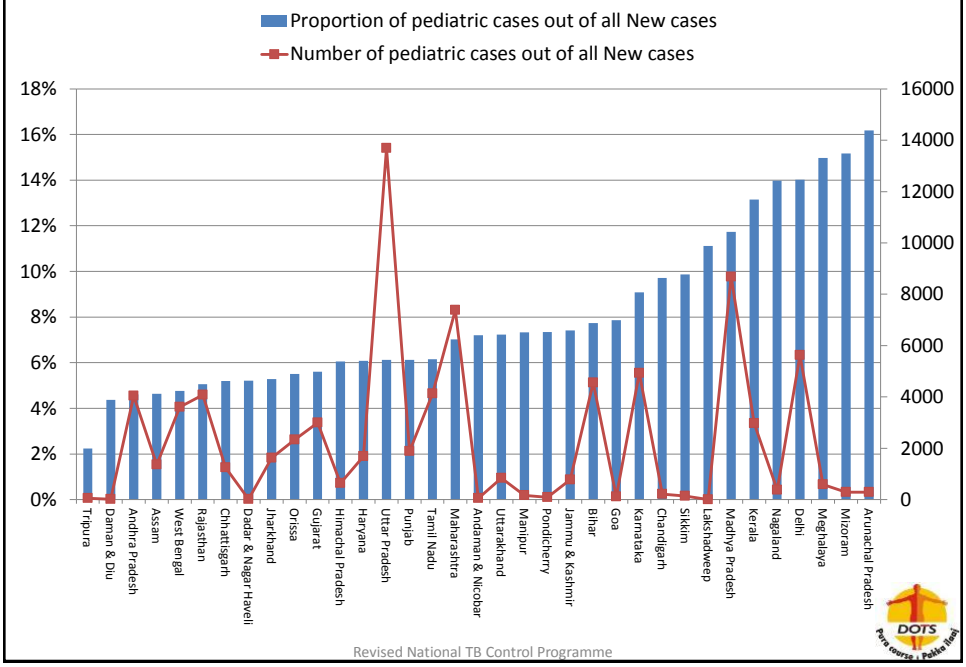
Trend of Pediatric TB cases out of all New TB cases under RNTCP



Revised National TB Control Programme

Proportion of Pediatric TB cases among all New TB cases, 2013



Revised National TB Control Programme

In summary

- In 2013, there were an estimated 550 000 cases among children
- An estimated 80 000 HIV-negative children died from TB
  - No estimates available for childhood TB deaths in HIV coinfected
  - TB mortality is unacceptably high given that most deaths are preventable
- Children currently contribute an estimated 6-10% of the TB cases in high burden countries
- Now realisation has set in that the roadmap to Zero deaths due to TB will have to pass through childhood TB
- Need to integrate more effectively with Child survival strategies

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Module 2 :

Natural History of Childhood TB

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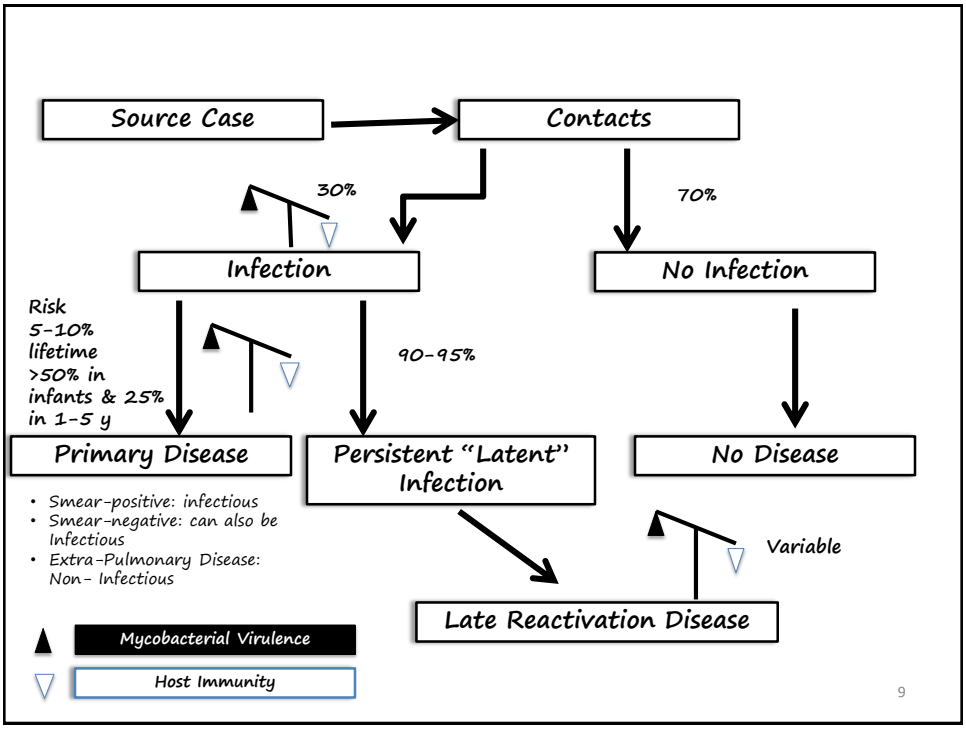

Risk factors for TB infection and disease in children

For TB infection

- Increased exposure
  - Living in high TB endemic communities
  - Children of families living with HIV
  - Overcrowding
  - Air pollution incl ETS
- Source case
  - Cavitary disease /Smear positivity
  - Cough frequency / Cough hygiene
  - Delay in treatment of adult case
- Lack of contact screening
- Contact with source case
  - Closeness of contact
  - Duration of contact

For TB disease

- Young age
  - Especially 0-2 years
- HIV infection
  - Risk of infection and disease
- Other immunosuppression
  - Malnutrition
  - Post-measles
- Not BCG vaccinated
  - Risk of disseminated disease
- Lack of prophylaxis

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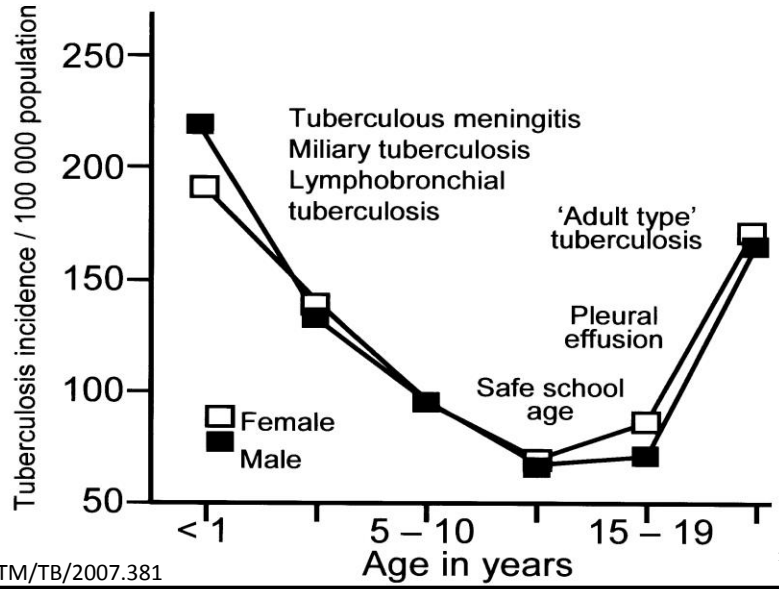

WHO/HTM/TB/2007.381

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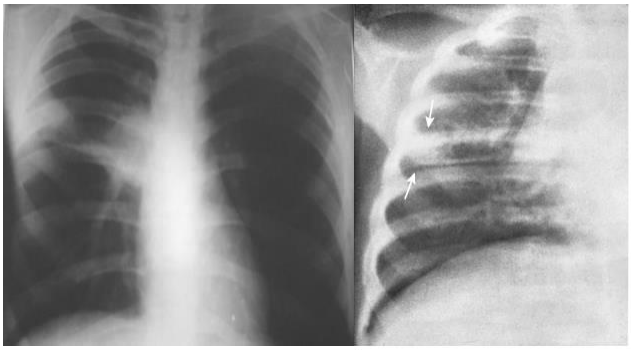
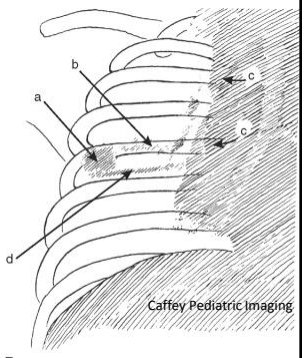
Radiological picture of a typical Ghon's Complex



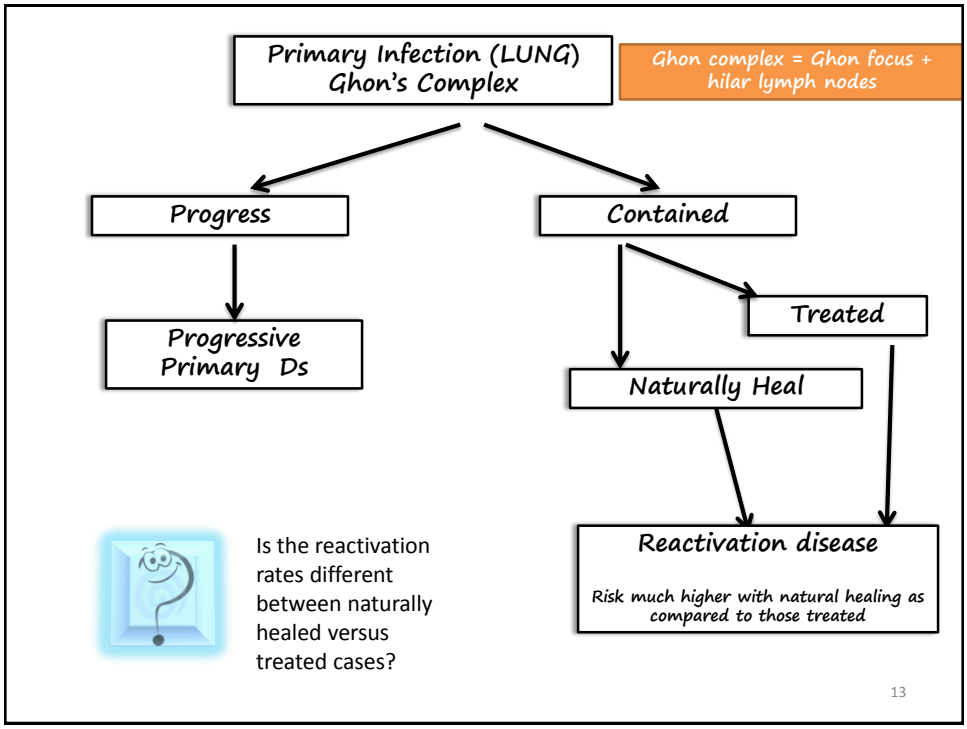


Three features common to primary infection are

(1) Patient may have non-specific mild symptoms which can go un-recognised,

(2) Primary lung foci are usually quite small relative to large hilar nodes, and

(3) Primary foci may resemble pneumonia & be located within any lobe


Primary Infection (LUNG)
Ghon's Complex
Ghon complex = Ghon focus + hilar lymph nodes
Progress
Contained
Progressive Primary Ds
Treated
Naturally Heal
Reactivation disease
Risk much higher with natural healing as compared to those treated
Is the reactivation rates different between naturally healed versus treated cases?
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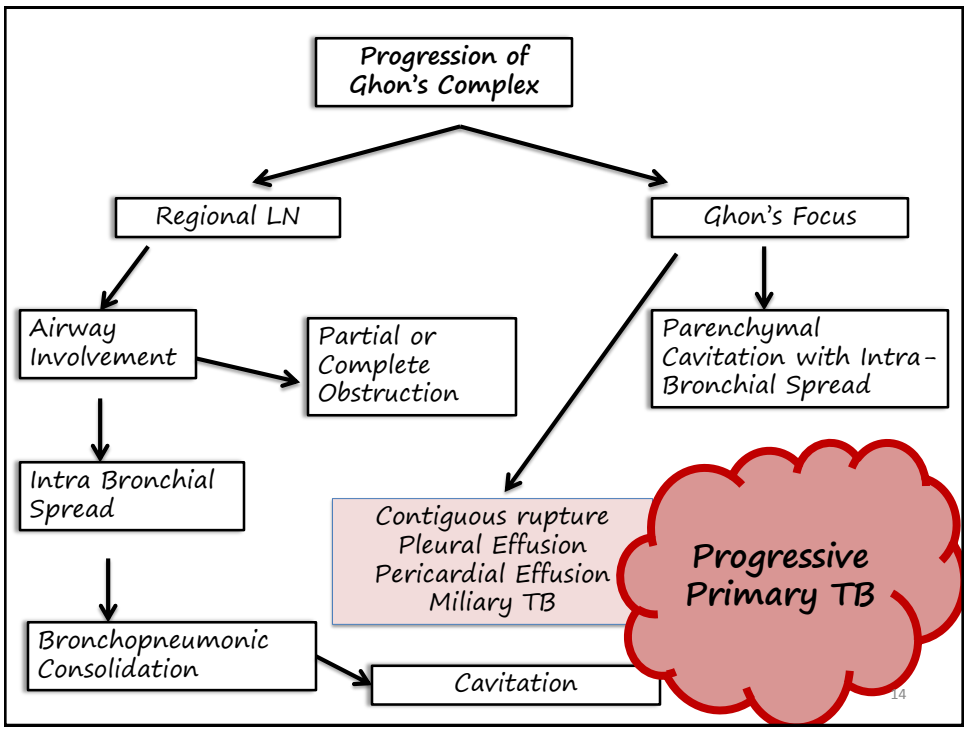
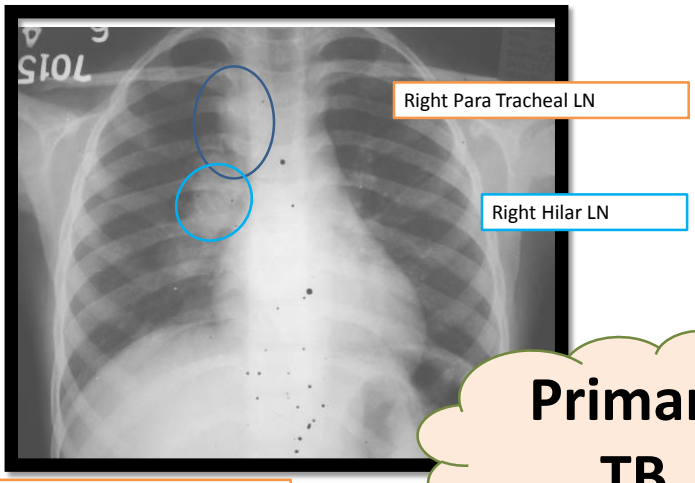

Progression of Ghon's Complex
Regional LN
Ghon's Focus
Airway Involvement
Partial or Complete Obstruction
Parenchymal Cavitation with Intra-Bronchial Spread
Intra Bronchial Spread
Contiguous rupture
Pleural Effusion
Pericardial Effusion
Miliary TB
Progressive Primary TB
Bronchopneumonic Consolidation
Cavitation
14



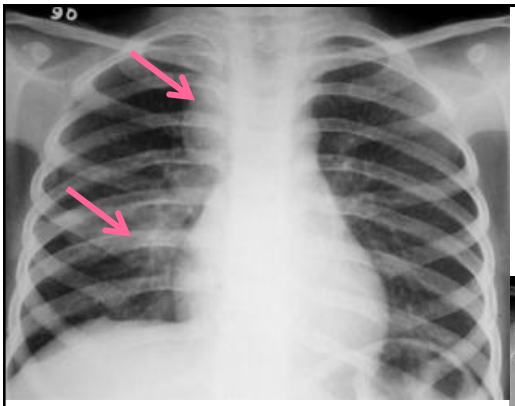
Right Para Tracheal LN

Right Hilar LN

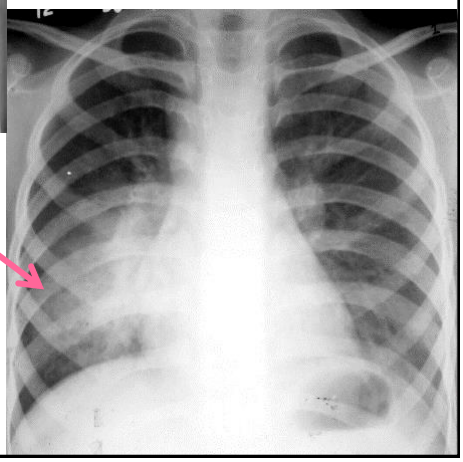
Primary TB

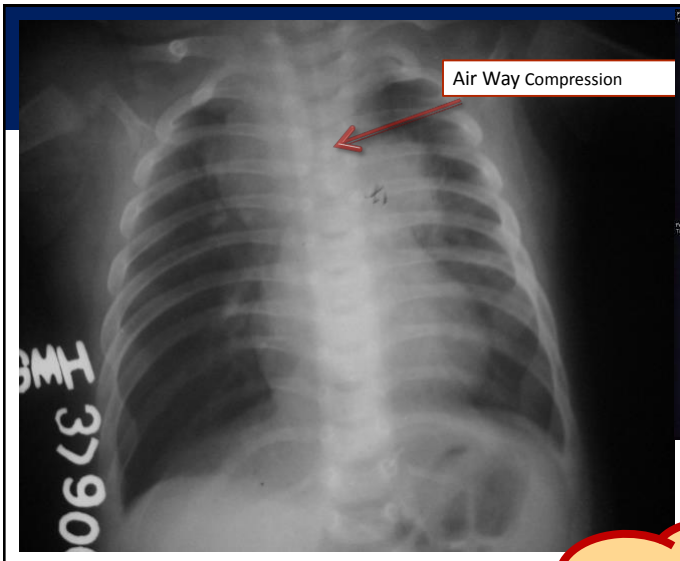
Lymph Node Disease
NO Airway Compression
No Obstruction/Collapse

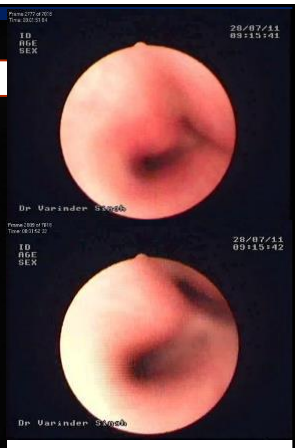
Please comment upon the Chest X-ray



Pulmonary Primary complex



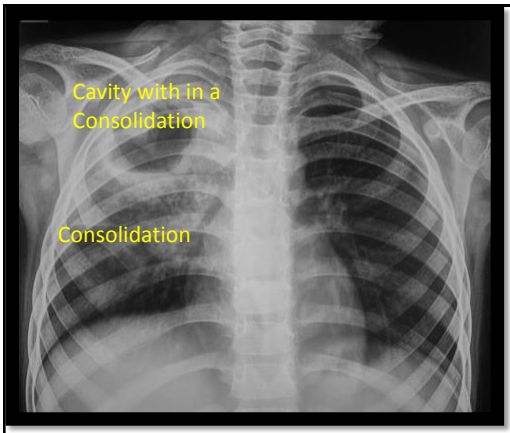




Lymph Node Disease with Airway Compression
No Obstruction/Collapse

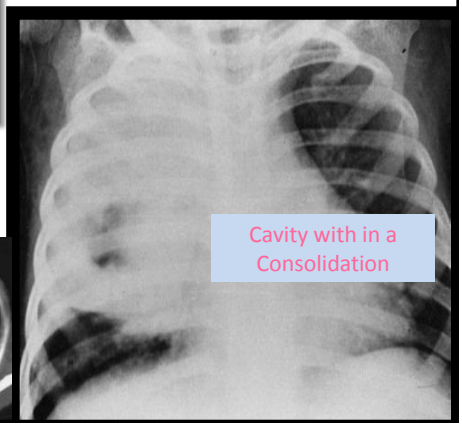
Progressive Primary TB

he Chest X-ray

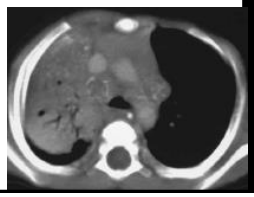


Progressive Primary Disease

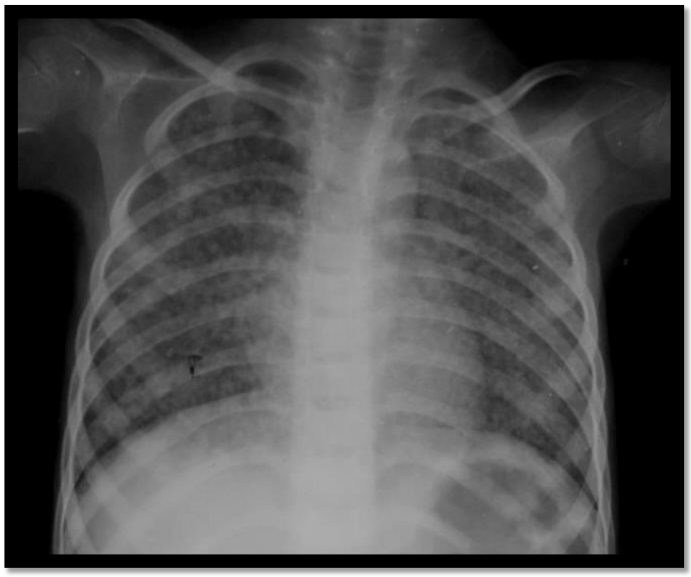
Parenchymal cavitation with Consolidation



Please comment upon the Chest X-ray



Miliary TB



Reactivation or Post Primary tuberculosis

Disease of adolescence and adulthood

50- 90% of cases result from reactivation of a previously dormant primary infection

Predilection for apical or posterior segment of upper lobes or superior segment of lower lobes

Focal or patchy heterogeneous consolidation, consolidation with cavitation, pleural extension

Tuberculomas are also seen but rare.

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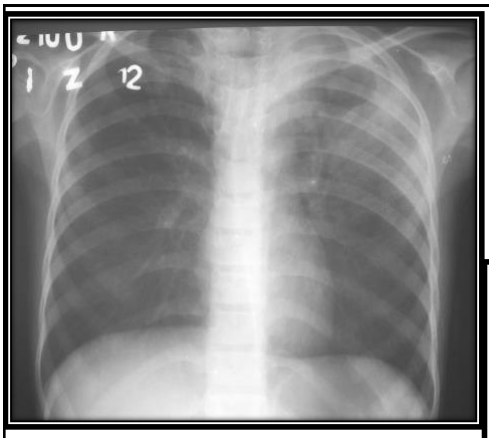

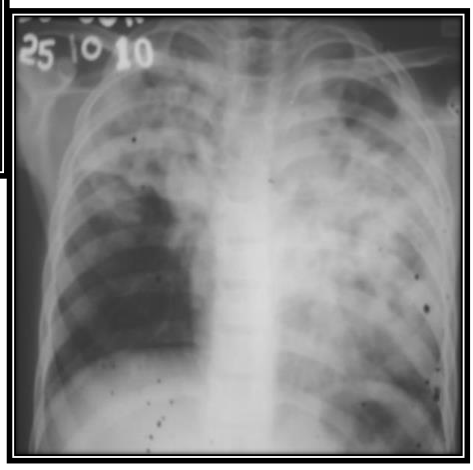

Cavitory pneumonia
Lt UL

Module 3 :

TB DIAGNOSTICS - PART I

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Who is a TB Suspect?
Symptom Characterization

Common Symptoms

- Fever for 2 weeks or more
- Unremitting cough for 2 weeks or more
- Loss of weight >5% of the weight in past 3 weeks
- Peripheral Painless swellings
- Meningitis of insidious onset
- Spine gibbus
- Any non specific symptoms in a contact of an infectious TB case

When do you suspect TB in a child?

Case

- Victor, 3 year old child
- h/o cough for 2 months
  - Dry
  - More for past 3 days
- Low grade fever for same duration
- Not growing wel
- Fussy eater
- Father has chronic cough
  - Has recd several sets of antibiotics with no relief
- o/e
  - Wt 10.7 kg
  - Mild pallor
  - No lymphadenopathy
  - Chest:
    - Bilateral crackles and wheezes
  - Rest NAD

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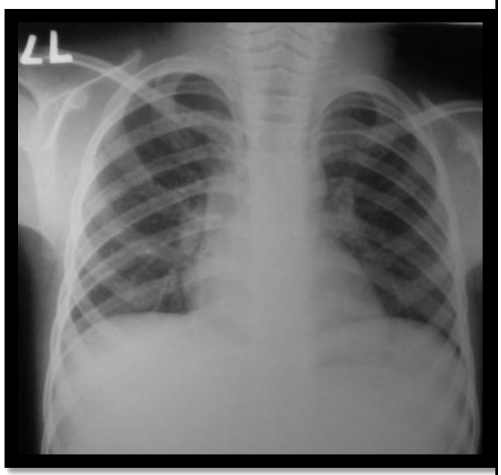
Investigations

- Tuberculin Skin test (PPD test)

  14mm in transverse axis

- ESR 32mm

- TB Elisa positive IgG and IgM



Diagnosis Pulmonary Koch's
Started on ATT (for new case) along with bronchodilators
Has come for a review

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Case Review

- Victor has chronic cough and is not thriving well- TB like symptoms
- TST positive
- ESR raised
- Father has chronic cough
- CXR suggestive
- TB Elisa positive both IgG and IgM

- Basis for ATT justified

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Case review

- Victor, 4 year old child
- h/o cough for 2 months
  - Dry
  - More for past 3 days
- Low grade fever
- Not growing well
- Fussy eater
- Father has chronic cough
- Has recd several sets of antibiotics with no relief

- o/e
- Wt 10.7 kg
- Mild pallor
- No lymphadenopathy
- Chest:
  - Bilateral crackles and wheezes
- Rest NAD

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TB like symptoms are common and non specific

Chronic cough – reported in up to 20% of children from poor area

Not growing well

- Relatively a soft sign
- common with poor feeding habits or
- heavy worm infestation or
- food insecurity
- It could just be a perception and not real (objective measure)
- Always keep in mind the fallacies related to objective weight measurement
  - Machine errors or errors in method
  - If weighed with clothes- a lot of error can happen, particularly if layers of winter clothes are removed

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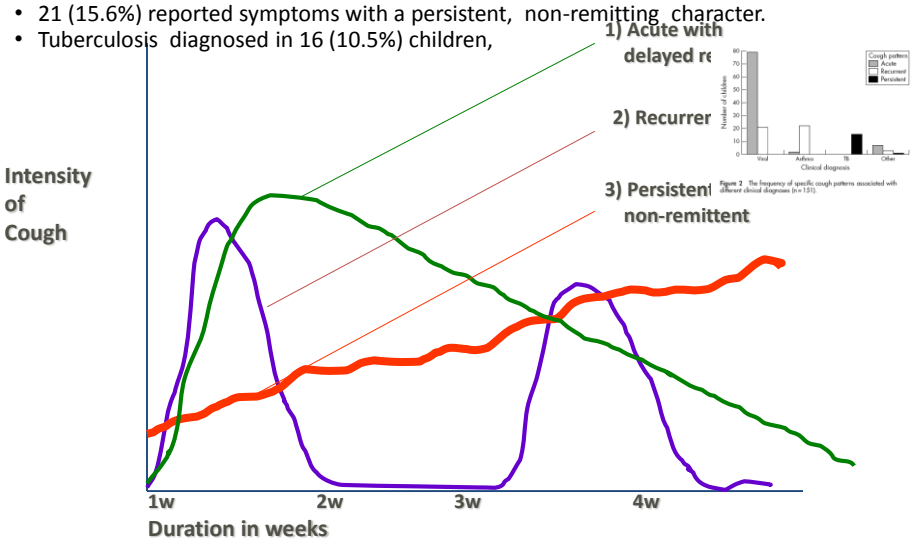
TB like symptoms are common, but can be useful if well characterized

Defining cough - duration and pattern

- Prospective study - Cape Town, N= 151, 0-13 yrs; cough of 2 weeks or more;
- 21 (15.6%) reported symptoms with a persistent, non-remitting character.
- Tuberculosis diagnosed in 16 (10.5%) children,



Arch Dis Child 2005;90:1162–1165

Symptom Characterization for TB suspect

Persistent unexplained fever

- Definition: persistent (>2 week) and unexplained fever (>38C) reported by a guardian or objectively recorded at least once.

Persistent cough

- Definition: persistent (>2 weeks), non-remitting cough

Definitive Weight Loss/ failure to thrive

- A definite weight loss (more than 5 % in past 3 months) with no other apparent cause should prompt detailed history, examination and investigation including investigation for TB

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Detailed review

- Victor, 3 year old chil
- h/o cough for 2 mon
  - Dry
  - More for past 3 days
- Low grade fever
- Not growing well

- Fussy eater
- Father has chronic cough
- Has recd several sets of antibiotics with no relief

- Cough on and off for 2-3 months
- Gets somewhat better with treatment but then recurs
- Fever never documented
- Predominantly milk based diet, also takes more biscuits etc then regular diet

No lymphadenopathy

- Chest:
  - Bilateral crackles and
- F

- Father has seasonal cough and is a smoker
- Never treated for TB

History of Contact/ Exposure

In a symptomatic child, contact with a person with any form of active tuberculosis within last two years may be significant

- Unrecognized coexisting pulmonary involvement

Exposure to an infectious TB patient (any case with laryngeal, airway or lung involvement) in past 2 years

- prompt detailed examination for likelihood of the disease, as early as possible

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Detailed review

- Victor, 3 year old chi
- h/o cough for 2 mon
  - Dry
  - More for past 3 days
- Low grade fever
- Not growing well
- Fussy eater
- Father has chronic cough
- Has recd several sets of antibiotics with no relief

- Cough on and off for 2-3 months
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No lymphadenopathy

- Chest:

nd

- Father has seasonal cough and is a smoker
- Never treated for TB

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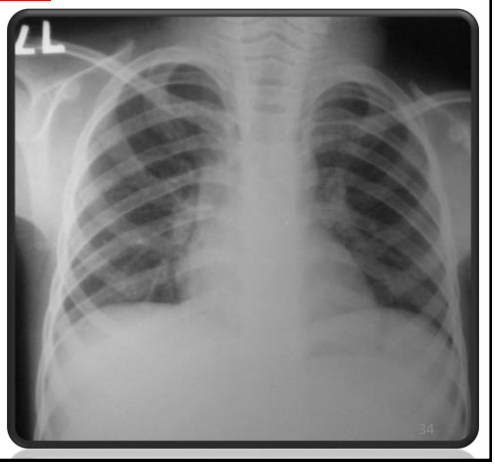
Case review

Victor's Basis of ATT

- ~~Victor has chronic cough and is not thriving well - TB like symptoms~~
- TST positive
- Father has chronic cough but unlike TB
- CXR suggestive - primary complex
- Basis for ATT justified

Please comment upon the Chest X-ray



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Chest radiology - Why is it so important?

CXR is an important tool for diagnosis of pulmonary TB in children

Primary childhood TB being paucibacillary makes microbiological diagnosis (gold standard) difficult

The reading of skiagrams is a special skill and must take into account

- Both inter and intra-individual variations.
- Problems with quality of films and technical issues
- Variations of normal, artifacts, thymus etc.

Clinicians must learn this skill and sharpen it to improve TB diagnostic

Several factors can lead to errors in TB diagnosis on chest radiology leading to under as well as over diagnosis

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Radiological manifestations of TB

Highly Suggestive

- Patterns like
  - Hilar Lymph nodes
  - Chronic fibrocavitatory disease
  - Miliary pattern
- REMEMBER
  - Specificity increased in a child with TB symptoms and positive TST
  - These are still not diagnostic and have differential diagnosis

Non Specific radiology

- Patterns like
  - Consolidations
  - Non homogenous opacity
  - Ground glassing
  - Thin walled cavities
- REMEMBER
  - In such situations microbiology is very important (GA/IS).
  - If negative:
    - Take specialist opinion
    - Consider other investigations like CT Chest, flexible bronchoscopy for evaluation of persistent pneumonia

Please comment on radiological manifestations of TB

What we intend to do in this module?

Interactive Session on radiograph reading

You shall be shown a random mix of radiographs which may be

- Normal or
- Abnormal and TB highly suggestive or
- Abnormal but Not TB specific

Please comment as requested

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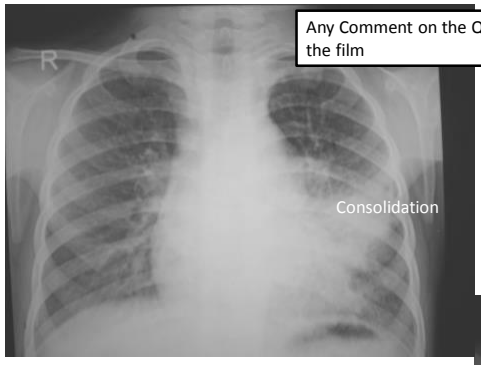
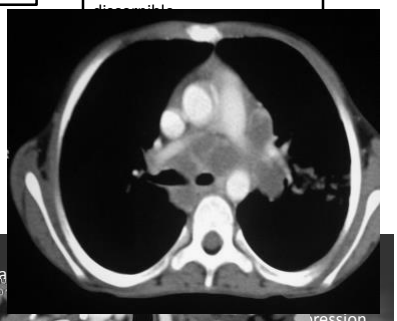
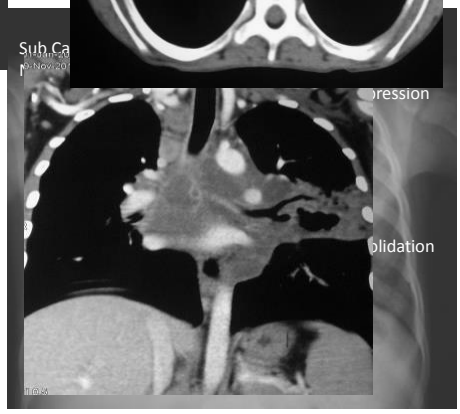






Evaluate the skiagram and comment on
- Normal/ abnormal
- If abnormal- what is your assessment
- What is our interpretation- TB – suggestive, not suggestive

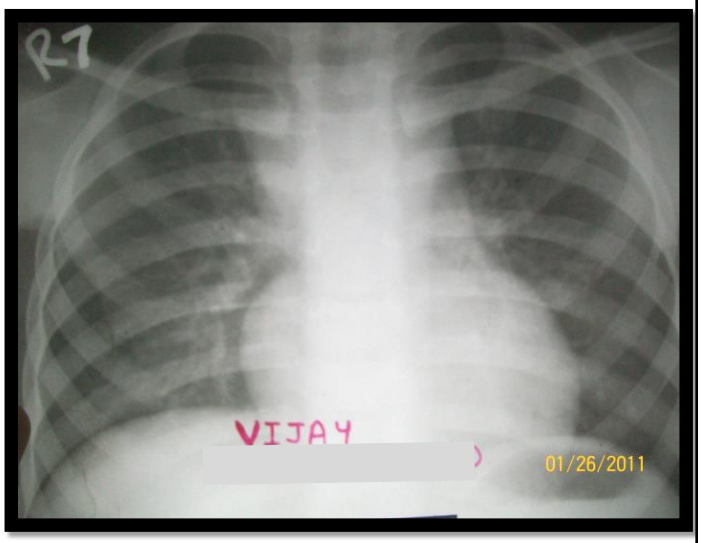
Please comment upon the Chest X-ray

Evaluate the skiagram and comment on

•Normal/ abnormal

•If abnormal- what is your assessment

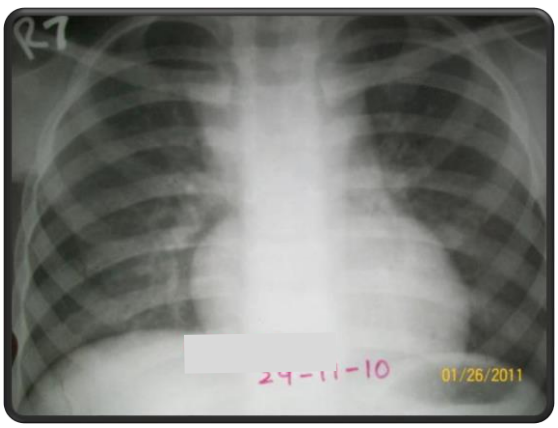
•What is our interpretation- TB – suggestive, not suggestive



Please comment upon the Chest X-ray

Comments:

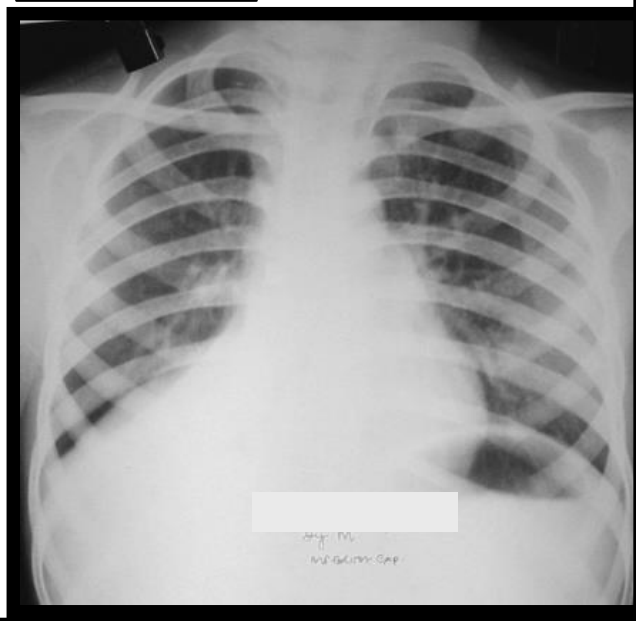
- Likely Normal
- Apparent widening of superior mediastinum is seen as the film is in expiratory phase (4 anterior end of the ribs seen here; in good inspiration more than 5 ant ends of the rib should be seen above the dome of diaphragm)
- Apparent hilar prominence is also due to exp film. Its contour is like that of a vessel – concavity outside. Hence no hilar adenitis



Normal
TB not suggestive

Any Comment on the Quality of the film

Under Penetrated
As spine not at all discernible



Evaluate the skiagram again and
Review your findings

Remember to comment:

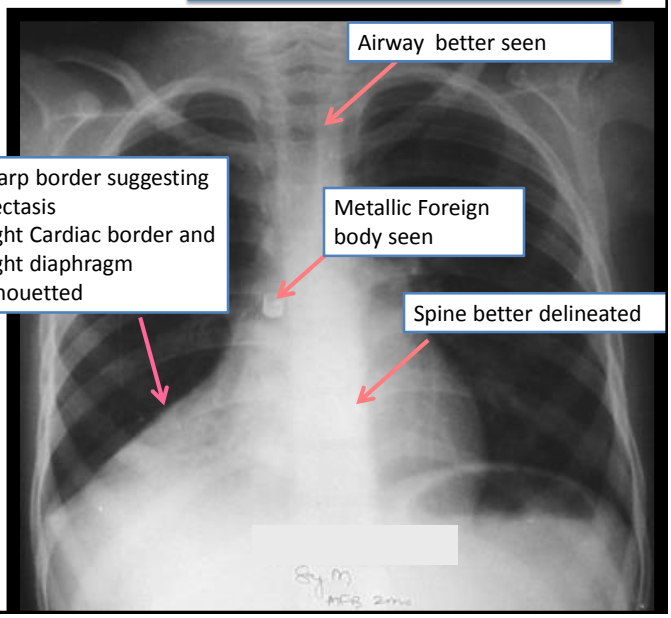
•Normal/ abnormal

•If abnormal- what is your assessment

•What is our interpretation- TB – suggestive, not suggestive

Please comment upon the Chest X-ray

Combined atelectasis
RML +RLL

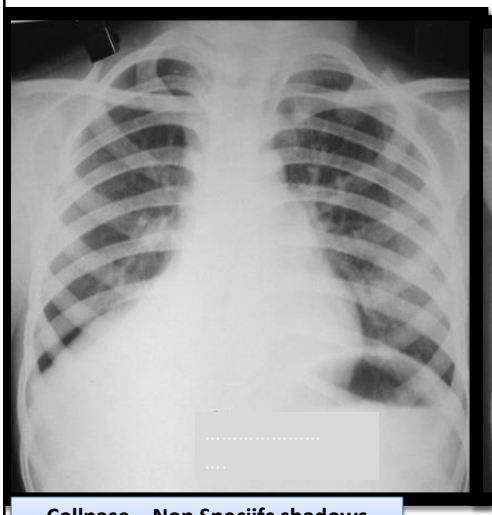


Evaluate the skiagram and comment on

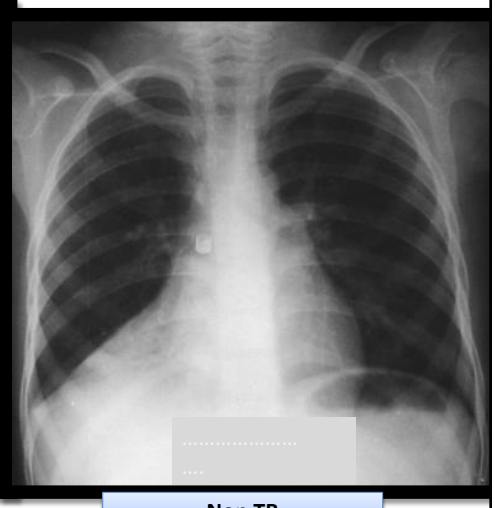
•Normal/ abnormal

•If abnormal- what is you assessment

•What is our interpretatio TB – suggestive, not suggestive



Collpase – Non Speciifc shadows Could be TB



Non TB

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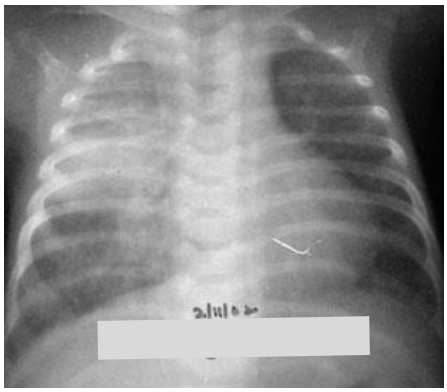
Chest X-ray quality



Evaluate the skiagram and comment on

•Normal, abnormal

•If abnormal- what is your assessment

•What is our interpretation- TB – suggestive or not suggestive

A 2mo old child presented with cough, fever and rapid breathing for about 10 days

Mother is under investigation for fever for 2 months

Chest X-ray quality

umonic
right

Review gram of the same case. What do you think now?

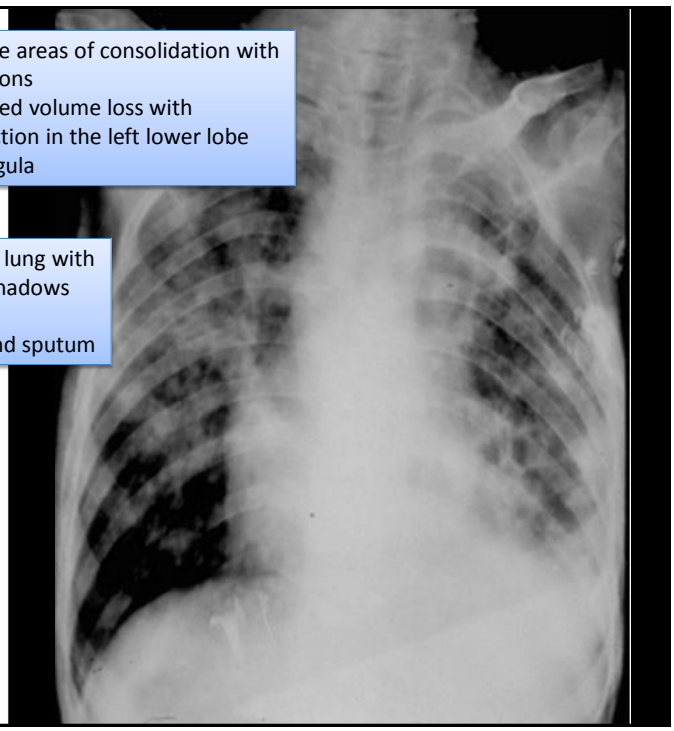
Differe e in exposure can make a major difference in the probable diagnosis and hence the management.

Multiple areas of consolidation with cavitations
Left sided volume loss with destruction in the left lower lobe and lingula

Evaluate the skiagram and comment on

Might represent an old TB lung with re-activation since fluffy shadows present
Co-relation with history and sputum

•What is our interpretation- TB – highly suggestive, not suggestive

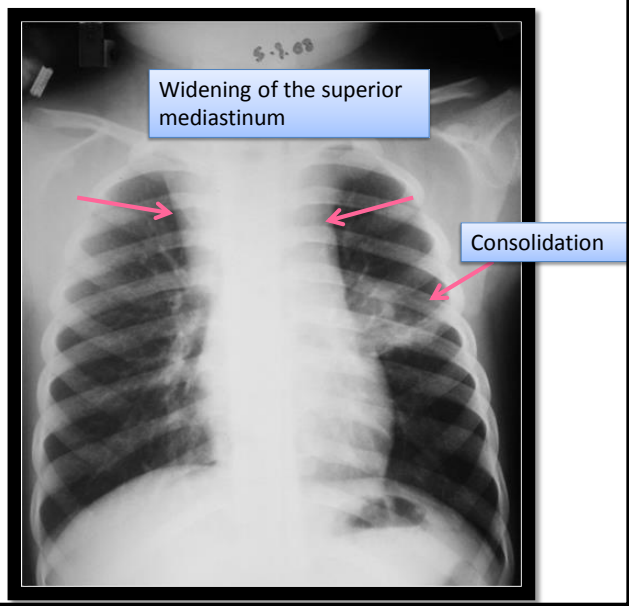


Evaluate the skiagram and comment on

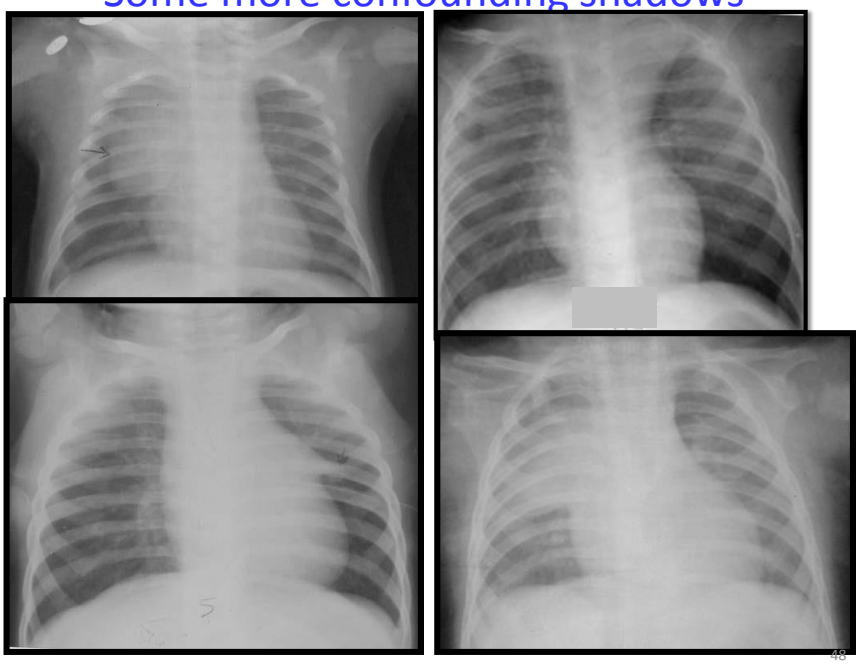
•Normal/ abnormal

•If abnormal- what is your assessment

•What is our interpretation- TB – highly suggestive, not suggestive



Some more confounding shadows



Summation Shadows

Evaluate the skiagram and comment on

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•If abnormal- what is your assessment

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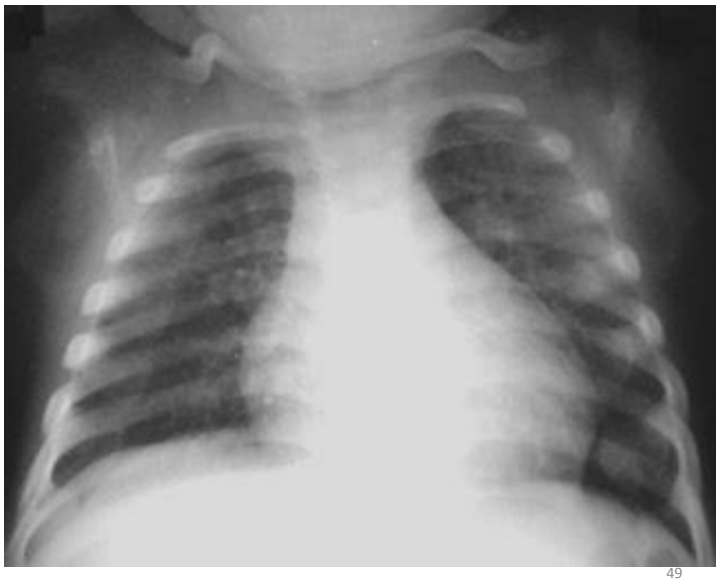

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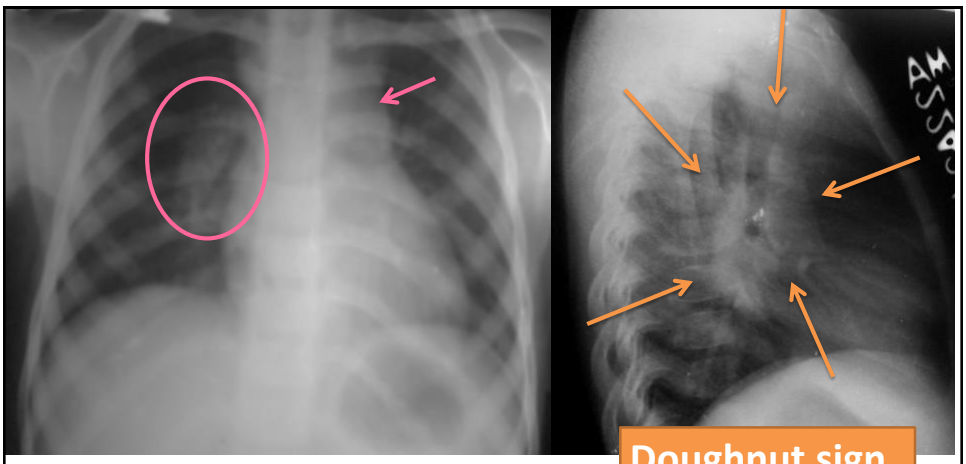


Doughnut sign

Evaluate the skiagram and comment on

•Normal/ abnormal

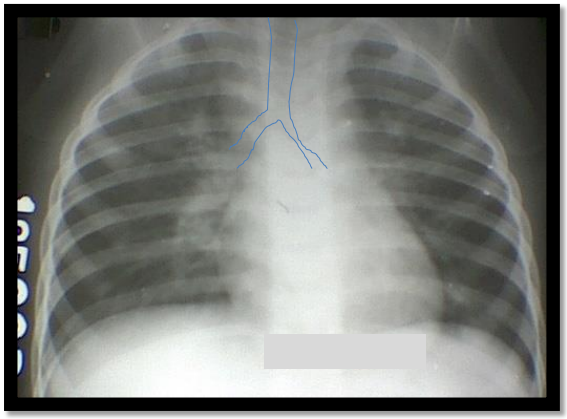
•If abnormal- what is your assessment

•What is our interpretation- TB – suggestive / not suggestive

Lymphadenopathy : Frontal radiographs

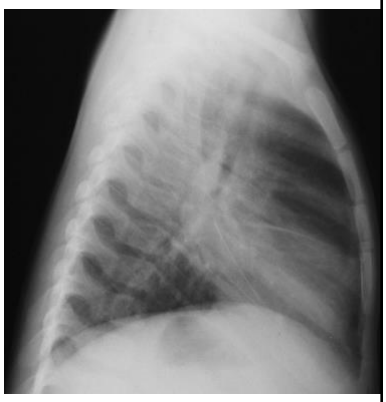
- Direct signs:
  - Sharply demarcated and lobulated density or

    Ill-defined with vague borders, occupying the hilum & obliterating hilar point
  - Other structures making up the mediastinum & hilum can obscure it
- Indirect signs:
  - Contour & calibre of trachea
  - Impression on the tracheobronchial tree as well as splaying of carina can be shown with high-kilovolt filtered radiographs

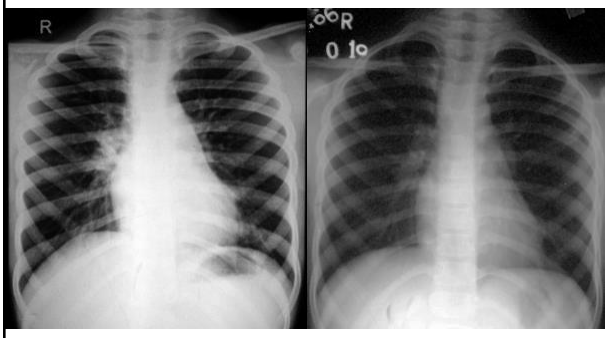


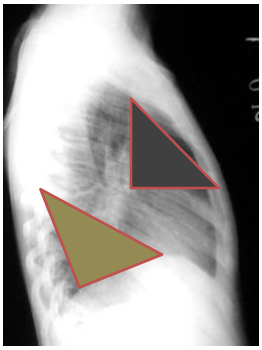
Lateral Chest films

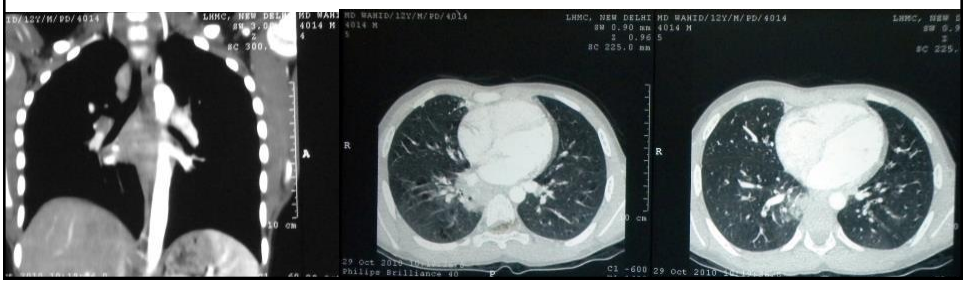
- Good to visualise retrocardiac disease and hila
- Dough nut sign
  - Lobulated densities posterior to the bronchus intermedius
  - Completes the inferior portion of a 'doughnut'-shaped density;
    - Upper half is seen in normal individuals as an up-side-down 'horse-shoe' made up of the RPA and LPA and the aortic arch
- Picks up 12-19% additional cases
- Allows view of the 'hidden areas' like left lower lobes which are hidden behind the heart
- Summation Shadow
  - Better delineation of soft miliary shadows
- Radiation cost – 3x frontal view



W, child with chronic cough







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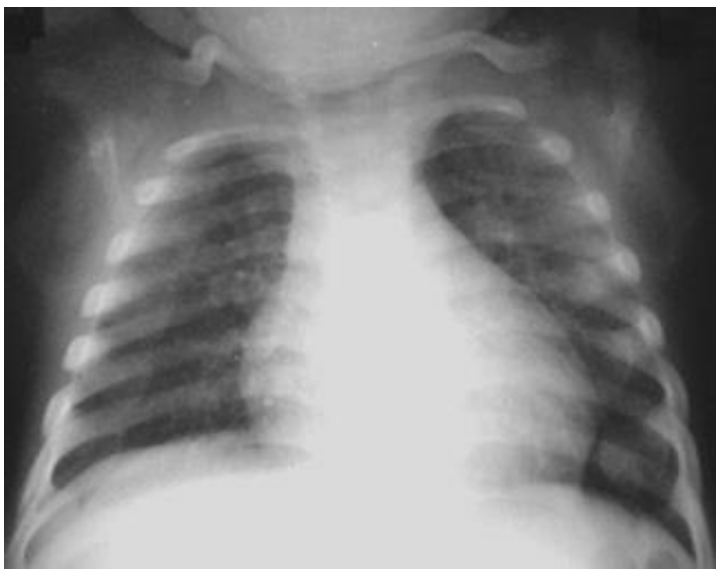
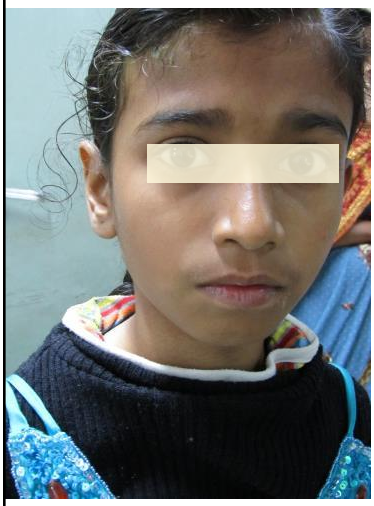
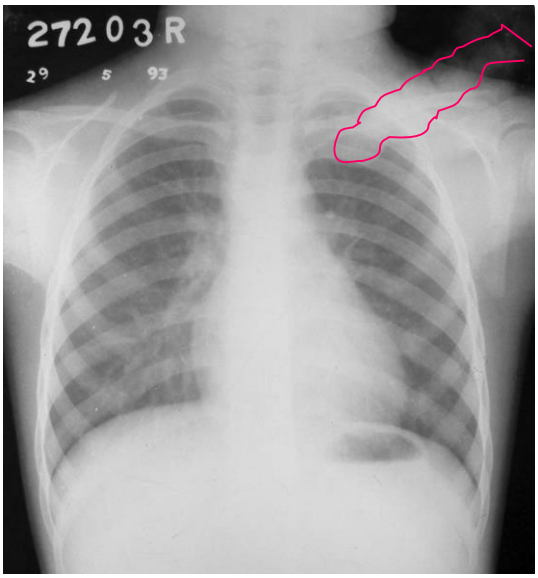
- If abnormal- what is your assessment
- What is our interpretation- TB – suggestive, not suggestive

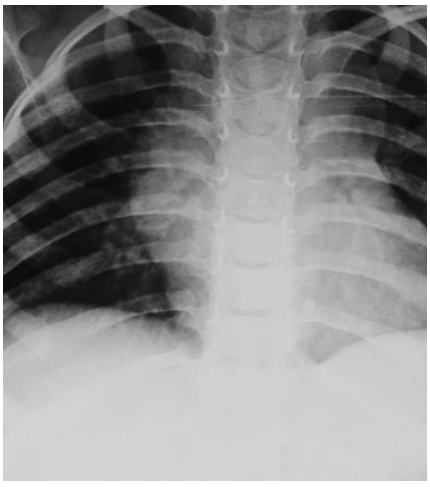


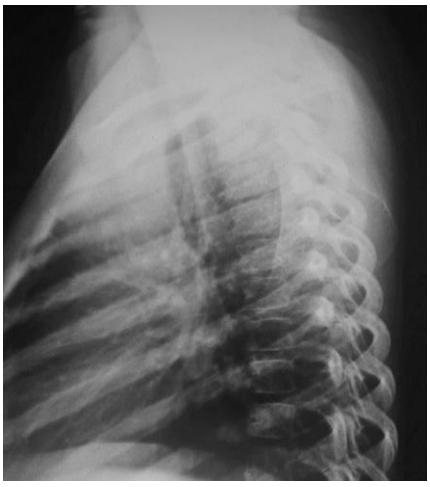
Hair mimicking as coin lesion





CXR of a 2y boy





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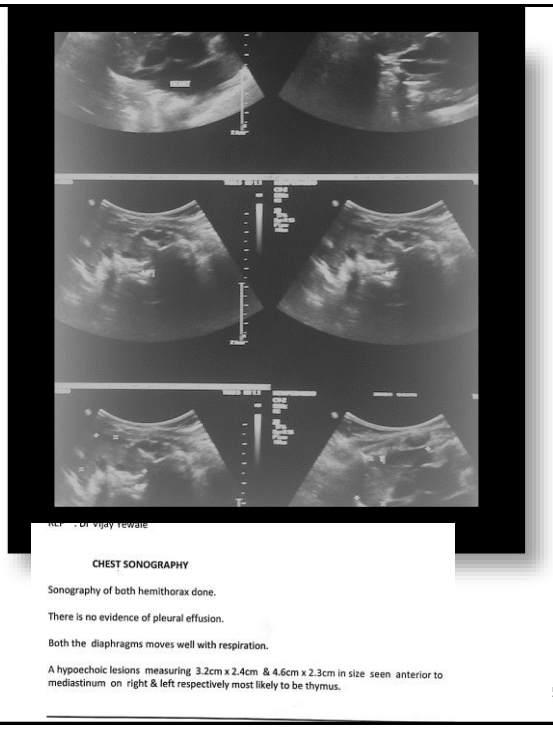
USG Chest sugg of Thymus



CHEST SONOGRAPHY

Sonography of both hemithorax done.

There is no evidence of pleural effusion.

Both the diaphragms moves well with respiration.

A hypoechoic lesions measuring 3.2cm x 2.4cm & 4.6cm x 2.3cm in size seen anterior to mediastinum on right & left respectively most likely to be thymus.

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Use of other radiological methodology for Pulm TB: USG Chest

USG useful tool for

- Pleural effusion
- Thymus vs ant LN
- Identifying best place for aspiration/ FNAC/ biopsy in a peripheral lesion

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Use of other radiological methodology for Pulmonary TB: CECT Chest

- Not routinely recommended for diagnosis of PTB due to high radiation cost
- May be useful in cases of PUO with or without lesion on CXR
- Important tool for work up of persistent pneumonia not fitting into a recognizable pattern
- Shows greater anatomical details
  - Mediastinal lymph node size & its character (necrotising or not)
  - Hidden areas
  - Better depiction of the types of shadows- consolidation vs atelecto-bronchiectasis

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How good is CT for detecting intra-thoracic lymphadenopathy?

- Certainly more sensitive
- May be it is too sensitive for our current thinking gestalt- risk of over interpretation as every lymphnode picked up may not be abnormal.
  - Lymphnodes and mildly enlarged lymphnodes can be normal or seen a variety of conditions
- There are reading errors too
  - only moderate agreement between readers
  - difficulty in distinguishing lymphadenopathy from normal thymus and
  - unable to distinguish normal from pathological nodes without a predetermined size threshold for abnormality

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Andronikou et al. Pediatric Radiology 35, 2005 : 425 – 428

CT Chest- signs considered suggestive of TB

Cavity, tree- in-bud pattern - highly associated with smear positivity in children

Lymphadenopathy (rim enhancement) and collapse – more often negative smear

Pol J Radiol, 2014; 79: 120-125

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Summary

Reading of radiograph is important skill

Remember the TB suggestive and not suggestive shadows on chest x-ray

Adenitis, miliary and chronic fibro cavitary lesions are considered TB suggestive radiological findings

Can be over and under read if the film is not properly projected (rotation, expiratory, under- or over- penetrated, motion or other artefact and cofounders like thymic shadow

Lateral views are useful

CECT and USG are contributory and recommended in select situations

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Tests For Tubercular Hypersensitivity (Infection) - Tuberculin Skin Test

Intra-dermal injection of PPD

Immunological test

- Elicits Delayed-Type Hypersensitivity (DTH)

Indicates

- Present or past infection with MTB
- Not necessarily disease

Used as:

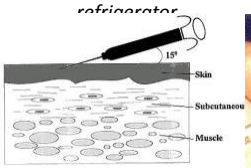
- Adjunct, to other tests, in the diagnosis of TB
- Screen children exposed to TB or at increased risk of M. tuberculosis infection
  - Contact with people with contagious TB
  - HIV-infected children

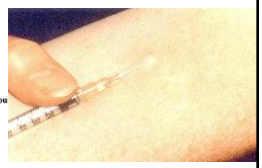
Tuberculin Skin Test – Which Tuberculin and What strength should be used?

- PPD-S is available in USA
- 5TU PPD-S had best discriminatory power between infected and not- infected.
- Rest of the world uses PPD RT 23
- 5 TU PPD-S = 2 TU RT23 with Tween80.
- Current recommendation -use 2TU PPD RT23, given intradermally
- Induration of 10 mm or more cutoff between infected and not- infected.

Technique of administration

- ***Preparation of site***
  - *5–10 cm (2–4 inches) below elbow joint, on ventral forearm*
  - *Place forearm palm-up on a firm, well-lit surface*
  - *The skin should not have barriers e.g. scars, sores, veins*
  - *Clean with alcohol*
- ***Preparation of injection***
  - *Check Expiry date and Tuberculin strength (2 TU of PPD RT23)*
  - *Use a single-dose syringe with a short (1/4 to ½ inches) 27-gauge needle with a short bevel*
  - *Load with 0.1 ml tuberculin*
- ***Injection of test drug***
  - *Insert needle slowly, bevel up, at angle of 5-15°*
  - *Needle bevel should be visible just below sk*
  - *Inject gently raising an Intradermal wheal o at least 6 mm diameter*
    - *If not, repeat at least 5 cm (2 inches) away from the original site*
- ***Record information***
  - *Date and time of test*
  - *Site location*
  - *Lot number of tuberculin*
  - *Tuberculin strength*
- ***Tell the patient***
  - *to avoid scratching the site,*
  - *Keep it lean and dry, and avoid putting creams/ lotions*
  - *Mention that getting the site wet with water is not harmful, but the site should not be wiped or scrubbed.*
- *Finally, return the tuberculin vial to the refrigerator*





Tuberculin skin test Video

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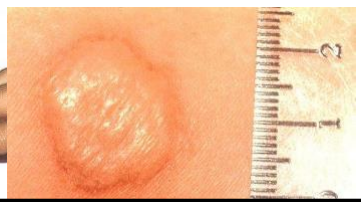
Test Reading: When to read

- Ideally between 48 and 72 hours
- Patient misses appointment
  - Comes beyond 72 hours up to 7 days
    - Negative – repeat other forearm
    - Still positive – interpret as positive
  - Comes beyond 7 days - repeat test in other forearm

Test Reading: How to measure

- *Measure only the induration (using a transparent ruler/scale)*
- Place "0" of ruler line on left edge of the induration.
- Read ruler line on the right edge of the induration as identified (use lower measurement if between two gradations on mm scale)
- Record measurement in millimeters (mm) usually across horizontal axis,
- Do not record as negative/positive. No induration = 0 mm
- In case there is huge erythema but no induration- it may be due to an inadvertent subcutaneous leak. In such situations the test is repeated on the other arm



Causes of False positive/negative TST

- False negative
  - Incorrect ***technique*** of administration or Interpretation
  - ***Improper storage*** of tuberculin
  - ***Immunodeficiency/suppression***
    - Primary
    - Secondary
      - HIV infection, SAM, etc
  - ***Infections***
    - Viral(e.g. measles, varicella)
    - Bacterial(e.g. Typhoid, leprosy, pertusis)
  - ***Vaccinated*** with live viral vaccine (within 6 wk)
  - ***Neonatal*** patients
  - ***Severe*** TB
- False positive
  - Incorrect ***technique*** of Interpretation
  - ***BCG*** vaccination
  - Infection with ***mycobacterium other than TB***

Tuberculin Skin Test (Mantoux's Test)

Summary

A positive Tuberculin skin test is defined as 10mm or more induration after 48-72 hrs using no more than 2TU RT23 tuberculin.

- In HIV coinfected, 5mm may be taken as the cutoff

Optimal strength of tuberculin to be used for diagnosis in children

- 2TU dosage considered most appropriate for routine diagnostic use
- If not available; no more than 5TU should be used but remember that higher strengths give more false positives
- Non-availability of a standardized tuberculin in India: cause of concern

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TST Summary

Limitations

- SPE and PPV limited in BCG and NTM exposed
  - BCG can cause positive reactions
  - But uncommonly over 10mm and >15mm are rare (1 TU)
- SENS and NPV limited in HIV-infected, recently exposed, young and malnourished children

A positive Mantoux's test suggests infection with MTB and not TB disease

A negative test does not always rule out TB infection

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Schaaf, PIDJ, 2006, Shams, 2006, Hesseling Thorax 2008

Frequently asked questions

Q1. My patient has a TST >20 mm. Should I start him on ATT?

- Any reaction more than the cut off JUST suggests infection.
- Strength of reaction does not discriminate between infection and disease

Q2. My patient has a TST which has got ulcerated. Should I start him on ATT?

- No. This also does not suggest disease

Q3. The patient did not come for reading at 72 h. What should I do?

- If there is a positive reaction, then it can be read upto 7 days
- If there is no reaction or <10 mm then repeat on the other forearm or a site away from the previous test on the same arm

Q4. Should I use a two-step testing. Is it more sensitive?

- It has no added value for diagnosis in children in endemic situations.

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Frequently asked questions

Q5. Should I repeat a TST after the completion of ATT?
- It does not help in guiding duration of treatment.
- Once the child is infected TST is likely to stay positive

Q6. In children with reactivation or re-infection what happens to TST?
- It does not help in detecting a re-infection or reactivation

Q7. In my experience BCG test is very useful when TST is negative? What do you suggest?
- Of No Use
- High false positivity and is not recommended due to lack of standardisation

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Interferon γ Assays [IGRAs]

- *In vitro* stimulation of whole blood with Mtb specific antigens like ESAT-6, CFP-10 and Tb7.7
- Quantiferon Gold in tube test (TM) and Elispot-TB (TM) are the 2 major commercially available tests.
- Both IGRAs and TST are tests to detect **Latent TB infection.**
  - ***"Indirect tests' -*** *do not* detect actual TB bacilli but immune response that suggests past or present exposure to TB bacilli.
- **Both IGRA and TST tests cannot distinguish between latent TB infection and active TB disease.**

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IGRA: Benefits

Requires a single patient visit to conduct the test

Results can be available within 24 hours

Does not boost responses measured by subsequent tests

Prior BCG (bacille Calmette-Guérin) vaccination does not cause a false-positive IGRA test result

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IGRA: Limitations

Blood samples must be processed within 8-30 hours after collection while WBC are still viable

Errors in collecting or transporting blood specimens or in running and interpreting the assay can decrease the accuracy of IGRAs

Limited data on the use of IGRAs to predict who will progress to TB disease in the future.

Limited data on the use of IGRAs for:

- Children younger than 5 years of age;
- Persons recently exposed to *M. tuberculosis*;
- Immuno-compromised persons; and
- Serial testing.

Test is expensive

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Module 4:

TB Diagnostics Part 2 (Microbiology, etc)

How does on confirm TB in a child? How difficult it is?

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How feasible is Bacteriological Diagnosis?

Hurdle 1

- Access to specimen is hurdle
  - Most children do not expectorate
  - Even if they have sputum, do not cough violently enough to bring it up
  - Tend to swallow rather than spit it out
  - Unlike adults the specimen needs retrieval in children

- *Do we have a better (easy to get and process) specimen?*

Hurdle 2

- Low Sensitivity of Smear and moderate sensitivity of culture examination in Children

- *Can we improve the yield of these investigations?*

How do we access the respiratory specimen when a sputum cannot be brought up spontaneously?

- Gastric Aspirate and Induced Sputum video

Do we have a better sample?

GA/ gastric lavage

- Needs over night fasting
- Needs hospitalization
  - Now can be done in Ambulatory setting
- More invasive
- Needs better trained staff

Induced Sputum

- Fasting not needed
- Ambulatory setting
- Less invasive
- Can be learnt easily by paramedics
- Risk of transmission to provider higher as provokes cough

Yield shall be an important deciding factor

Are there any other respiratory specimens which can be used?

Role of Bronchoscopy and BAL for Pulmonary TB

- Bronchoscopic findings of mucosal involvement is more likely to yield AFB in BAL
- Findings like compression of airways or caseation or bronchiectasis with mucosal ulcerations suggest TB pathology
- Add on test and stand alone does not give better yield than GAs

Indications of Bronchoscopy & BAL

- Definite utility in children with persistent pneumonia.
  - performed if routine investigations for TB are inconclusive
  - Useful to rule out alternative diagnosis
- Should we do it in ALL patients who have Sputum/GA negative with characteristic radiology OR use it SELECTIVELY?
  - Largely guided by Facilities available
    - Perhaps should be dictated by need for a definitive diagnosis
  - DR suspect:
    - defaulter, relapse, treatment failure
    - Extent of disease: localized vs extensive
    - Type of contact: on CAT II or MDR therapy
  - Co-morbid conditions: HIV, Immunocompromised etc.

What tests do we have to test respiratory specimens effectively?

- Smear for AFB
  - ZN staining,
  - Fluorescent microscopy
- Cartridge Based Nucleic Acid Amplification Test (CBNAAT)
- Liquid cultures (MGIT®)
- Solid cultures (Lowenstein Jensen Media)

With use of molecular tests (PCR based technologies) it is preferred to use the term Bacteriologically positive TB to Smear positive TB

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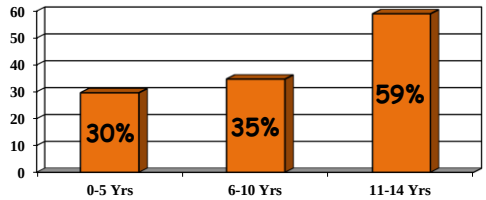
BACTERIOLOGICAL DIAGNOSIS – ACID FAST BACILLI ON SMEAR OR M TB ISOLATION

- Smear is the cheapest, simple, point of care confirmatory test,
- High level of agreement, increases with increased number of bacilli on smear
- Smear Less preferred test dt several issues
  - Problems in getting the specimen
    - young children do not bring up and spit sputum
  - Poor sensitivity as Primary disease is paucibacillary
  - Extra-pulmonary T B -a significant problem in children less often AFB positive
- Yield can be improved with Mtb Cultures
  - but expensive, not routinely available and take time
  - Certainly useful if suspecting Drug resistance

Sensitivity of Smear Examination in Children

- Varied reports due to different mix of patients
- Reported **smear positivity** in new childhood cases (NITRD, Delhi data; n=1098)



- AIIMS-KSCH Delhi TB group study
  - N=403,
  - Smear positive 11% ; Culture Positive 33%
- LED microscopy increase the yield of smear marginally (by about 10%; say from 11% with conventional to about 12% with LED)

Sharma S, et al. Int J Tuberc Lung Dis 2008
Pediatr Infect Dis J 2013;32:1313–1317

Does the type of disease affect bacteriological diagnosis?

	Smear	Culture	Over all yield
Primary complex	6%	22%	23%
Progressive primary	18%	46%	47%
Pleural effusion*	5%	28%	32%

*** The smear or culture yield depicted here is from respiratory specimens like GA/ IS and not from pleural fluid**

Delhi TB group study (N=403)

Pediatr Infect Dis J 2013;32:1313–1317

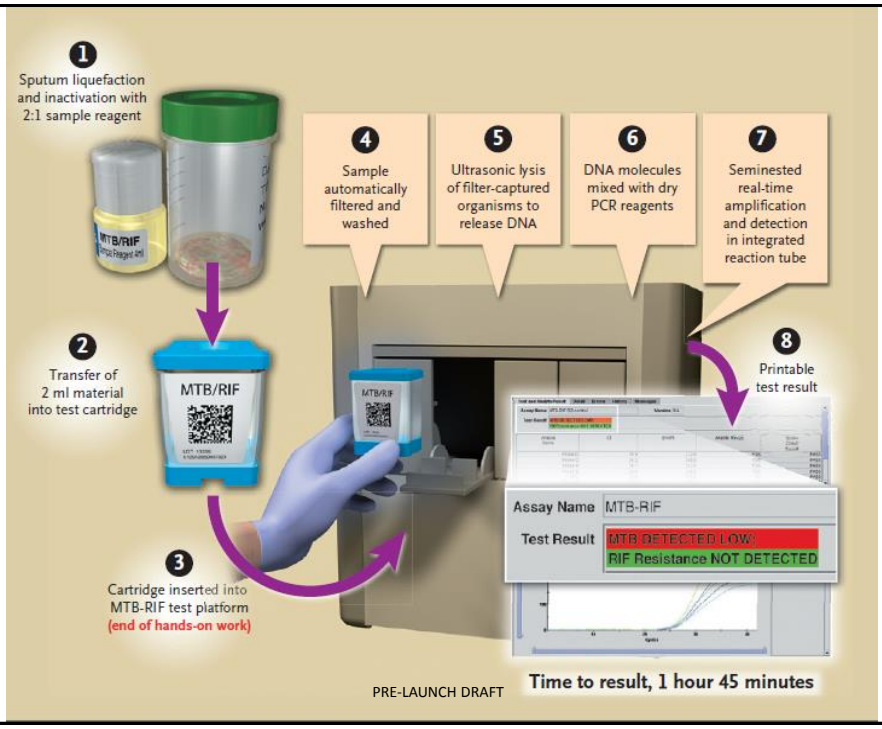
What is CBNAAT?

CBNAAT
- Currently available in country as Xpert MTB/RIF™ (aka Gene Xpert)

Cartridge Based-
- Closed system, automated processing unlike earlier PCR based technologies
- Less prone to contamination

Real time PCR
- amplified DNA is detected as the reaction progresses in "real time".

Nested PCR
- involves two sets of primers (for Mtb and for Rif resistance), used in two successive runs of polymerase chain reaction
- Detects M tb & RIF resistance in < 2 hours



Childhood respiratory specimen and GX performance

- More sensitive than smear microscopy for both sputum (90·0% vs 30·0%) and GA (68·8% vs 25·0%) as compared in Mtb Culture positive cases

  Bates et al Lancet Infect Dis 2013
- However, over all yield in the respiratory specimens is about as much or less than culture.
- Remember Mtb culture has a sensitivity of about 45-55% in children

EXPERT REVIEWS

Diagnosis of extrapulmonary tuberculosis using the Xpert® MTB/RIF assay

Expert Rev. Anti Infect. Ther. 10(6), 631–635 (2012)

Xpert versus other tests	Sensitivity	Specificity
Culture	79.0%	97.3%
Composite diagnostic gold standard	81.3% (95%CI: 76.2–85.8)	99.8% (95% CI: 99.4–100)
Smear positive disease	99.0%	
Smear-negative disease	70.3%	

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EXPERT REVIEWS

Diagnosis of extrapulmonary tuberculosis using the Xpert® MTB/RIF assay

Expert Rev. Anti Infect. Ther. 10(6), 631–635 (2012)

Specimen	Sensitivity	95% CI
Tissue biopsies	75%	
Fine Needle Aspirates	88.3%	82–95
Gastric aspirates	78.7%	68–89
Pus samples	87.3%	67–100
Cerebrospinal fluid	85.7%	67–100
Urine	87.5%	71–100
Lower sensitivity for		
Pleural fluid	44.4%	21–67
Body fluids (Pericardial, peritoneal, Synovial)	50%	19–81

Expert Rev. Anti Infect. Ther. 10(6), 631–635 (2012)

RNTCP: Bacteriological Evidence

Attempt bacteriological diagnosis in all cases

- Collect at least 2 samples

Where sputum is not available for examination or sputum microscopy fails to demonstrate AFB, use alternative specimens

- GA, IS, BAL
- Dending upon the feasibility, under the supervision of a pediatrician

CB NAAT (Xpert™) / Culture greatly increase the yield

- Always attempt, where available
- Cost will perhaps limit to using it with only one specimen or may be pooled specimens
- Always use in DR TB suspect

National strategy – Testing for drug resistance by culture or molecular methods for all retreatment TB cases Ultimately to cover all pediatric TB cases

To summarise, Available Diagnostic tests for TB

Direct

- **Smear:** positive in only 10-15% of children
- Commonly performed on sputum and gastric aspirates
- **Culture** : slow and cumbersome requiring sequential procedures for isolation and in-vitro drug sensitivity testing
- **CBNAAT:** Rapid reliable WRD which also tells abour Rif resistance

Indirect

- **Chest radiography:** often non specific findings, inter and intra observer variation
- **TST:** is only a marker of infection not disease

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TB Serology by ELISA

Poor specificity / poor sensitivity

- **Recommendation 6** *(new)*

Commercial serodiagnostics should not be used in children suspected of active pulmonary or extrapulmonary TB, irrespective of their HIV status

(Strong recommendation, very low quality of evidence for the use of commercial serodiagnostics)

Source: *Commercial serodiagnostic tests for diagnosis of tuberculosis: policy statement*. Geneva, World Health Organization, 2011 (WHO/HTM/TB/2011.5)

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ESR

Too many pretest variables

- Anemia
- Fasting
- Method
- Coagulant
- No specificity

No role in diagnosis

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Final review

Let us review our case finally
Victor's Basis of ATT

- ~~Victor's has chronic cough and is not thriving well- TB like symptoms~~
- TST positive ?? 10 TU
- ~~Father has chronic cough but unlike TB~~
- ~~CXR suggestive - primary complex~~
- ESR 32mm ---- So What?
- ~~TB Elisa positive IgG and IgM~~
- No attempt at microbiological diagnosis

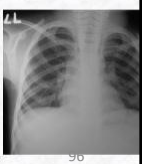
- Basis for ATT justified
  - NOooooo……

- H/o cough for 2 months
  - Dry
  - More for past 3 days
- Low grade fever for same duration
- Not growing well
- Fussy eater
- Father has chronic cough
  - Has had several sets of antibiotics with no relief

- O/E
  - Wt 10.7 kg
  - Mild pallor
  - No lymphadenopathy
  - Chest:
    - Bilateral crackles and wheezes
  - Rest NAD

- Tuberculin Skin test (PPD test) 14mm in transverse axis with 10 TU
- ESR 32 mm
- TB Elisa positive IgG and IgM

- NO ATTEMPT AT BACTERIOLOGICAL DIAGNOSIS



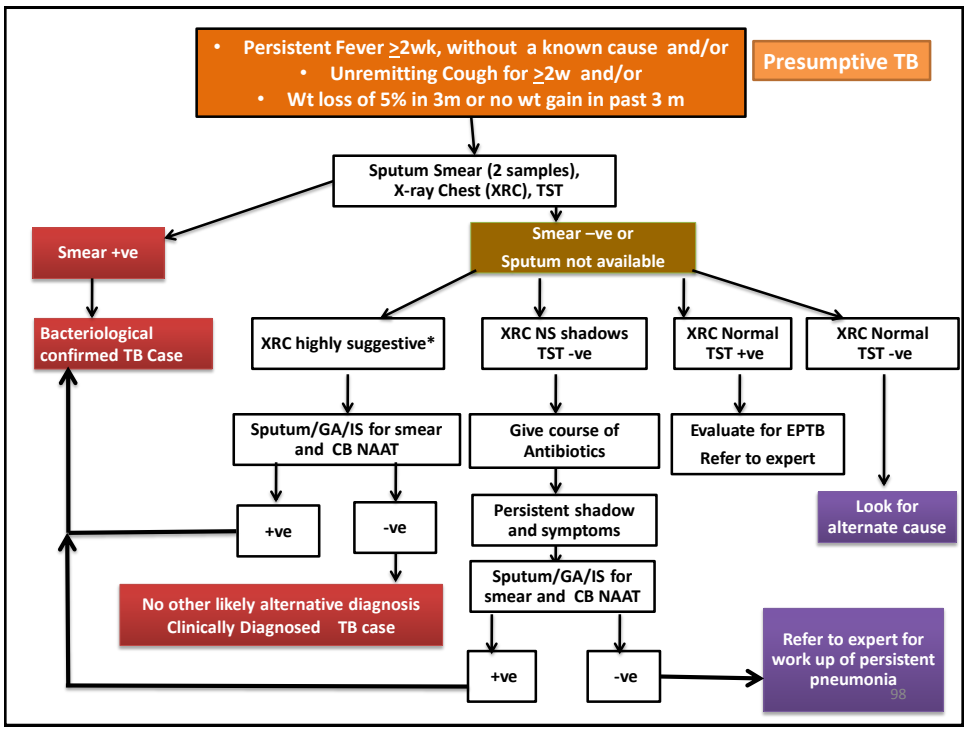
96

MODULE 5

Diagnostic algorithm- PULMONARY TB

How does it all add up?

97



Important Notes to the Algorithm

1. This algorithm is for children who are likely to have drug sensitive disease i.e. have not received ATT previously ever and are not Drug resistant TB Suspects (defaulters, relapse, treatment failure, HIV).
2. Proper Characterization of symptoms is very important starting point. Weight loss or not gaining weight should always be documented with appropriate and proper weighing.
3. Whenever smear is used for diagnosis at least 2 samples should be sent while a single sample is subjected to CB NAAT. Where CB NAAT is doable, smear examination may not be done except for children with spontaneously expectorated sputum when seen for the first time. If a specimen is positive by any of these methods, the disease is labelled as Bacteriological confirmed TB.
4. Highly suggestive Chest X-ray refers to skiagrams showing either Miliary or lymphadenopathy (hilar or mediastinal) or chronic fibro-cavitatory shadows.
5. Non Specific Chest X-ray: Refer to patterns other than highly suggestive like consolidations, inhomogenous shadows or bronchopneumonia, etc.
6. Antibiotics like linezolid or any quinolone should not be used as they have anti-TB action.
7. Children with persistent symptoms, non specific shadows and negative smears and negative other samples (GA/IS) by CB NAAT should be referred to experts for further work up of persistent pneumonia.
8. All TB cases diagnosed must be offered testing for HIV.

99

Case Alpha

- 13 y old boy
- Presented with
  - Fever X 4 weeks
    - Daily, documented upto 1
  - Cough X 4 weeks
    - Daily, persis tum (yellowish, moderate in amou ptysis
  - W past weeks
    usly 50 kg; current weight 45 kg

Is he a TB Suspect?

100

- Persistent Fever ≥2wk, without a known cause and/or
- Unremitting Cough for ≥2w and/or
- Wt loss of 5% in 3m or no wt gain in past 3 m

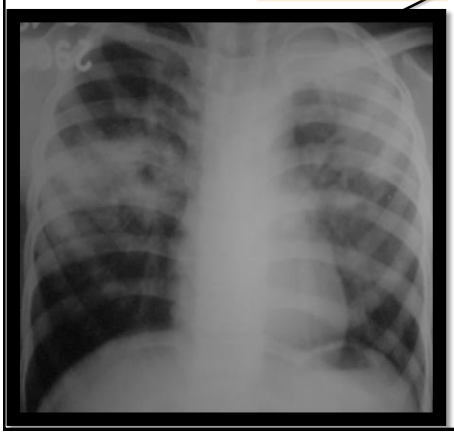
Presumptive TB

Sputum Smear (2 samples), X-ray Chest (XRC), TST

Smear Negative

Smear –ve or Sputum not available

Check CXR



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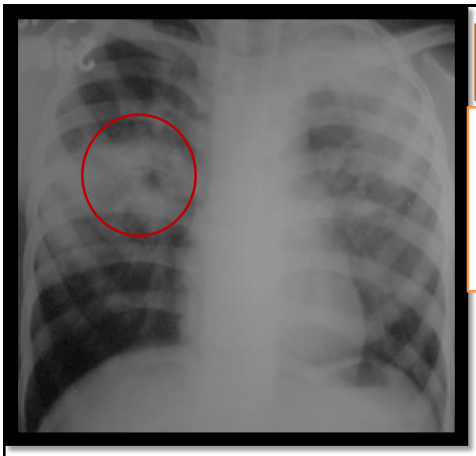


Is the Xray suggestive of TB?

Cavitation with a surrounding consolidation
Thick Walled
Other areas of consolidation
Nodular inhomogenous opacifications left side

Sputum is Mtb Negative on CB NAAT

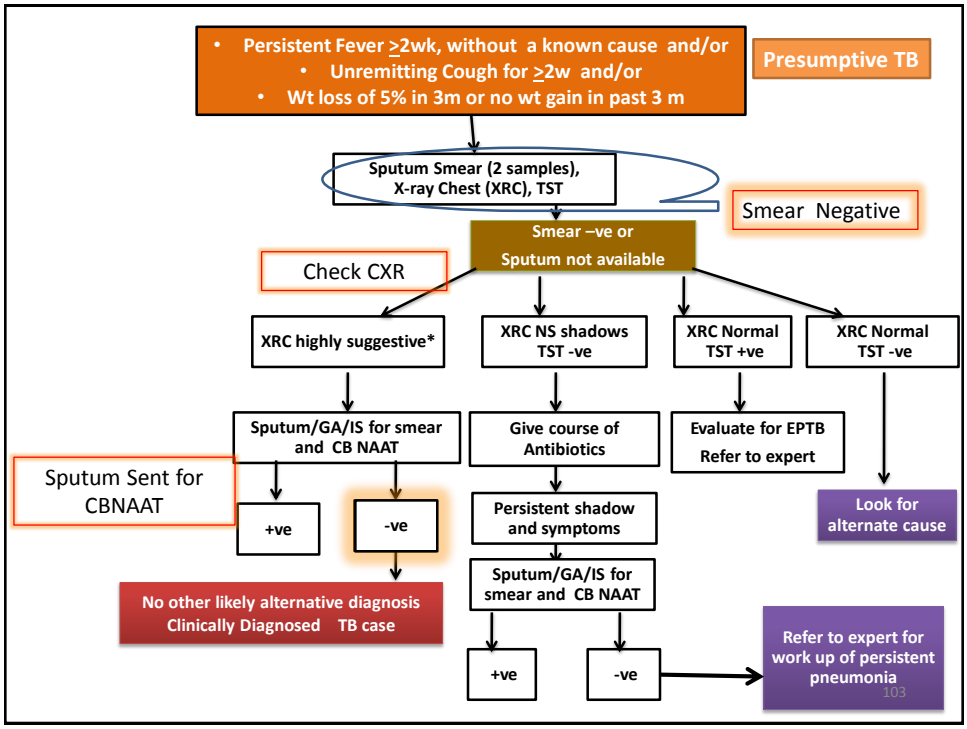
Clinically Diagnosed Pulmonary TB

Radiological changes highly suggestive of TB

- *Hilar/paratracheal lymphadenitis with or without parenchymal lesion,*
- *Miliary TB,*
- *...ia.*

Symptoms + radiology = chronic cavitatory pneumonia

102



11 yr Female

- Fever
  Initially low grade, off & on
- Cough - Dry
- Decreased appetite

2 months

- Received oral and iv antibiotics from outside: no response
- Workup from outside
  - Hb 9.9gm%, TLC 11700, P_{81} L_{19} , Platelet 3.52 L, ESR 55
  - TST 3mm 2TU
  - CXR Left MZ infiltrates and cavitatory lesion
  - Sputum not available

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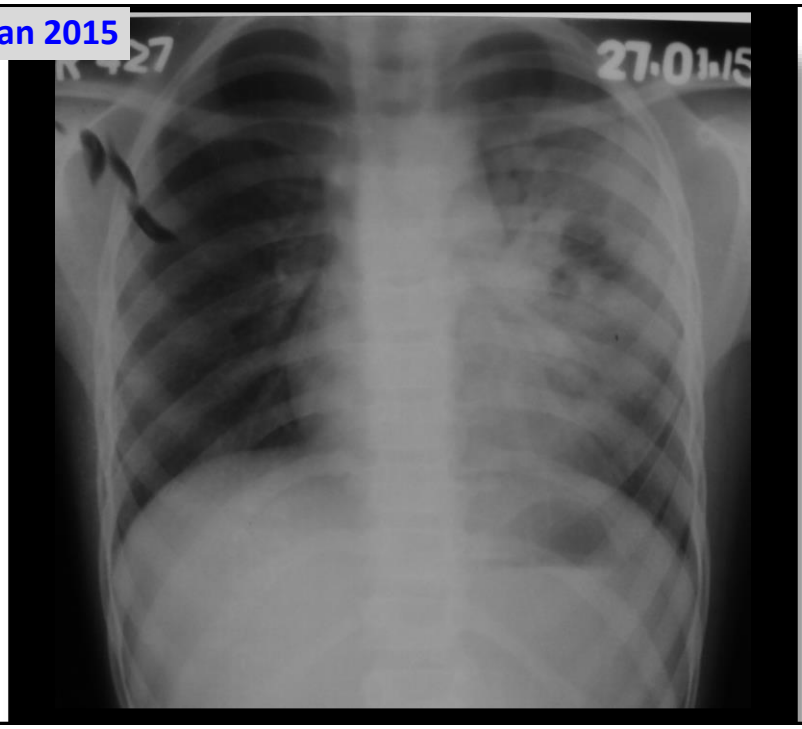
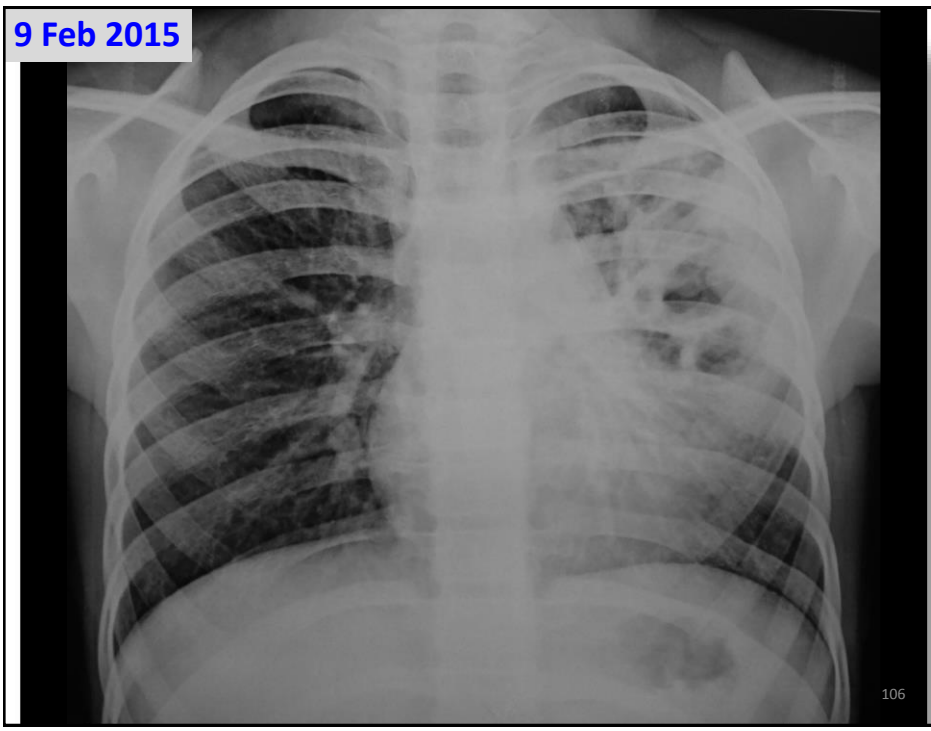
27 Jan 2015

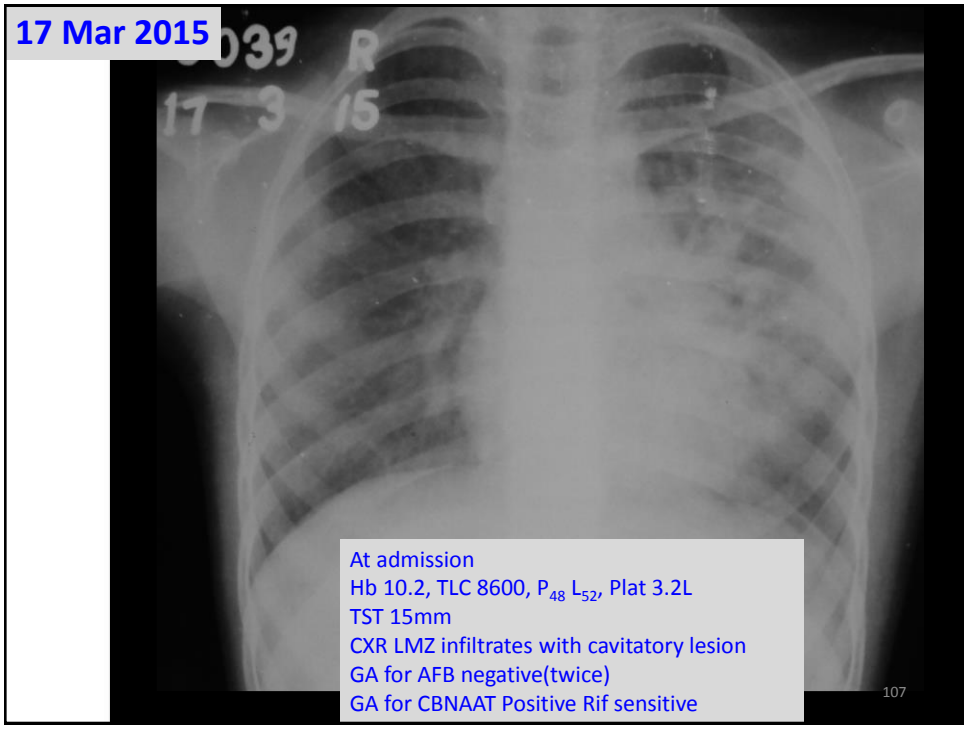


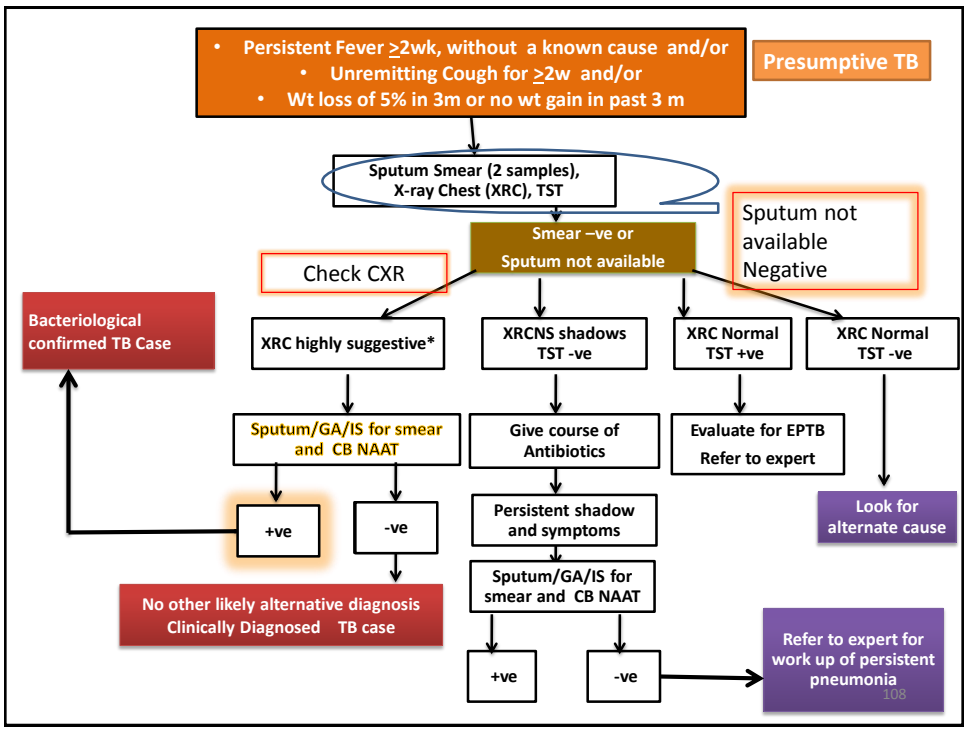
105

9 Feb 2015



106

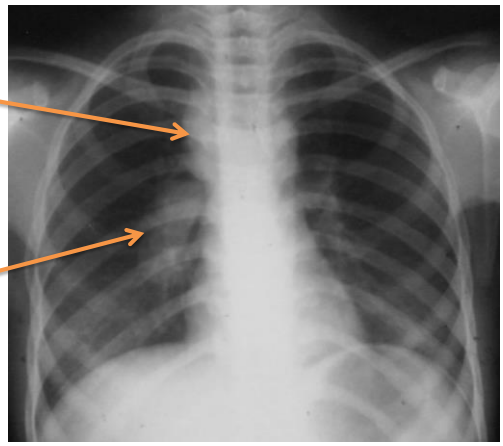

17 Mar 2015
At admission
Hb 10.2, TLC 8600, P_{48} L_{52}, Plat 3.2L
TST 15mm
CXR LMZ infiltrates with cavitatory lesion
GA for AFB negative(twice)
GA for CBNAAT Positive Rif sensitive
107


• Persistent Fever ≥2wk, without a known cause and/or
• Unremitting Cough for ≥2w and/or
• Wt loss of 5% in 3m or no wt gain in past 3 m
Presumptive TB
Sputum Smear (2 samples), X-ray Chest (XRC), TST
Smear –ve or Sputum not available
Sputum not available Negative
Check CXR
Bacteriological confirmed TB Case
XRC highly suggestive*
XRCNS shadows TST -ve
XRC Normal TST +ve
XRC Normal TST -ve
Sputum/GA/IS for smear and CB NAAT
Give course of Antibiotics
Evaluate for EPTB Refer to expert
Look for alternate cause
+ve
-ve
Persistent shadow and symptoms
Sputum/GA/IS for smear and CB NAAT
No other likely alternative diagnosis Clinically Diagnosed TB case
+ve
-ve
Refer to expert for work up of persistent pneumonia
108

Case Gamma

- 10 y boy
- Presenting complaints:
  - Cough X 4m
    - Dry, persistent, no clear relation to URI although had coryza in between.
  - Increased respiratory rate X 4m
    - Not associated with fever and persisting with gradual increase in severity
  - Fever X 4 m
    - Off and on (no clear documentation)

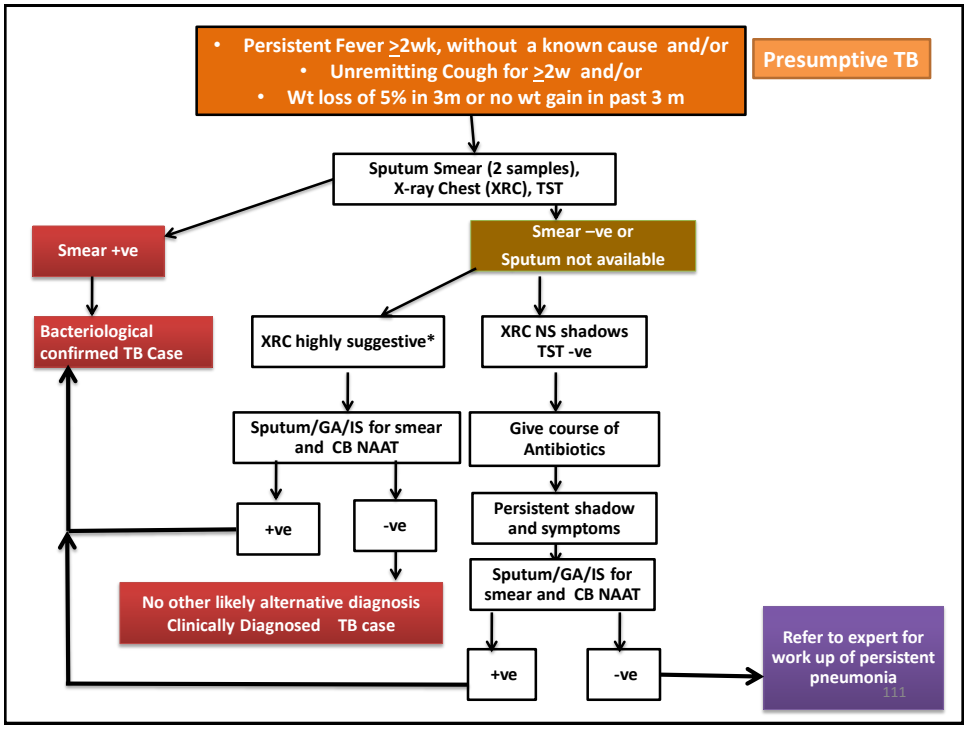
109



Is the Xray suggestive of TB?

Radiological changes highly suggestive of TB

- Hilar/paratracheal lymphadenitis with or without parenchymal lesion,
- Miliary TB,
- Chronic cavitary / fibrocavitary pneumonia.



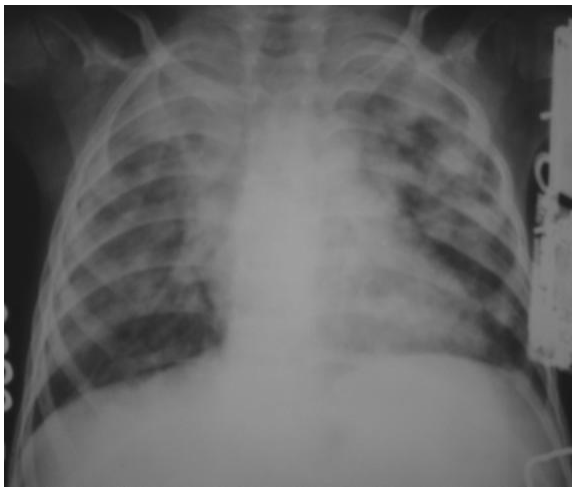
4 yr Female

- Fever
  Initially low grade, off & on
- Cough - Dry
- Decreased appetite

2 months

- Received oral and iv antibiotics from outside: no response
- TLC 11700, P65 L35, ESR 55
- TST 3mm 2TU
- CXR Left MZ infiltrates and cavitatory lesion
  - Sputum not available

112



Comment on the X-Ray

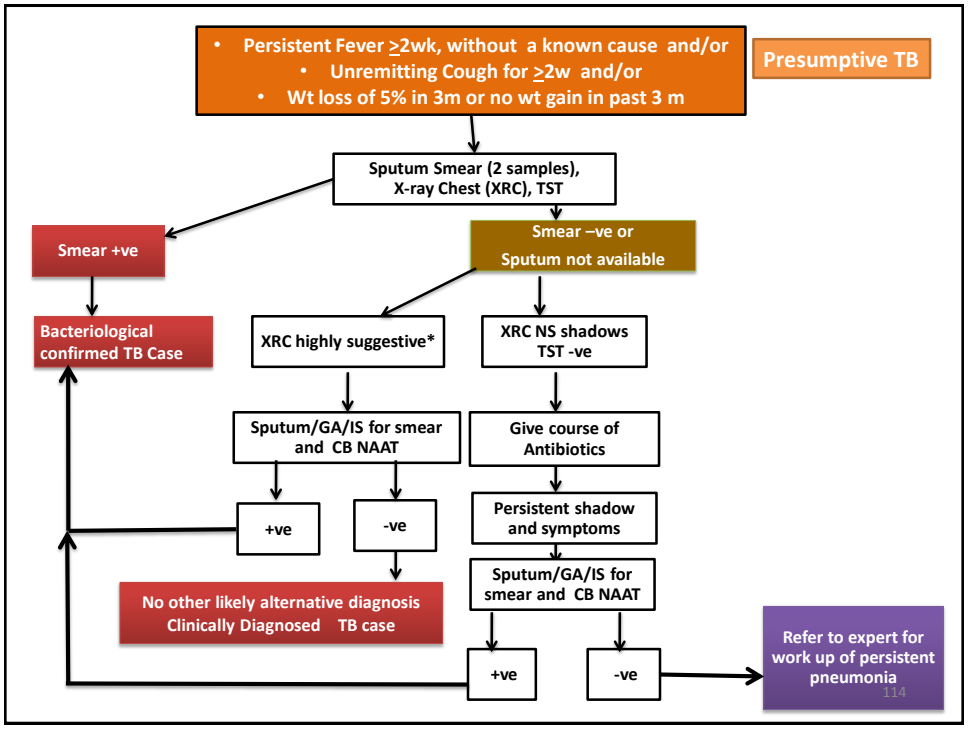
Is the Chest Xray suggestive of Tuberculosis

Inhomogenous nonspecific parenchymal shadows seen in both upper lobes

Mantoux 3 mm with 2 TU

Radiological changes highly suggestive of TB

- *Hilar/paratracheal lymphadenitis with or without parenchymal lesion,*
- *Miliary TB*
- *Chronic cavitary / fibrocavitary pneumonia.*



Summary

- New diagnostic algorithm incorporating usage of new technology like CBNAAT which is more sensitive than ZN Smear or LED Fluorescent microscopy
  - also far more costly and may be less easily be available.
- At the initial step, If self expectorated sputum is available
  - smear may be done
- All suspects with negative results and in all other situations, CB NAAAT (where available) shall be preferred to smear examination.
  - Facilities for these test available under RNTCP labs (free of cost) as well through a network of accredited private labs at a subsidised price through Initiative for Promoting Affordable Quality TB Tests (IPAQT).

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Summary

- Algorithm is best suited for children who are new cases (i.e. have not received ATT previously ever or for <4 weeks) and likely to have drug sensitive disease (no exposed to a known MDR source case)
- For Drug resistant TB Suspects (Treatment after interruption, recurrent TB, failure and HIV patients), bacteriological confirmation along with first line drug sensitivity should be considered upfront
  - use any of the available WHO approved technologies like MGIT culture sensitivity/ Line probe assay / CBNAAT.

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MODULE 6

Lymph node TB diagnostics

How does LN TB present and how do you diagnose it?

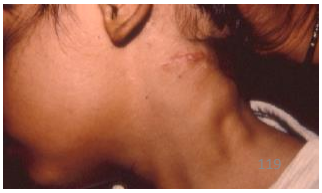
117

Lymph node Tuberculosis

- Lymph node TB is one of the most common forms of EPTB
- Cervical lymph nodes are most common site
  - With or without associated disease of other lymphoid tissue
- Maximum prevalence was in 5-9 y.

Clinical features

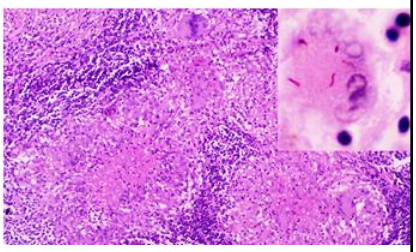
- Enlarging masses over weeks to months
- Usual cervical: jugular, posterior triangle, supraclavicular
- Others: axillary, inguinal
- Systemic symptoms commonly seen
  - Local manifestation of a systemic disease
  - Pulmonary route of entry of the pathogen → hilar and mediastinal LN

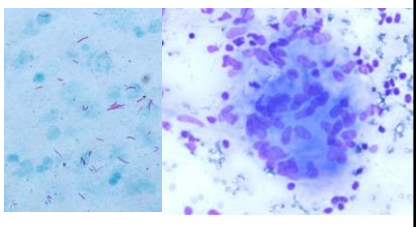


119

Diagnosis

- Fine needle aspiration
  - Cytology
    - Sensitivity 77- 98%
    - Specificity 97-100%
    - Diagnostic accuracy 97-99%
  - AFB smear 10-15% sensitive
  - Culture 20-50%
  - Xpert for MTB Rif™
    - 35% positive vs 7% Smear (TB FIND study)
- Excision biopsy
  - Histopathology, Smear and Culture





120

Smear/Culture using FNA

- Bacteriologic yield: 20- 80% (greater in HIV infected)
- In a study from N Ethiopia (n=437, 1-70y old)
  - 52% of cases were culture positive
  - Among the 200 culture negative cases, 31% (61) cases were additionally diagnosed by Xpert Mtb Rif™.
  - None of the isolates was NTM

Biadglegne F, et al. PLoS One. 2013 Dec 9;8(12):e81918

121

Other tests

Chest Xray

- 5- 40% of patients may have pulmonary/ pleural abnormalities
  - Hilar/ mediastinal lymph nodes
  - Parenchymal lesions
  - Pleural effusion

TST positive in >70%

Ultrasonography

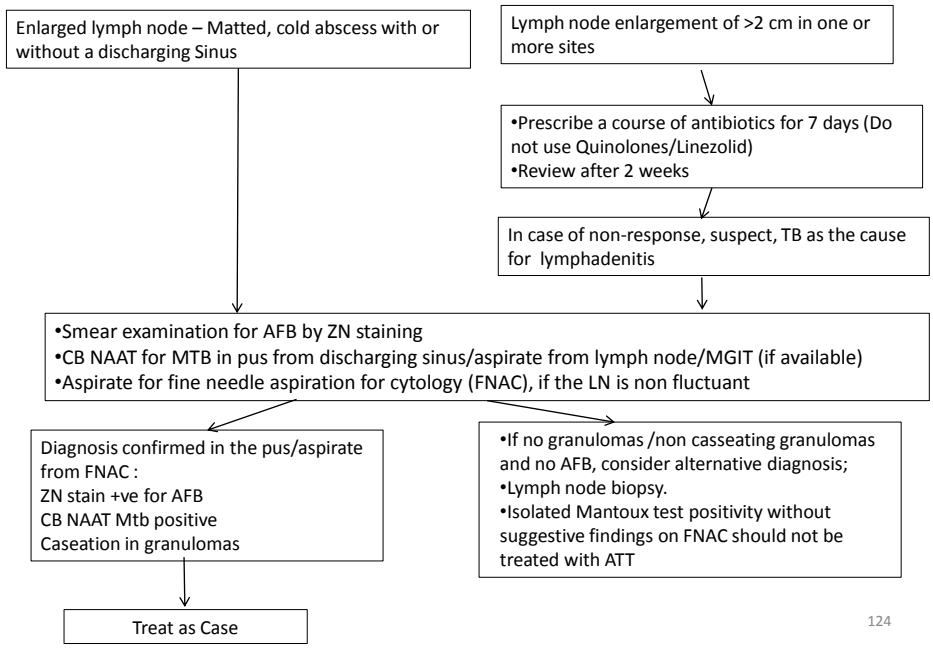
- Utility is in guiding for FNAC in non palpable or deep seated nodes
- Central hypoechogenecity where present is considered suggestive of TB

122

Expected response

- Resolution of systemic features
- Gradual decrease in size of lymph nodes
- Some children do not have any change in the size of the nodes, though systemic symptoms improve.
  - Ruling out alternative diagnosis id very important in this situation
- Enlargement of nodes while on ATT
  - Immune phenomenon: DTH (caseation, enlargement of nodes, AFB may be absent)
  - Drug resistant TB (generally associated with systemic manifestations: fever, weight loss, poor appetite, FNAC: AFB may be positive)

Algorithm for Lymph Node TB



MODULE 7

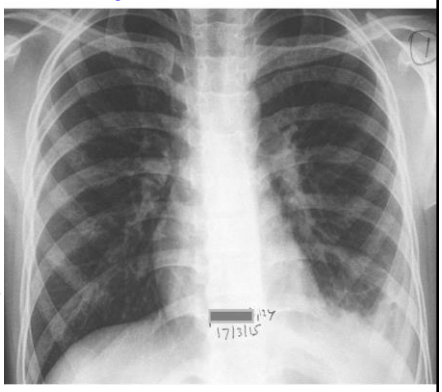
Pleural TB diagnostics

How does Pleural TB present and how do you diagnose it?

125

Case Summary

- 10 y boy
- Fever with chills } x 7 days
- Mild cough
- Antibiotics on OPD basis
- No h/o contact with TB Case
- Admitted on 17/3/15



Do you think this can be a TB Effusion?
Your comments

126

Investigations

- CBC -Hb 10.8, 7980 N68, L22
- ESR 85 mm in 1st hr.
- TST negative
- Pip +Tazo for 7 days

Can TB effusion present with high fever?

Does CBC help ?

Can ESR be of help ?

Does a negative TST rule out TB ?

(TB pleural effusion is hypersensitivity reaction)

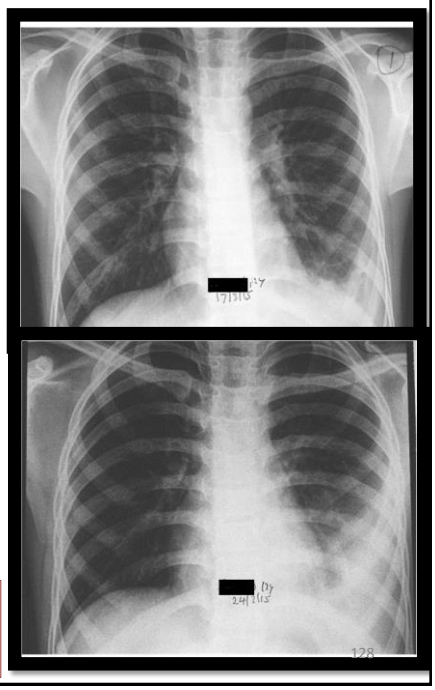
127

Follow up

- Fever persists
- Pl fluid aspirated
  - 870 cells, L 80
  - Protein 3.8 g/dl

- Pl fluid interpretation and diagnostic clue
- What is the role of ADA ?
- What else could have been done on the pleural fluid sample - Role of CB NAAT?
- Can GA/IS be of help ?
- Role of CT chest ?

About 28% - 40% of the children with PE, M tb positive on GA/ IS culture. Definite role for bacteriological studies of the respiratory specimens



128

Pathogenesis

Rupture of a sub-pleural TB focus or mediastinal LN

↓

The small number of bacilli in the pleural fluid produces a granulomatous reaction.

↓

Triggers an inflammatory response mediated by T cells (previously sensitized to the TB antigen)

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Diagnosis

Definitive:

- Smear or culture positive or CBNAAT for M TB from sputum, gastric aspirate, or pleural fluid
- Pleural biopsy
  - Pleural tissue histopathology compatible with TB (caseating granulomas with Langerhans giant cells, epithelioid cells, and lymphocytes)

Probable:

- Compatible clinical picture with positive TST & one of the following:
  - Lymphocytic pleural fluid (>50%),
  - Exudative fluid (protein >3 g/dl or
- In most circumstances diagnosis can be made by:
  - Long history, Non sick child, Xray showing effusion, effusion: straw coloured, exudative and lymphocytic pleocytosis, mantoux >10mm

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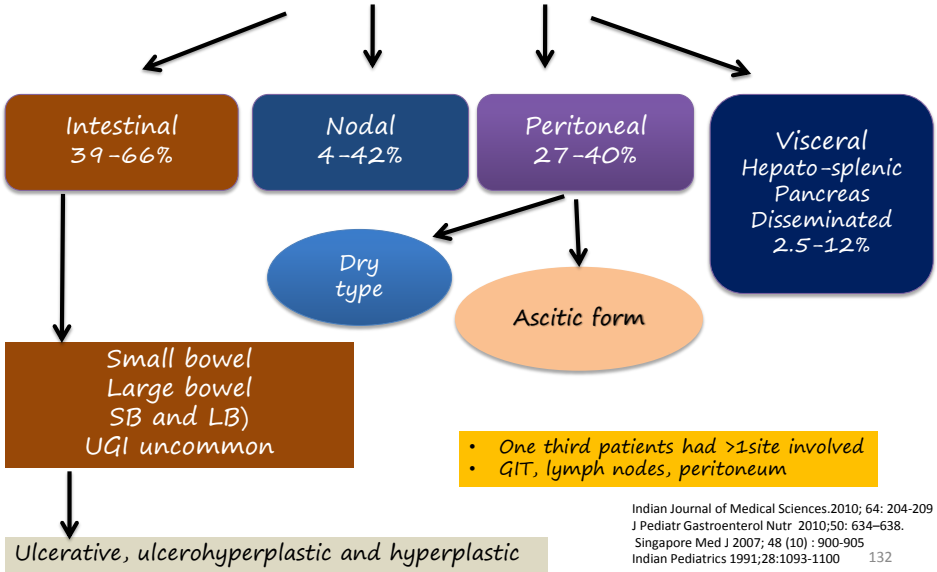
MODULE 8

Abdominal TB diagnostics

How does Abdominal TB present and how do you diagnose it?

131

Forms of Abdominal Tuberculosis



- One third patients had >1site involved
- GIT, lymph nodes, peritoneum

Indian Journal of Medical Sciences.2010; 64: 204-209
J Pediatr Gastroenterol Nutr 2010;50: 634–638.
Singapore Med J 2007; 48 (10) : 900-905
Indian Pediatrics 1991;28:1093-1100

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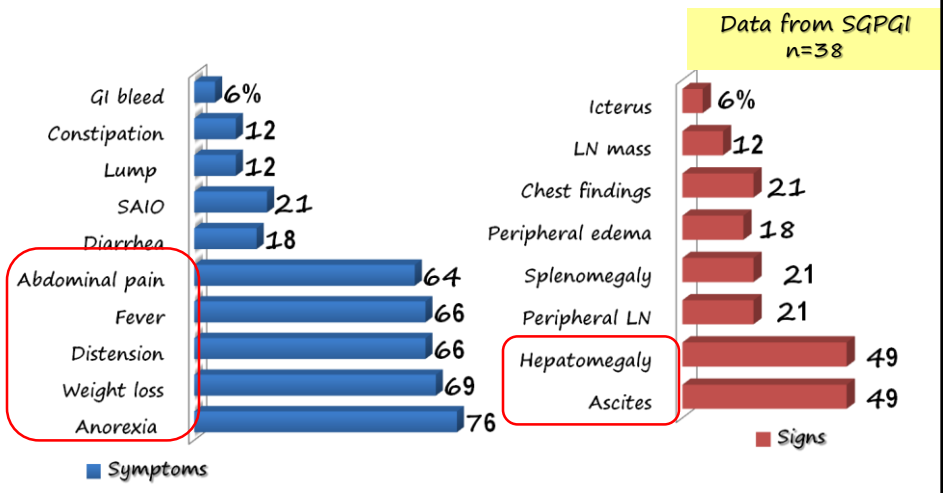
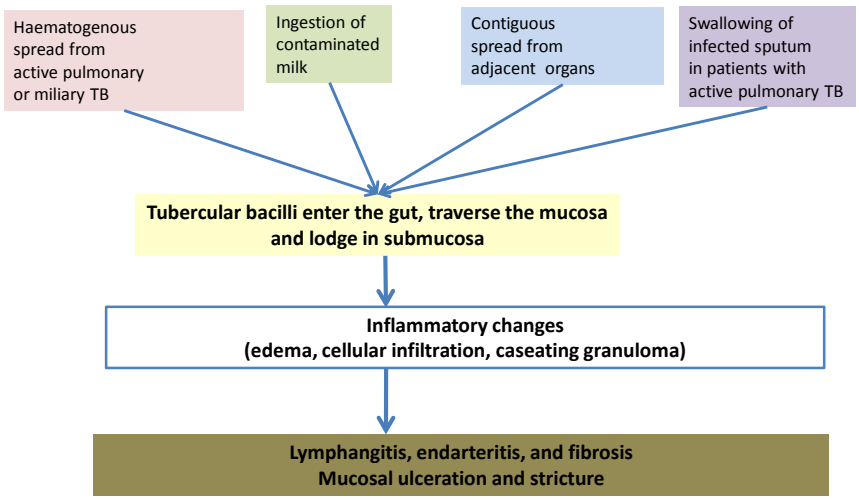
Clinical features



133

Pathogenesis



Am J Gastroenterol 1998;93:692– 696.

134

Case : 16yr boy

SGPGI

Weight loss +
Anorexia +

Wt-40kg (10th-25thcentile)
Ht-163 cm (50th-75th centile)
Mild Pallor + , BCG scar +
No lymphadenopathy
Systemic exam. normal

Hb:9.3, Plt 1.7 lakh/mm^3 , ESR: 21, **Alb: 2.9**
TST 24mm , X ray chest normal

USG: mesenteric multiple **lymph nodes (largest 2cm)**

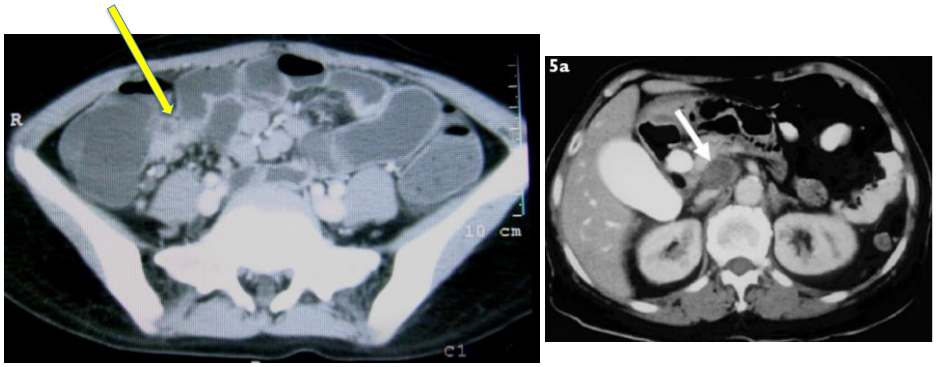
Pain abdomen and Non- bilious vomiting

Feb 2011 — June 2011

135

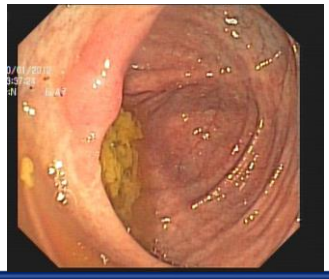
Case : 16yr boy

CT enteroclysis



Multiple lymph nodes with necrotic hypodense centre (right image) with thickening of IC valve and terminal ileum (left image)

136



Diagnosis
Abdominal Tuberculosis
(ileocaecal tuberculosis with mesenteric lymphadenoapthy)

- **Colonoscopy:**
- ✓ Nodularity in terminal ileum
- ✓ IC valve normal
- **Biopsy normal**

USG guided lymph node FNAC:
Epithelioid granuloma, ZN staining AFB +

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Case : 9 yr boy

Fever, anorexia, weight loss
Generalized abdominal distention with mild pain abdomen and partial relief after defecation

X 2 months

No h/o jaundice/edema/loose stools/blood in stools/vomiting/ No contact with Koch's

No pallor/icterus/clubbing/LAP, JVP normal
P/A: soft, mild distention, no organomegaly, ***ascites ++***
Other systems- NAD(chest/CNS/CVS)

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Investigations

Haemogram: Hb-10.7 MH, Plt-247, TLC-6000, ESR-63
LFT : S bilirubin-0.6, SGOT/PT-100/88, S alb 3.7, INR-1.2,
CXR- normal
Sputum AFB- negative twice

Ascitic fluid:
- Protein - 5.4 gm/dl
- Glucose - 67 mg/dl
- **TLC-500 (N-10%, L-90%)**
- **ADA – 51 u/L** **(NOT RECOMMENDED)**
- **SAAG- 0.9**
- Ascitic fluid AFB –negative, TB culture awaited
- Imp Exudative Ascites

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CT Enterography

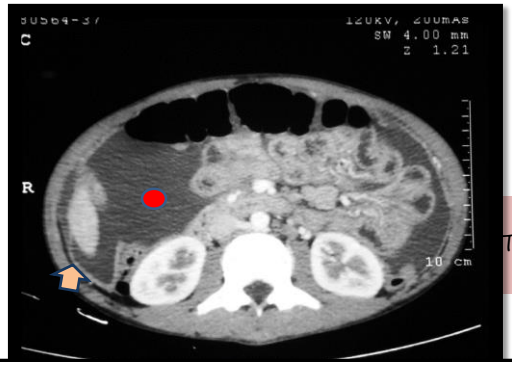
Moderate ascites (Red dot) with enhancement in visceral peritoneum (arrow head). Few internal septations seen

Thickened omentum (13mm),

Large and small bowel loops normal

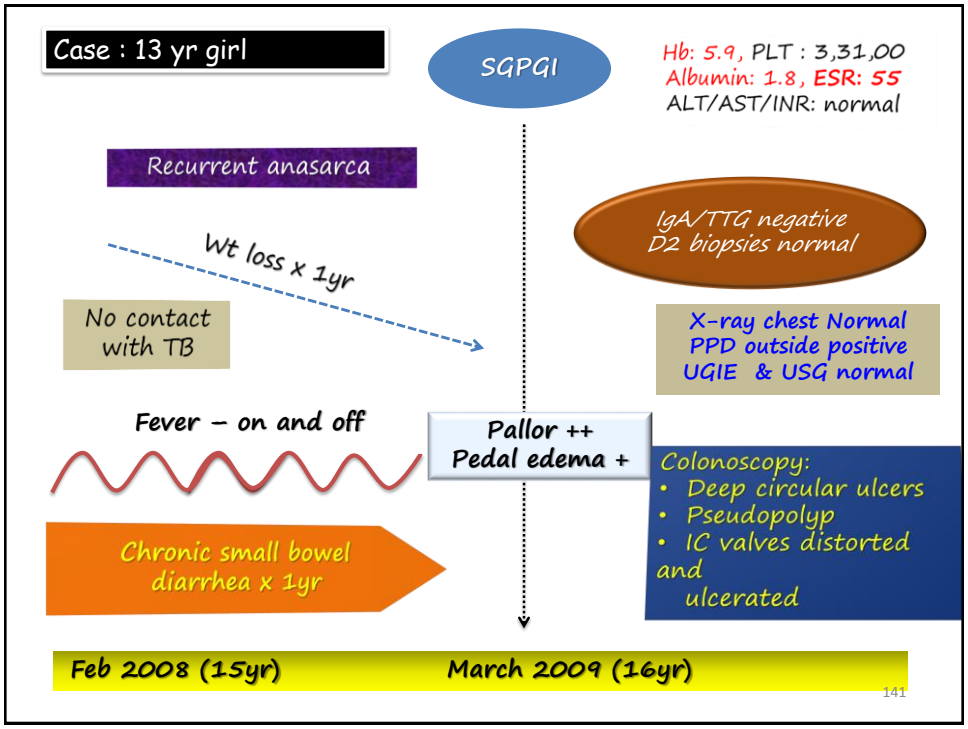
Multiple enlarged mesentric LN (size ~10mm)

Liver/spleen/pancreas/biliary tree, kidneys -normal



Diagnosis
Tubercular ascites
Started on ATT

140



Diagnosis ? Crohn's disease or Intestinal TB

Features	Patient	CD	Intestinal TB
Past h/o /family h/o TB	No	-	++ (~35%)
Symptom duration	12mo	Longer (~54mo)	Less longer (~23mo)
Chronic diarrhea	yes	++ (85%)	+(38%)
Blood in stools	no	++ (68%)	± (17%)
Peri-anal lesions	no	++ (30%)	± (7.5%)
Extra intestinal symptoms	no	++ (45%)	± (13%)
High fever (without abscesses)	yes	±	++
Partial Intestinal obstruction	no	+ (26%)	++ (55%)
Ascites	yes	Rare	Commoner,15%

AJG 2010; 105:642-51

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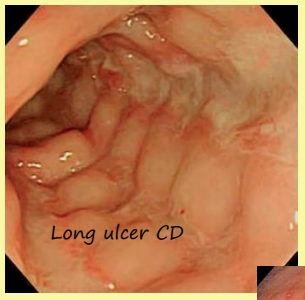
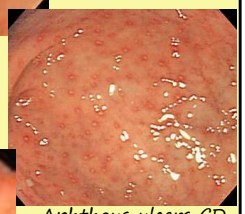
Crohn's disease or Intestinal tuberculosis

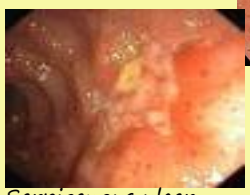


CD

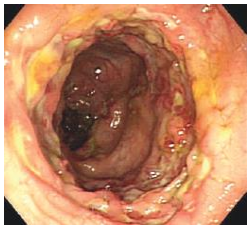
Long ulcer CD



Aphthous ulcers CD

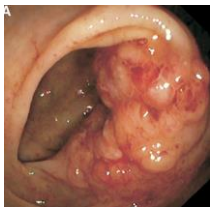


Serpigenous ulcer

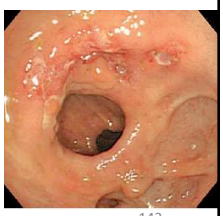


Transverse ulcers

ITB



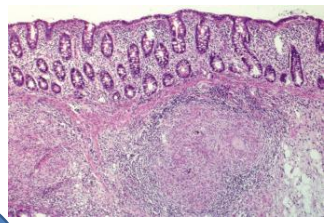
Ulcerohypertrophic
Mass in caecum

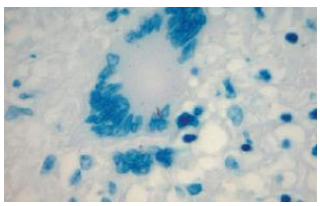


Patulous IC valve with ulcers

Intestinal TB or Crohn's ?

Colonic biopsies: Caseating granulomas
AFB+





ATT for 6mo (2HRZE +4HR)
Symptoms resolved
Colonoscopy: improvement
Wt gain: 5kg/yr Ht gain:7cm/yr

Radiological studies in abdominal TB

Plain Xrays: Not diagnostic

- **may show :**
  - Enteroliths
  - Perforation
  - Features of intestinal obstruction

Ultrasonography (USG) initial modality of choice and may pick up

- Lymphadenopathy
- Peritoneal thickening
- Omental thickening and bowel wall thickening
- Ascites

Contrast enhanced CT and CT enterography

- provide adequate cross sectional imaging in depicting various forms of abdominal TB

Barium studies

- Gold standard in diagnosing strictures, fistulae, erosions, *etc.*

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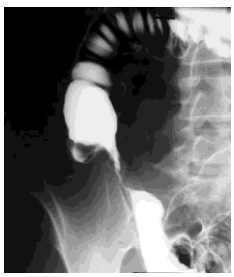
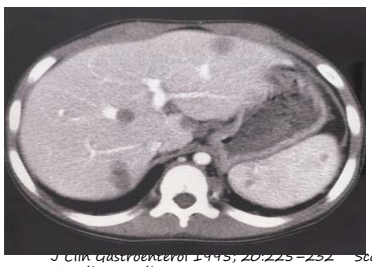
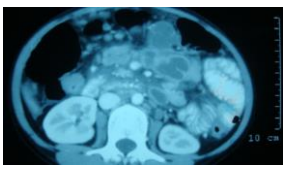
Abdominal TB: imaging

CT enterography	Ileo-caecal area commonest Uniform and concentric bowel thickening Contracted, pulled up caecum, Ileocaecal angle is distorted and often obtuse Strictures short (usually <3 cm)
USG/ CECT	Abdominal LN with central necrosis, conglomerate, peripheral enhancement
	Mesentery thickening>15mm
	Caked omentum, multiple SOL liver/ spleen, loculated ascites

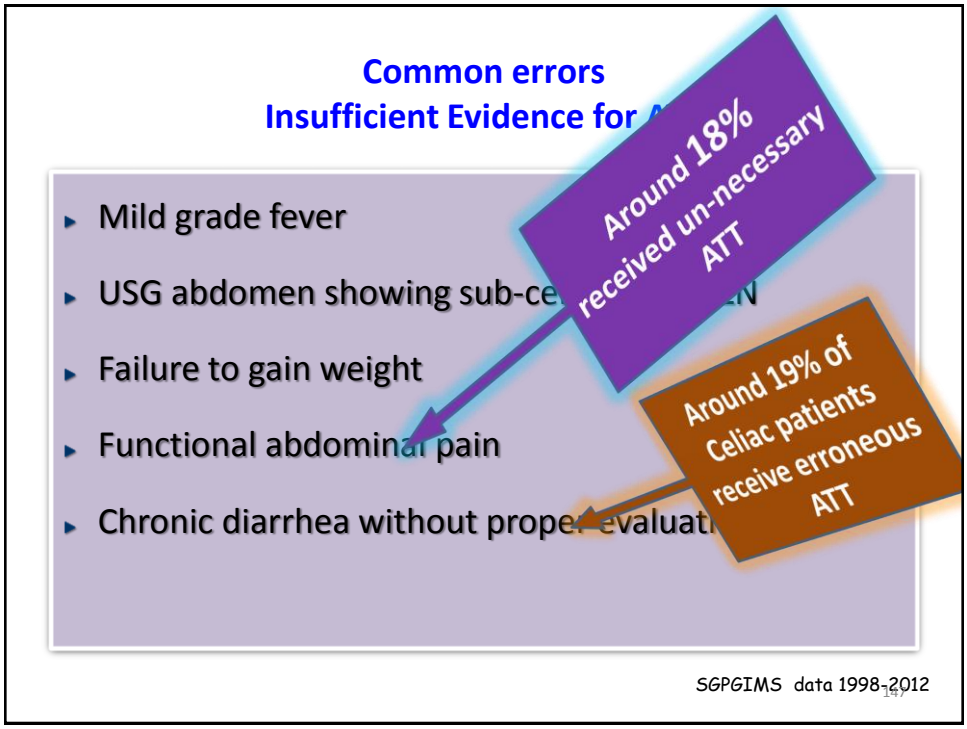


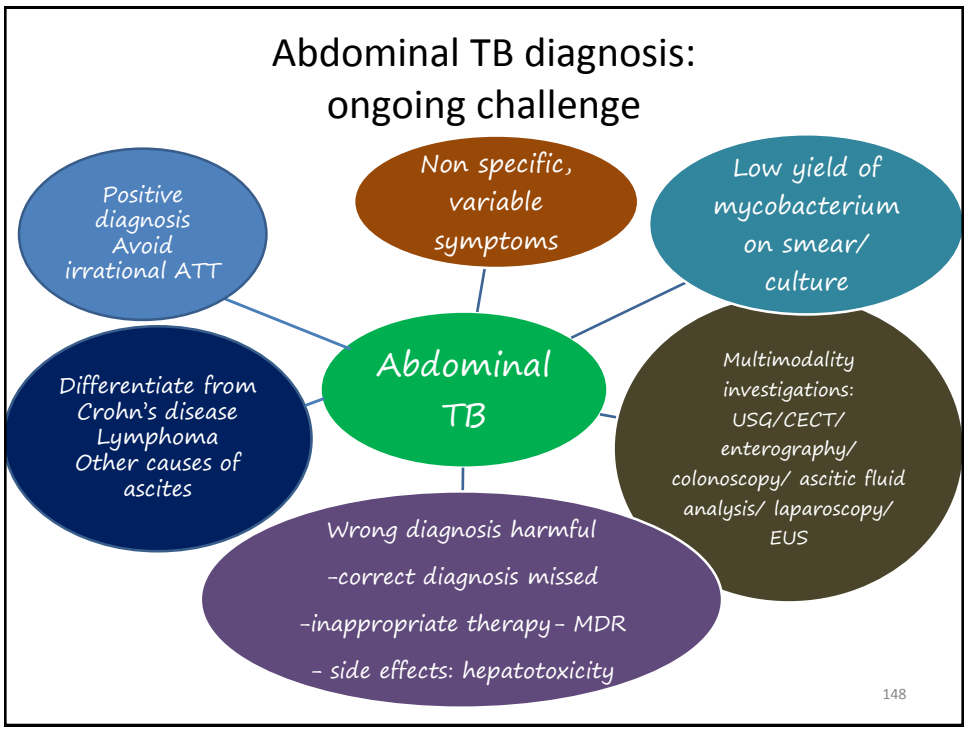




J Clin Gastroenterol 1993; 20:225–232 Scand J Gastroenterol 2008; 43:1224–1231 / Indian Peadiatr1993; 30: 1149-53

146


Common errors
Insufficient Evidence for
Mild grade fever
USG abdomen showing sub-ce
Failure to gain weight
Functional abdomin pain
Chronic diarrhea without prope evaluat
Around 18% received un-necessary ATT
Around 19% of Celiac patients receive erroneous ATT
SGPGIMS data 1998-2012
147


Abdominal TB diagnosis: ongoing challenge
Positive diagnosis Avoid irrational ATT
Non specific, variable symptoms
Low yield of mycobacterium on smear/ culture
Differentiate from Crohn's disease Lymphoma Other causes of ascites
Abdominal TB
Multimodality investigations: USG/CECT/ enterography/ colonoscopy/ ascitic fluid analysis/ laparoscopy/ EUS
Wrong diagnosis harmful
-correct diagnosis missed
-inappropriate therapy- MDR
- side effects: hepatotoxicity
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MODULE 9

Neuro TB diagnostics

How does Abdominal TB present and how do you diagnose it?

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11 years old, Girl

10 days back

Headache x 10day
mild off-on

Vomiting x10days
1-2/day

Fever x10days
mild, undocumented, off-on

7 days back

GTCS
Short lasting **single** episode

2 days back

Altered sensorium x2 day
Initially mild
Past few hours
Not recognizing parents
Not indicating bladder bowel
Not asking **feeds**

No h/o of Cough, Ear discharge, Pyoderma, Rash
No h/s/o Cr Nerve or Focal neurological deficits,
No h/o Koch contact, Weight loss,
Has received some injectables, but nature not known.

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Clinical Examination

General examination	CNS examination
Underweight child	E1 V2 M4
BMI 12.9 (< 5 th centile)	Neck rigidity +
Head circumference Normal	Fundus B/L mild disc congestion
Afebrile, Normotensive	Rest Cranial Nerve Normal
	Tone generalized increased
	DTR brisk
	Plantars B/L Upgoing
	Rest systemic examination NAD

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Summary

Insidious onset Meningoencephalitis with seizures with raised ICT

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Investigations

- Hb 12.7 gm%, TLC 11500, DLC N70% L30% PLT 2.66 Lac.
- KFT/LFT/Ca/SE – WNL
- CSF
  - Cytology 95 cells (100% Poly)
  - Proteins 141 mg/dl Sugar 48 mg/dl (Corresponding blood sugar 120mg/dl)
  - Gram stain/ Pyogenic culture – negative
  - AFB stain negative, Genexpert could not be sent
- TST Negative
- HIV- NON REACTIVE
- Gastric Aspirate For AFB – Smear Negative (Twice)
- Contact survey – Normal

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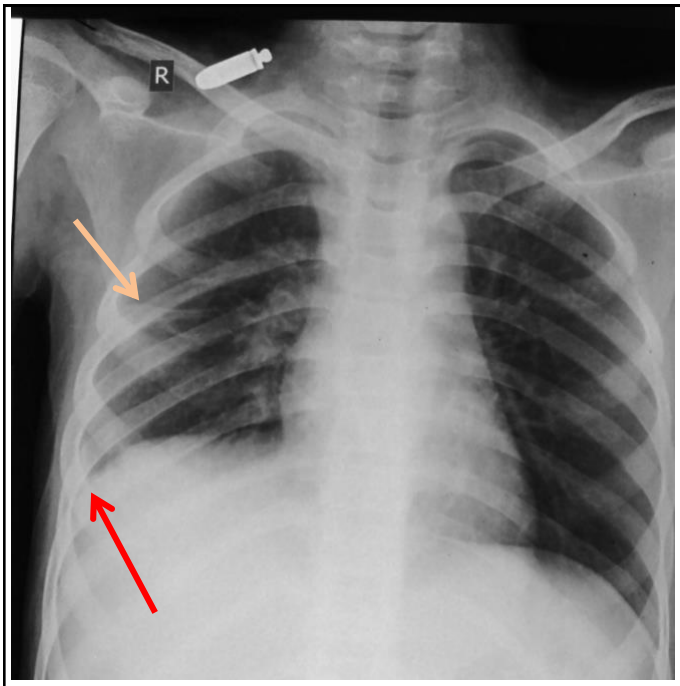

- **Present CXR :**

  Right side Pleural effusion (red arrow)

  Fluid in Rt horizontal fissure

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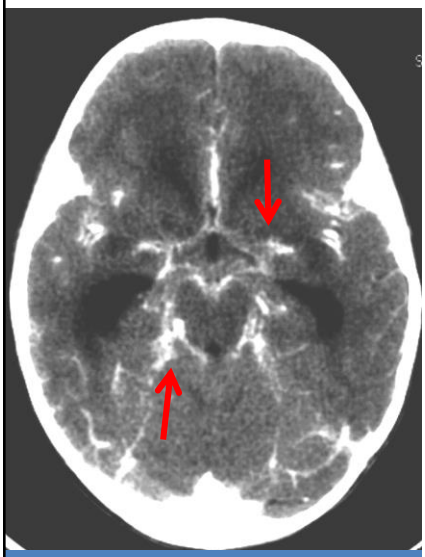
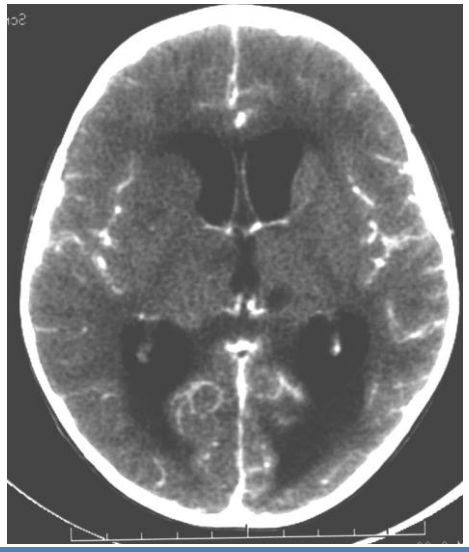
CT- TBM



Thick Basal Exudates



Communicating Hydrocephalus

Summary

Insidious onset meningo-encephalitis with hydrocephalus with Right sided pleural effusion

What do you think is the etiological diagnosis?

- TB Meningitis (TBM)
- Pyogenic meningitis
- Aseptic meningitis
- Partially treated pyogenic meningitis (PTPM)

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Differential diagnosis

Patient findings / Differentials	Insidious onset prolonged symptoms	Raised ICT	Asymptomatic Pleural effusion	Basal exudate/ Hydrocephalus	CSF 95 cells	CSF 100% Poly	Sugar 48 mg/dl (<50%)
Pyogenic Meningitis	X	√	X	X	X (100-10000)	√	X (< 40)
Aseptic Meningitis	X	X	±	X	√ (Rarely >1000)	X	X (normal)
PTPM							
Brain abscess	√	√	X	X (ruled out on imaging)	√ (5-200)	X	X (normal)
TBM	√	√	√	√	√ (10-500)	X Occ in very early ds	√ (<50)

Pleural tap was dry and
GA for CBNAAT was Mtb Positive

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Lesson learnt- Every effort should be made to look for evidence at extra-cranial sites

- CXR
  - If CXR suggestive GA/Sputum for AFB/BAL
- USG abdomen
- Peripheral lymphnodes
- Liver
- Bone marrow
- Urine
- Ascitic fluid

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TBM

- Most commonly presents 6 months to 4 years of age
- Most severe form of tuberculosis in children
- Uniformly leads to mortality if not treated timely and effectively

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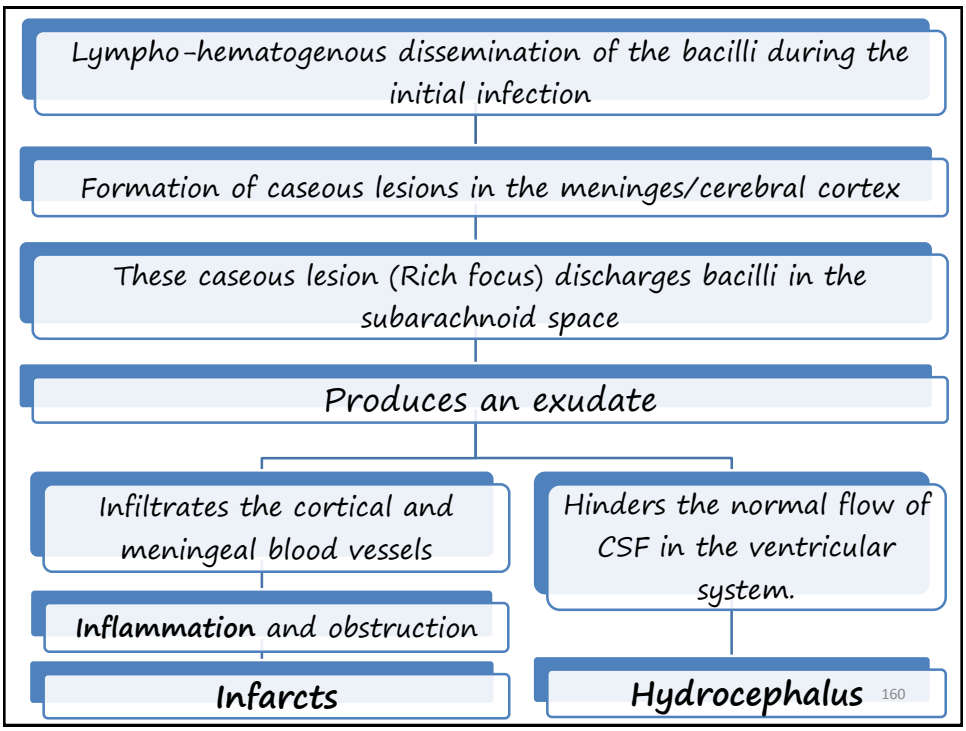

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Divided in three clinical stages

- Usually **progresses over several weeks from stage one to three**
- Infants and young children may progress rapidly over days

The stage at which treatment begins **predict the prognosis**: progressively worsening from stage 1 to stage 3

Stage 1

- Typically lasts 1 to 2 weeks.
- Nonspecific symptoms.
- Fever, headache, irritability/ drowsiness, malaise, anorexia, inadequate weight gain or weight loss, stagnation or regression of development milestones

Stage 2

- Begins abruptly.
- Characterized by increased intracranial pressure, meningeal irritability, and vasculitis without marked changes in sensorium.
- Clinical constellation lethargy, nuchal rigidity, Kernig and Brudzinski signs, seizures, hypertonia, vomiting, cranial nerve palsies with basal meningitis and other focal neurological deficits

Stage 3

- Coma, hemiplegia or paraplegia, decerebrate posturing, deterioration in vital signs and finally death

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Investigations

CSF ANALYSIS

- Cytology
- Sugar and Protein
- Smear for AFB
- CSF culture and sensitivity
- CB-NAAT
- **ADA (Not recommended) XXXXX**

INVESTIGATIONS FOR TB ELSEWHERE

- X ray chest/ CT Chest
- TST
- Sputum/GA for AFB
- USG/CT abdomen

BRAIN IMAGING

- CECT/Contrast MRI Brain

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Investigations

CSF EXAM- must

- **Gross** Mostly Clear
- **Cytology** Leukocyte Count : 10 to 500 cells/mm^3 (occasionally higher)
- Majority lymphocytes (polymorphs in early illness)
- **Biochemistry**
  - Glucose usually < 40mg/dl (CSF glucose/blood glucose < 0.5)
  - Protein Elevated > 100 mg/dl
  - ADA - not recommended

TST may be non reactive in 50 %

CXR normal in 20-50% patients

- Nevertheless every effort should be made to look for other evidences since many a time it is these extra-cranial lesions (e.g. pulmonary, peripheral lymph node) that clinch the diagnosis of TBM

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Neuroimaging

CECT head is the initial modality

- Can have any/ many of these
  - Basal meningeal enhancement
  - Hydrocephalus
  - Tuberculoma(s)
  - Infarcts in different areas, especially the basal ganglia
  - Pre-contrast basal hyperdensity (on CECT imaging)
- May even be normal !

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Thwaites G et al. *J Infect 2009; 59: 167–87*

Neuroimaging

Contrast MRI has higher sensitivity than CECT for the detection of abnormalities such as meningeal enhancement, infarcts, and tuberculomas especially of lesions involving the brainstem

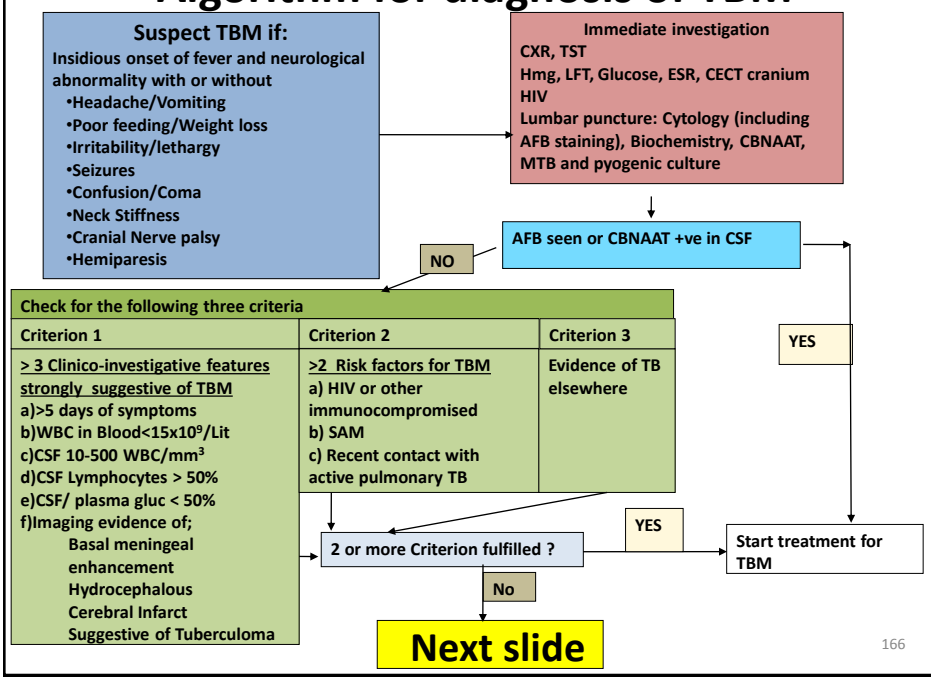
Usually preferred when CT is inconclusive and suspicion is high

Cryptococcal meningitis, CMV encephalitis, toxoplasmosis, sarcoidosis, meningeal metastases, and lymphoma (more common with HIV) can result in similar radiological findings

165

Thwaites G et al. *J Infect 2009; 59: 167–87*

Algorithm for diagnosis of TBM



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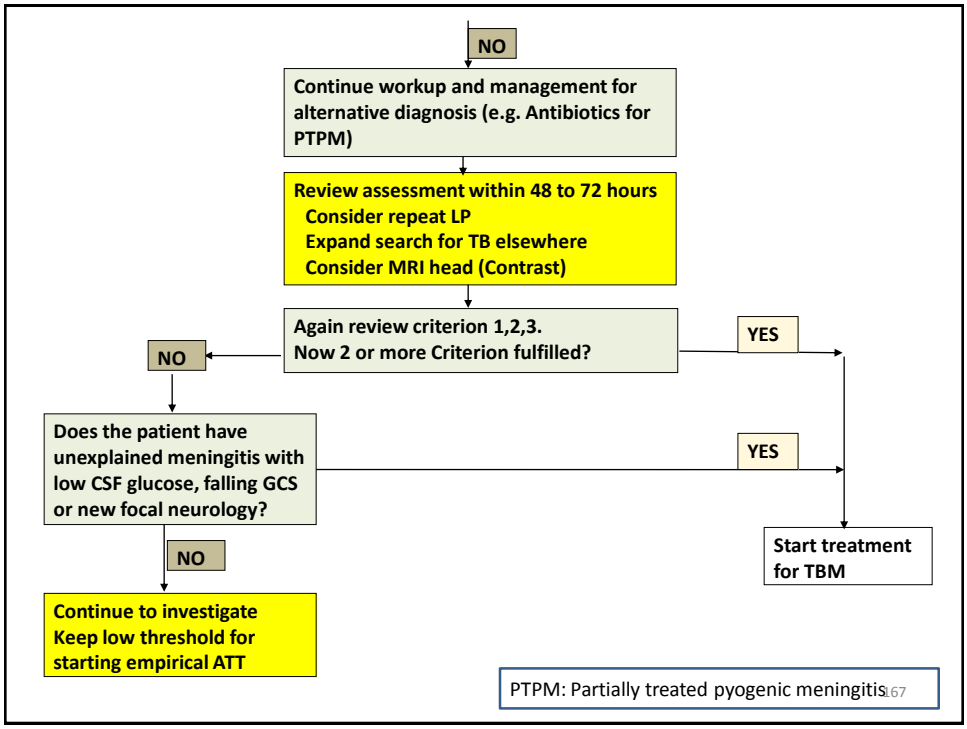
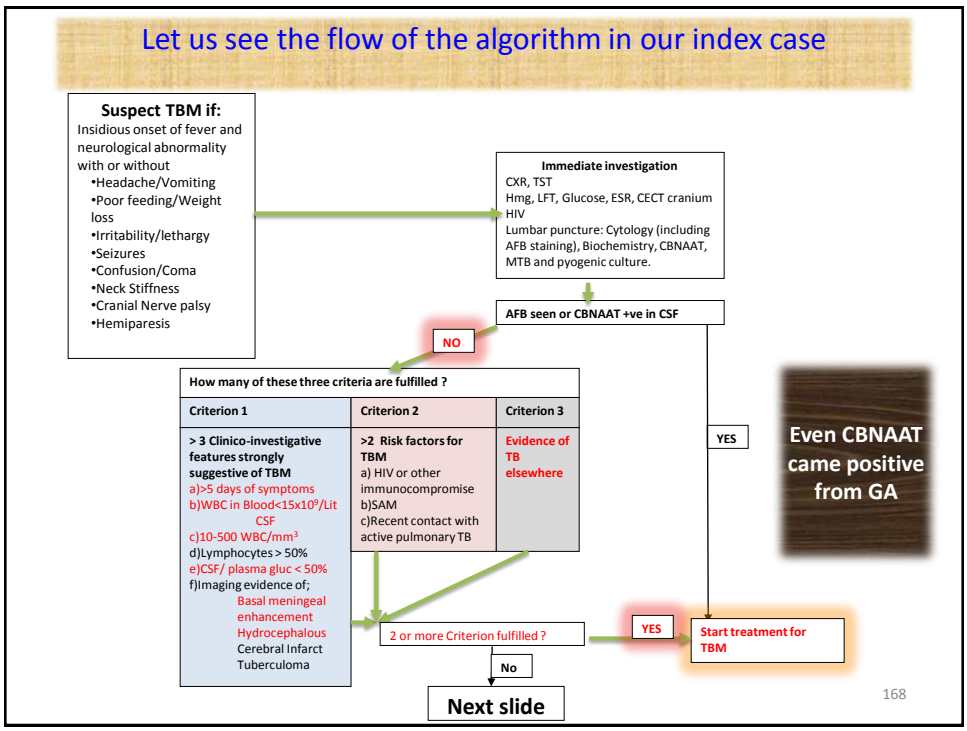

NO
Continue workup and management for alternative diagnosis (e.g. Antibiotics for PTPM)
Review assessment within 48 to 72 hours
Consider repeat LP
Expand search for TB elsewhere
Consider MRI head (Contrast)
Again review criterion 1,2,3.
Now 2 or more Criterion fulfilled?
YES
NO
Does the patient have unexplained meningitis with low CSF glucose, falling GCS or new focal neurology?
YES
NO
Start treatment for TBM
Continue to investigate
Keep low threshold for starting empirical ATT
PTPM: Partially treated pyogenic meningitis
167


Let us see the flow of the algorithm in our index case
Suspect TBM if:
Insidious onset of fever and neurological abnormality with or without
•Headache/Vomiting
•Poor feeding/Weight loss
•Irritability/lethargy
•Seizures
•Confusion/Coma
•Neck Stiffness
•Cranial Nerve palsy
•Hemiparesis
Immediate investigation
CXR, TST
Hmg, LFT, Glucose, ESR, CECT cranium
HIV
Lumbar puncture: Cytology (including AFB staining), Biochemistry, CBNAAT, MTB and pyogenic culture.
AFB seen or CBNAAT +ve in CSF
NO
YES
How many of these three criteria are fulfilled ?
Criterion 1
> 3 Clinico-investigative features strongly suggestive of TBM
a)>5 days of symptoms
b)WBC in Blood<15x10⁹/Lit
CSF
c)10-500 WBC/mm³
d)Lymphocytes > 50%
e)CSF/ plasma gluc < 50%
f)Imaging evidence of;
Basal meningeal enhancement
Hydrocephalous
Cerebral Infarct
Tuberculoma
Criterion 2
>2 Risk factors for TBM
a) HIV or other immunocompromise
b)SAM
c)Recent contact with active pulmonary TB
Criterion 3
Evidence of TB elsewhere
Even CBNAAT came positive from GA
2 or more Criterion fulfilled ?
YES
Start treatment for TBM
No
Next slide
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Treatment

- **ATT x 12 months {appropriate based on new (2HRZE+10HRE) or old case(2HRZES+1HRZE+9HRE)}**
- **Steroids**
  - Prednisolone 2 mg/kg/d (or equivalent dose dexamethasone: 0.6 mg/kg/day))in divided doses, for at least 4 weeks and then tapered over next 4 weeks
- **Decongestive therapy**
  - As needed
  - Mannitol, Acetazolamide, Glycerol
- **Antiepileptics**
  - As needed
- **Surgical intervention, if raised ICT not controlled by medical management**
  - Shunt / EVD/ Ventricular tap

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Hydrocephalus

Common complication of TBM

Timely recognition of Intracranial hypertension and shunt placement markedly reduces morbidity and mortality

Substantial benefits from ventricular drainage in children with tuberculous meningitis associated with hydrocephalus even in TBM stage III

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CNS tuberculosis other than TBM

Tuberculoma

- A manifestation of CNS tuberculosis
- Presents as intracranial space occupying lesion (ICSOL)

• Location • Size • Peri-lesional edema	predicate the manifestations →	• Seizures • Headache • Neurological focal deficits

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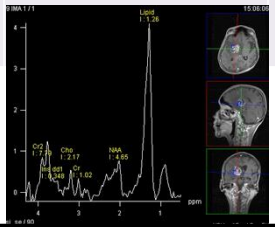
	Parameters	Tuberculoma	NCC
CECT	Appearance	>2 cm, irregular thick outline, marked perilesional edema	≤ 2cm, regular, thin, rounded outline with variable edema,
	Location	Infratentorial or supratentorial	Predominantly supratentorial
	Midline shift	More likely	Less likely
Contrast MRI	Appearance	T2 - usually hypointense core	usually T2 hyperintense core, eccentric Dot, scolex best seen on FLAIR or DWI images
	MRS	Lipid peak present	Lipid peak absent
	T2 relaxation time	Shorter (83-290 ms)	Longer (305-1365 ms)



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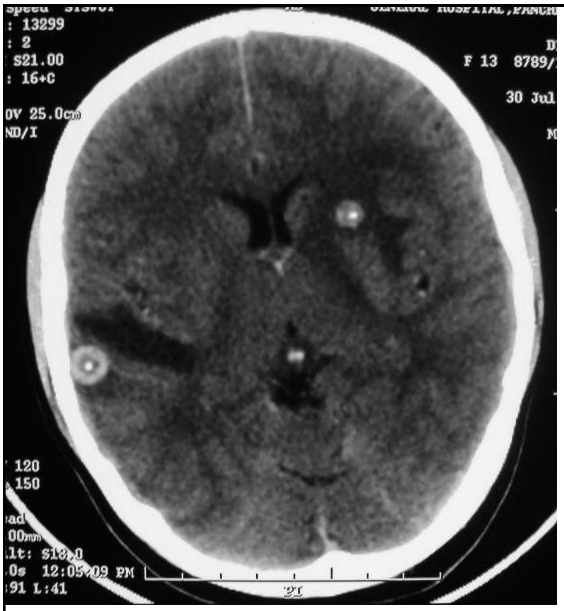

CECT cranium

- Small size
- Smooth outer margin
- Central calcification

Likely diagnosis ?

Neurocysticercosis

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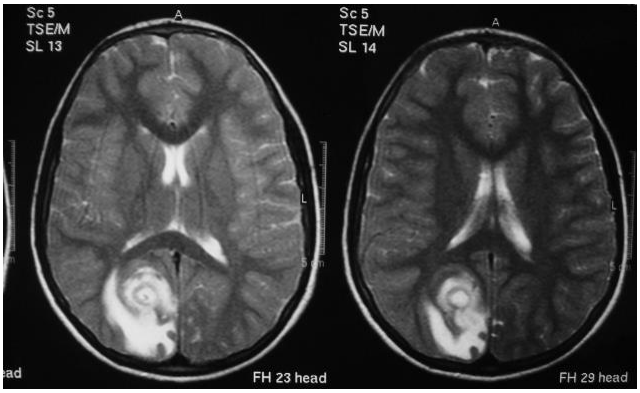
MRI features -NCC vs Tuberculoma



NCC:

- *T2 Axial image at the level of the basal ganglia shows small cystic lesion in the right medial occipital lobe, with thin walls, hyperintense inside, with eccentric dot suggestive of scolex.*
- *Also note the perilesional edema*
- *(Findings in favour of NCC: location, size, intralesional T2 hyperintensity, rounded regular thin margins)*

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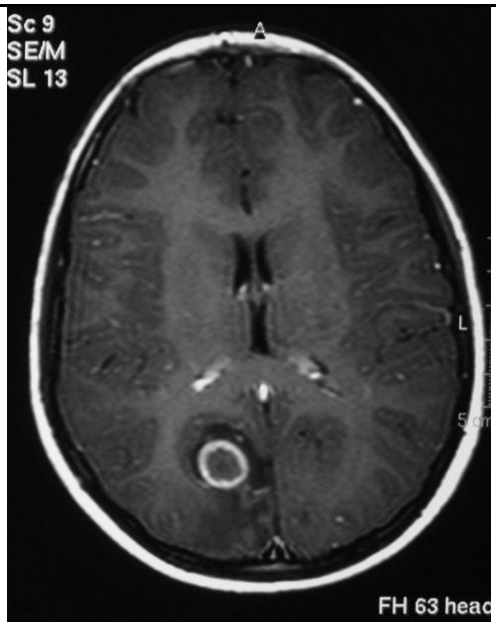
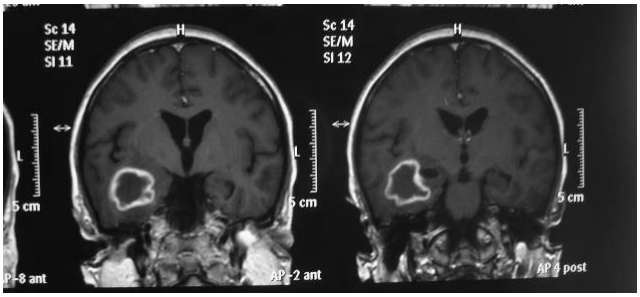


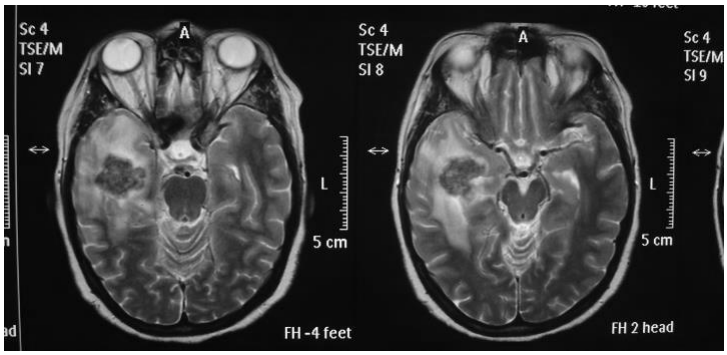
Same patient as previous image: contrast enhanced T1 image showing ring enhancing lesion in the right medial occipital lobe

175



Tuberculoma: contrast enhanced coronal T1 weighted image showing large enhancing lesion with irregular margins in the right temporal lobe

176



Same patient as previous slide:

- T2 weighted axial MRI images at the level of the midbrain showing large lesion in right temporal lobe with irregular margins and intralesional T2 hypointensity.
- Note the presence of perilesional edema

- Findings favoring tuberculoma: Size, irregular margins, T2 hypointensity, perilesional edema

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MODULE 10

Bone and Joint TB diagnostics

How does Bone and Joint TB present and how do you diagnose it?

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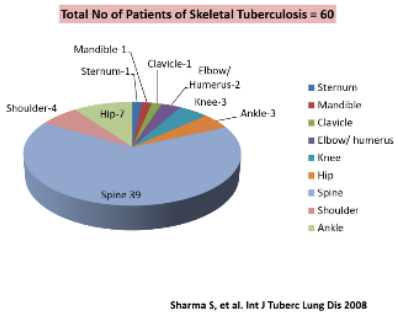
Presentation

Roughly accounts for 5-15% of all EPTB and 2-5% of all TB in children and adults

Common presentations

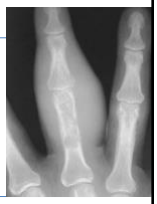
- Potts spine (50% of osteoarticular TB)
- Dactylitis
- Arthritis (as extension from the metaphysitis)
- Osteomyelitis
- Uncommon: Reactive arthritis (Poncets), tenosynovitis and bursitis



Sharma S, et al. Int J Tuberc Lung Dis 2008

Dactylitis (spina ventosa)

- Tuberculous osteietis , the dactylitis form, often affects children
- multiple or consecutive bones can be involved



Clinical presentation

- short tubular bones of the hands and feet in children affected; typically the proximal phalanx of the index/middle fingers and middle/ring finger metacarpals are affected.
- often follows a benign course without pyrexia and acute inflammatory signs

X-ray features:

- involved bone shows a diaphyseal expansile lesion
- a periosteal reaction is uncommon
- healing is by sclerosis.

Clinical features of Potts spine

Back pain (insidious onset)

- Most common site thoracic, followed by lumbar/ cervical
- Pain may be localized over the involved vertebra or could be referred due to root pains

Local tenderness or deformity

Fever and constitutional symptoms in only 1/3

Neurologic complications

- Paraparesis (present in 20-50%), can be early or late
- Cauda equina syndrome
- 15% of patients have a paradoxical response with increased neurologic deficit following therapy
- Risk of kyphosis later in life; especially in children below 7-10 years

Diagnosis- Radiology

Plain X ray

- Abnormal only when 30-50% of bone loss has occurred
- Shows end plate erosion, decrease height of vertebra, collapse and narrowing of discal space and paravertebral soft tissue shadow

MRI is the most sensitive (nearly 100%)

- Marrow edema
- Destruction of adjacent vertebral bodies and opposing end plates
- Destruction of intervening disc
- Occurrence of prevertebral, paravertebral, and epidural abscesses

Treatment

Chemotherapy

- Current guidelines recommend 12 mths therapy 2 HRZE and 10 HRE
  - Available data suggests that 6 months therapy is perhaps as effective as longer treatment

Surgical

- Definitely in those with progressive neurologic deficit
- Persistent pain, spinal instability
- High risk of future kyphosis:
  - age less than 7-10 years,
  - Two or more vertebral body collapse,
  - existing kyphosis of 30 degree,

MODULE 11

TREATMENT OF TB

How do you treat TB?

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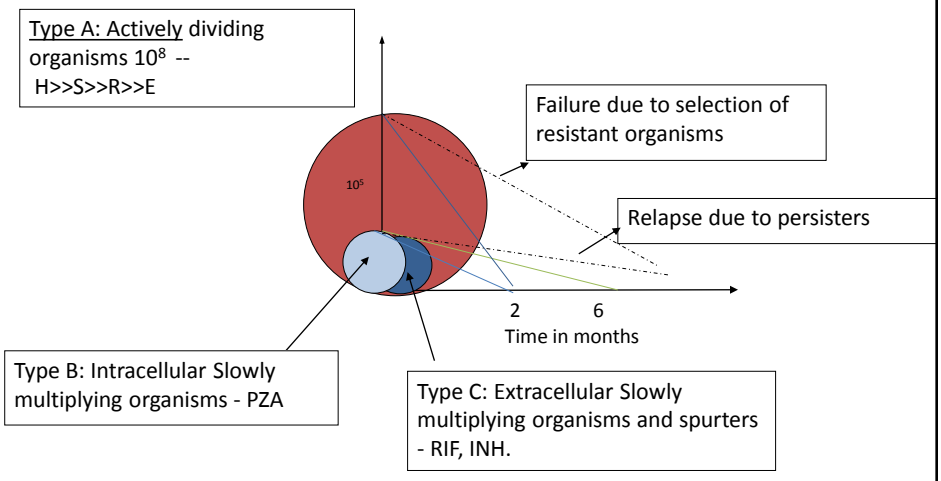
Basis of Chemotherapy of Tuberculosis



- The three type of the populations are in constant dynamic relationship.
- Different drugs are effective in different metabolic populations, requiring a combination therapy for treatment. (Modified from Grosset J, Clinics in Chest Medicine 1980;1:231-41)

The number of bacilli may be different in different lesions

- PPC, $10^4 – 10^5$,
- PPD 10^6, Cavity 10^9
- Chances of primary drug resistance
  - INH 10^{-6}
  - RIF 10^{-8}
  - INH and RIF 10^{-14}

Childhood TB is paucibacillary disease, chances of primary drug resistance are less

Bacillary characterisitics and Treatment Plan

TB Treatment needs multidrug therapy which can be biphasic

Initial part when more bugs, use more drugs

Drugs like PZA which work only in acidic environment useful only in IP when there is inflammation and not later part of the disease

Possible to treat TB with intermittent therapy- due to lag period effect (bacilli multiplication stops for hrs to days after exposure to drugs; it is dose dependent for some drugs.

Shall need higher doses

- Field studies suggest that:
  - The most efficacious intermittent therapy is thrice a week regimen
  - Intermittent therapy is not safe without observation
  - there is little margin for missing any doses.

Phases of Treatment

Intensive Phase (IP)	Continuation Phase (CP)
Early rapid Killing of Mtb, prevents deterioration and death	Eliminates most residual bacilli
Reduced infectivity	Reduces failures and relapses
Sputum conversion in 80-90%	Small number of bacilli left: fewer drugs are required
Addition of Z reduces duration to 6 months due to its sterilizing effect	In presence of background resistant to the companion drugs; more drugs needed to prevent amplification of drug resistance
Addition of E is useful if initial drug resistance to INH is high	

Rationale of DOTS

Ensures treatment for entire course

- Right drugs
- Right doses
- Right intervals
- Complete course

} Standardized drug regimens, Reduced emergence of Drug resistance

Ensures

- Adherence
- Completion of treatment

The pitfalls & errors in prescription and completion of ATT in India were too many and too hazardous to continue with the practice of unregulated treatment

IAP -RNTCP guideline 2012

Category of treatment	Type of patient	Regimens
New Cases (erstwhile category I and III*)	New sputum smear positive New sputum smear negative New extra-pulmonary	2HRZE+ 4HR
Re treatment Cases (erstwhile category II**)	Sputum smear positive relapse Sputum smear positive failure Sputum smear positive- treatment after default Others	2HRZES+ 1 HRZE+ 5HRE

*New categories includes former Categories I & III
**Previously treated is former Category II

TB Meningitis

Streptomycin can be safely replaced by Ethambutol in intensive phase

- Current evidence favoring safety and efficacy of Ethambutol,
- Lack of any value addition in efficacy using Streptomycin over Ethambutol
- Need to avoid problems of injection based treatment (lack of adequate muscle mass in malnourished, risks of unsafe Injections, need for a trained personnel, unpleasantness of the treatment).

Duration of treatment - 12 months

Seriously ill admitted

- For serious ill admitted children or those with severe disseminated disease/neurotuberculosis, likelihood of vomiting or non-tolerance of oral drugs is high in initial phase.
- Would be given ***daily supervised therapy during their stay in the Hospital using*** daily drug dosages.
- After discharge continue thrice weekly DOTS
- The mechanism to make the necessary drugs available would be developed by RNTCP.

WHO Guidance 2014

Children with TB living in settings with high HIV prevalence (or with confirmed HIV infection) should not be treated with intermittent regimens (that is, 2x-weekly or 3x-weekly doses)

During continuation phase, in settings with well-established DOTS, 3x-weekly regimens can be considered for children known HIV-uninfected

DAILY OBSERVED THERAPY is recommended for all cases

WHO THE STOP TB DEPARTMENT

Effect of Duration and Intermittency of Rifampin on Tuberculosis Treatment Outcomes: A Systematic Review and Meta-Analysis

Dick Menzies[1]*, Andrea Benedetti[1], Anita Paydar[1], Ian Martin[1], S... ndrew

In presence of pretreatment isoniazid resistance, three times weekly dosing during IP associated with significantly higher risks of failure and ADR.

Table 9. Adjusted incidence rate ratios ... egression)

Factor	... Resistance[a] IRR (95% CI)		
Initial drug resistance[d]			
DST not done/reported		3.0 (1.6 to 4.9)	N/A
Pan-sensitive strain	... (reference)	1.0 (reference)	1.0 (reference)
Isoniazid resistant	10.9 (5.9 to 20)	1.8 (1.2 to 2.6)	5.1 (2.3 to 11.0)
Streptomycin resistant	3.9 (1.4 to 11.0)	1.4 (0.9 to 2.2)	4.1 (1.6 to 10.0)
Poly-drug resistant (PDR)	33 (16 to 62)	1.8 (1.1 to 2.9)	10.0 (4.5 to 22.1)
Overall significance (*p* value)[c]	(<0.0001)	(<0.0001)	(<0.0001)

Effect of Duration and Intermittency of Rifampin on Tuberculosis Treatment Outcomes: A Systematic Review and Meta-Analysis Dick Menzies et al PLOS

INH mono-resistance- impact and solutions

Systematic review

- pooled results of 33 trials, nearly 2,000 patients with isoniazid mono-resistance
- on various regimens, some receiving their first treatment for tuberculosis, some being re-treated

Participants with INH drug-resistant bacteria, failure rates ranged from 9% to 45%

Lower relapse, failure, and acquired drug resistance rates were seen with

- longer duration of rifampicin treatment,
- daily therapy early in the treatment, and
- regimens that included a greater number of drugs to which the M. tuberculosis carried by the patient were sensitive.

Menzies D, Benedetti A, Paydar A, Royce S, Pai M, et al. (2009) Standardized Treatment of Active Tuberculosis in Patients with Previous Treatment and/or with Mono-resistance to Isoniazid: A Systematic Review and Meta-analysis. PLoS Med 6(9): e1000150

IAP RNTCP guidelines 2015

Category of treatment	Type of patient	Regimens
New (Old category I)*	New bacteriologically confirmed TB New Clinically diagnosed TB New extra-pulmonary	2HRZE+ 4HRE
Re treatment (old category II)**	Bacteriologically confirmed recurrent Microbiological positive failure Microbiological positive - treatment after default Others	2HRZES+ 1HRZE+ 5HRE

*New categories includes former Categories I & III, May be given intermittently where ever good supervision is feasible though daily supervised is the most favored option
**Re-treatment is former Category II
Others include patients who are Sputum Smear-Negative or who have Extra-pulmonary disease and have recurrence.

What all are the current recommendations?

"Strategy flux state"

- Feasibility Study with daily therapy and 3 drug CP to be done
- Till then RNTP continues
  - DOTS thrice weekly treatment ($2H_3R_3Z_3E_3$/ $4H_3R_3$) under RNTCP continue to be accepted for all cases.
  - Sick admitted cases may be given daily treatment during admission as daily DOTS is feasible.
    - Shifted to thrice weekly regimes after discharge
  - Current work being done on programme adaptation of daily DOTS including using family based DOT – to be launched in 100 districts

What Drug Doses do you use?

		Thrice weekly	Daily
Rifampicin	**R**	15 (12-17)	10-12 mg/kg (max 600mg/day),
Isoniazid	**H**	15 (12-17) mg/kg	10mg/kg (max 300mg/day)
Pyrazinamide	**Z**	35 (30-40) mg/kg	20-25mg/kg (max 1500mg/day)
Ethambutol	**E**	30 (25-30) mg/kg	30-35mg/kg (max 2000mg/day
Streptomycin	**S**	15 mg/kg	15 mg/kg (max 1gm/day)

- Drug Doses have increased – Please make a note

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Available Drug Formulations may not be apt

Commercial formulations

- Almost all have 1:2 ratio of INH to Rif instead of 1:1
- Available Triple combinations have much poorer ratios of all three drugs
- Individual drugs increase pill burden compared to combinations but allow appropriate dosing

Usage of FDCs

TB always requires multi-drug therapy and FDCs as a single formulation ensures

- Safety
- Simplified treatment
- No errors in missing one or more of the combination drugs
- Reduced risk of emergence of drug-resistant strains
- From programmatic view point it can simplify drug supply management, shipping and distribution;

WHO and IUATLD recommend the use of FDC formulations as routine practice

FDC tablets of good quality and proven bioavailability of rifampicin and in appropriate dosing combination should be used in the treatment of TB.

None of the available FDCs in the country currently meet these criteria

FDCs with appropriate dosing in pipeline (H 50, R 75, Z150) (10:15:30)

Writing TB prescription

Essential components of your prescription

- Diagnosis
  - TB/ Koch's not acceptable
  - Details needed
- Basis of diagnosis
- Type of patient
  - Past history of treatment
- Type of disease
- Treatment Plan

Module 11 : Treatment of TB cond.

Role of Adjunctive Therapy in TB

Steroids in TB: Scientific basis

Interaction between the microbial factors and host immunological factors in lung, lymph nodes, intracranial tuberculosis lesions:

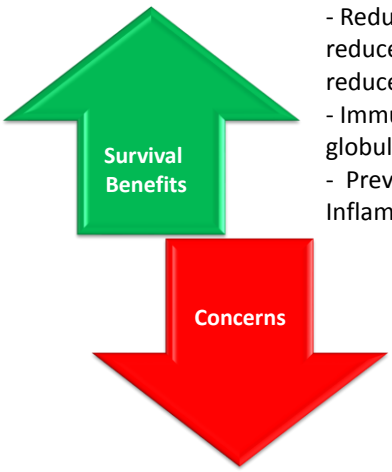
- May cause paradoxical worsening of symptoms due to release of pro-inflammatory markers like IL 2 and Interferon gamma

Majority recovers with continuation of therapy.

But in few circumstances may have severe life threatening manifestations and sequelae

In some of these circumstances there may be relief in symptoms if inflammation can be suppressed by steroids

Intracranial TB - Role of Corticosteroids



- Reduced inflammation in subarachanoid space: reduce cerebral and spinal cord edema and reduce intracranial pressure
- Immune Modulation: Lower CSF protein & globulin
- Prevent hydrocephalus/Infarction: Reduce Inflammation in blood vessels

Decreased **penetration of anti-tubercular drugs in CSF**

Impairment of **cellular defense** against Myc tuberculosis

Increased **GI bleeding**

ALL children with TBM should be treated with adjuvant steroids regardless of the disease severity

Steroids in TBM- Dosage

For TBM:

- Prednisolone: 2 mg/kg/d (or) (max 60 mg/day)
- Dexamethasone: 0.6 mg/kg/d)
- For 4 weeks, followed by a reducing course over 4 weeks

Any steroid in equipotent doses can be used

Thwaites G et al. British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children. Journal of Infection (2009)

Steroids in Pericardial TB

- **How does it help?**
  - Mortality, prevention of constriction or re-accumulation of pericardial effusion

In a multivariate survival analysis (stratified by type of pericarditis), prednisolone as adjuvant therapy led to

- Reduced overall death rate, and
- Substantially reduced risk of death from pericarditis
- Reduced mortality (RR 0.61 [ci 0.37-0.99])
- After 10 years, the great majority of surviving patients in all treatment groups were either fully active or out and about, even if activity was restricted
- Rest benefits are unclear

Q J Med 2004; 97:525–535

Steroids in Pleural TB

How does it help

- Reduced pleural fluid at 4 weeks: Yes
- Pleural thickening at 4 weeks: Yes
- Reduced pleural fluid at 8 weeks: No
- Lung function (later): No

When to use?

- Massive or bilateral

Engel ME. Corticosteroids for tuberculous pleurisy. Cochrane 2007

Adjuvant Therapy: Pyridoxine

- Vitamin B6 supplementation
  - Not routinely
  - Severe PEM
  - Pregnancy

Role of surgery

Limited direct role, Adjunctive role

- usually done after few days / weeks of ATT

Includes (but not limited to)

- Drainage of cold abscesses
- Removal of retained caseum from discharging superficial sinuses or from osteomyelitic areas
- Decompression of spinal canal in a spinal TB case with neurological deficit
- VP shunt for hydrocephalus
- Pericardiectomy for constrictive pericarditis
- Segmental or lobar resection in MDRTB (debulking diseased segments) or sequlae with complications e.g. B'ectasis with hemoptysis

New definitions

TYPE OF Patient			
NEW	A TB patient who has never had treatment for TB or has taken anti-TB drugs for less than one month is considered as a new case.	**NEW**	A TB patient who never received treatment for TB or received anti-TB treatment for less than one month.
Previously Treated	No such definition exists	**Previously Treated**	A TB patient who received anti-TB treatment for 1 month or more in the past.
Relapse	A TB patient who was declared cured or treatment completed by a physician and who reports back to the health facility *and is now found to be sputum smear positive* is a relapse case.	**Recurrent TB**	A TB Patient previously declared as successfully treated (cured/treatment completed) and is subsequently found to be bacteriologically confirmed TB case is a recurrent TB case.
Failure	Any TB patient who is smear-positive at 5 months or more after initiation of treatment is considered as failure.	**Treatment after Failure**	A TB patient whose anti-TB treatment failed at the end of the most recent course.
Treatment after default	A patient, who has received treatment for TB for a month or more from any source and returns for treatment after having defaulted i.e., not taken anti-TB drugs consecutively for two months or more and found to be smear-positive is a case of treatment after default.	**Treatment after lost to follow-up**	A TB patient previously treated for TB for 1 month or more and was declared lost to follow-up in their most recent course of treatment and subsequently found bacteriologically confirmed TB case. Example: TB patient not taken anti-TB drugs consecutively for one month or more and found to be bacteriological confirmed TB case after lost to follow-up.
Others	A patient who does not fit into the any of the types mentioned above. The reasons for labelling a patient under this type must be specified in the Treatment card and TB Register	**Other previously treated patient**	A TB patient who has been previously treated for TB but whose outcome after their most recent course of treatment is unknown or undocumented.
Chronic	A patient who remains smear-positive after completing regimen for previously treated but not initiated on MDR-TB treatment.	**Not required**	**not required**

Summary

Treatment of childhood TB has 2 categories: new treatment and re-treatment.

In continuation phase HRE is advised even for the new cases instead of the current HR in view of high prevalence of INH Mono-resistance and its likely risk of amplifying resistance against Rifampin.

Drug doses have been revised in view pediatric pharmacokinetic data.

DOTS remains the most important component of therapy to maintain the uniformity of regimen, drug doses and ensuring treatment completion

Re-treatment regimen of five drug is to be used only as a waiting regimen till the child is being evaluated for drug resistance.

Adjunctive Steroid therapy and surgery as indicated.

Module 12

Monitoring Treatment

How do we monitor and what do we monitor?

When to Assess

- 15, 30 days after start of therapy, End of IP, every 1 month till completion

What to assess

- **Appropriate therapy**
  - Has received correct combination in correct doses
  - Is accepting all drugs
  - Counsel about need to complete therapy and not missing doses
- **Response to therapy**
  - **Clinical Picture:** Symptoms, assessment of adherence, adverse effects, weight measurement (may need dose revision)
  - **Bacteriological:**
    - End of IP and end of treatment (Bacterial negativity- sputum, GA etc)
    - End of IP, extended IP (when extended) and CP of treatment
- **Co-morbid conditions:** HIV, SAM

How do we monitor and what do we monitor?

Follow up radiographs

- If slow resolution of symptoms (>4w) or persistent symptoms at end of IP
- Any deterioration at any time
- Not required in children who are improving except at the end of CP

What to do

- Children who are smear positive or symptomatic at 2mo of IP
  - Symptoms explicable by comorbidity
  - Extension of IP (3 mo instead of 2 mo)
  - Assess for Drug resistance

Clinical response

Commonly patients show defervescence, reduction in cough by the end of first 2-4 weeks

- Can take longer some times

Weight Gain usually starts by 4 weeks

- Nearly 25% do not show any significant weight gain on treatment

Any deviation/ delay shall make one suspicious

Issues in a child with Non -responding TB

Is this a non response- (often non resolution of symptoms)?

Is the patient taking his pills: correct regimen, correct dose, correct duration, adherence?

Is this a true "non response" TB or a "Non –TB?"

Is the symptom persistence due to unaddressed comorbidity or new infection

Is this a paradoxical reaction?

-TB IRIS ?

It is TB and it is not responding despite "correct" therapy!

- Dug Resistant TB ?

Most commonly because of poor regimen, adherence
Drug resistance though important but not a common cause

Let us review some
illustrative cases with non-response

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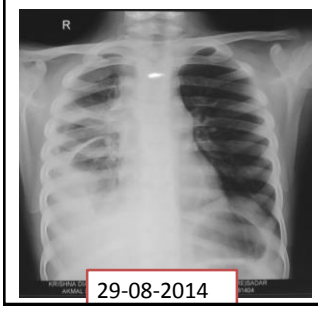
Case A

- 8 y boy
- Presenting complaints:
  - Fever : high grade, documented
  - Cough: dry, persistent

  } 1 month
- No h/o contact with TB patient



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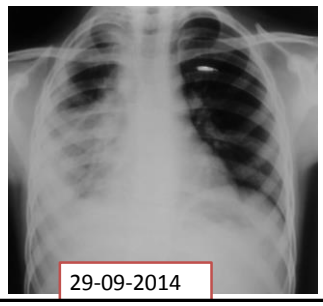

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Referred for evaluation for

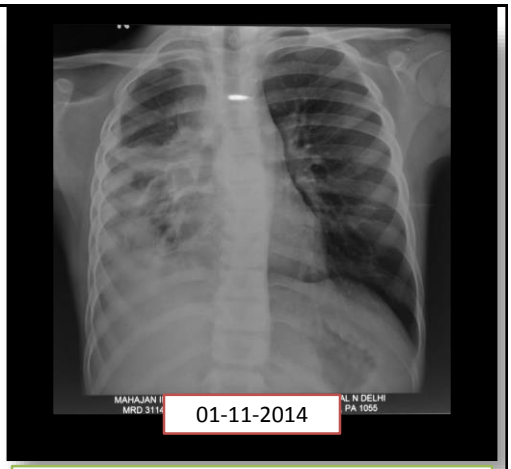
Non Response or Persistent radiological shadow

No Mantoux

GA or Sputum Not done outside

Pleural Tap Not Done outside

Well looking
Afebrile
No LAP/clubbing/pallor
Chest: Percussion Impaired
Signs of Rt volume loss & Air entry was equal
No sputum production
GA done - Negative for Smear
CXR – Underlying lung on Rt side has pathology
USG Chest: Minimal pleural effusion with septations, non tapable

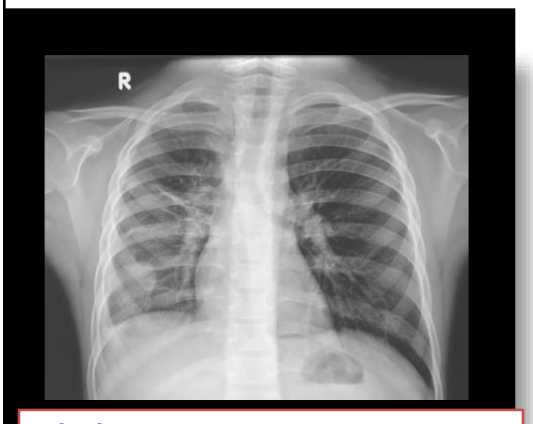


Flexible Bronchoscopy

- Caseation in the Right Upper Lobe bronchus completely obstructing opening of anterior segment
- Right lower lobe dirty mucosa
- Right middle lobe compressed from outside.

BAL sent for AFB stain, CB NAAT, MGIT

Follow up



- BAL
  - AFB stain negative
  - GeneXpert positive sensitive to R
  - MGIT no growth
- Started on CAT II ATT with steroids
- At 2 months
  - Well
  - Afebrile

Take home message

- True non response
- DRTB suspect- attempt bacteriological diagnosis
- Appropriate therapy in such cases

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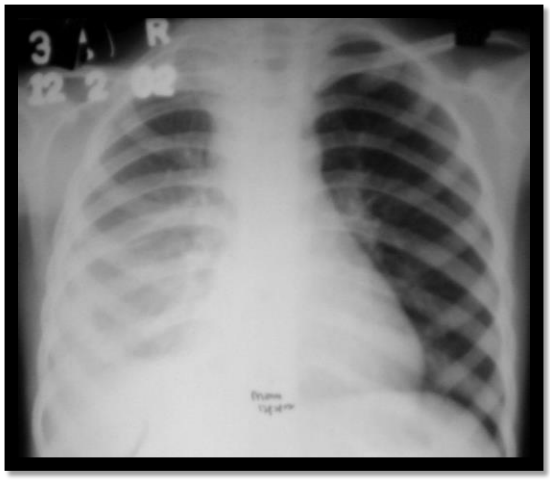
Instructive case – M at diagnosis



- 6 Yr M, Rt Pleural effusion, on 2 RHZ/ 4RH since Feb 2002

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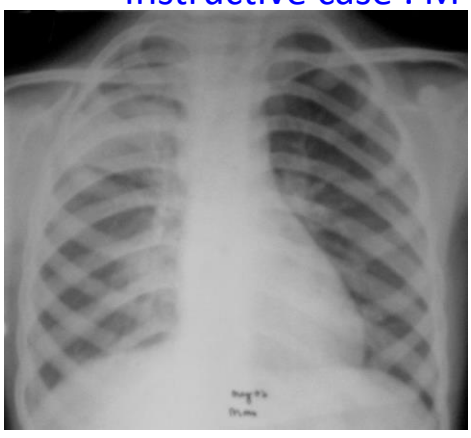
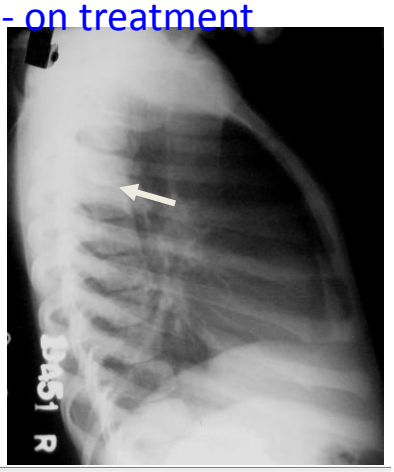
Instructive case : M - on treatment





3.5 month later a routine cxr due to some cough showed Rt U/L infiltrate, Effusion had improved

Baceriological examination on GA negative

FOB planned as failure cannot be ruled out.

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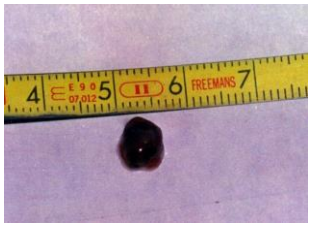
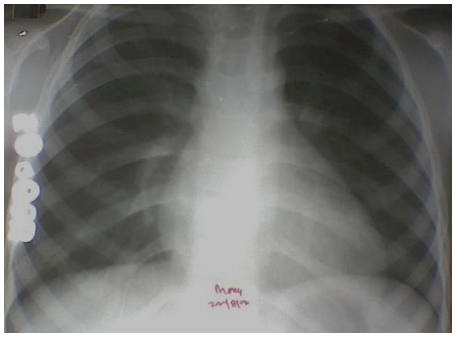
Instructive case: M





CXR end of treatment

Bscopy

- Hypertrophic granualtion tissue at Rt UL ant seg;

BAL

- AFB neg

No change done to treatment

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Fresh radiological lesions

- New lesions like the nodular opacities seen after the effusion starts clearing are not uncommon with TB pleural effusion
- Like wise some patients on ATT develop Pleural effusion on treatment

- **<u>May not be due to failure of therapy</u>**
  - Though it must be ruled out
    - GROW and SHOW LIVE BUG!!
    - Investigate and demonstrate resistance- utilize rapid diagnostics, where possible
- If none found – consider a paradoxical increase

Paradoxical response

Refers to enlargement of old lesions or unexpected appearance of new lesions during apparently adequate ATT

Generally occurs 3–12 weeks after beginning of therapy; most frequently after treatment for 6- 7 weeks, & lasts for ~2 months,

Generally self limiting; resolves without serious sequelae

- wide variability in duration of both of these periods

Usually regresses without a change of initial drug regimen

It usually occurs during treatment but can occur post treatment (as late as two years) in cases of lymph node TB.

Paradoxical response

- Also called paradoxical upgrading reactions (PURs)

Various types reported

- Increase in size of mediastinal lymph nodes or areas of pulmonary infiltration in pediatric patients with primary TB
- Appearance of new lung infiltrates in patients with extrapulmonary TB
- Development of TB pleural effusion
- Increase in size of effusion/appearance of effusion on the contra lateral side
- Appearance of new lymph nodes/ enlargement of original nodes
- Increase in size or number of tuberculoma/ infarctions / hydrocephalus on treatment of intracranial TB

Monitoring Adherence

- Adherence to therapy is monitored under DOT as the patient interrupting treatment are contacted and counselled for complete adherence
- To prevent any interruptions due to drug outages, once a case is registered all the drugs meant for complete therapy is kept in named dedicated box for the patient.
- Pill count and return of the empty blister packs is done for self administered treatment during the C.P.

Summary

- Initial visit within 2 weeks of start of therapy must lay emphasis on ensuring adequate therapy
- Sick babies and their caregivers often need support at this initial period of sickness so that they are able to adhere to complete therapy (all drugs in correct doses).
- Follow up of children is important with the pediatrician even if the child on treatment from a DOTS center
  - Follow up after 1 month, end of IP, monthly there after till end of treatment
- Bacetriological tests should be done at end of IP
- Routine repeat chest xray is not needed except at end of CP

Summary:
Occurrence of fresh symptoms or radiological signs on treatment

- Paradoxical reaction
- Immune reconstitution- HIV co-infection
- Co-morbidities
  - Bronchial hyper reactivity
  - Bacterial infection
- Drug failure ---drug resistance

4 yrs, F

- Presented with: fever, cough, weight loss
- Mother on ATT for 5 months
- Child was started on ATT for pulmonary TB (CAT I), primary complex on her chest xray
- Completed 4 m treatment.
- Went to her native place and stopped treatment
- Reported back 2 mo after stopping treatment; symptoms of cough and fever recurred for past week.

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- How will you manage this patient now?
- Check what has the brought the patient back to you
  - Fresh Symptoms
    - Check are they due to TB – resurgence
    - Co-morbidity
  - Routinely,
    - missed appointment due to social reasons

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What next?

- Khushboo was reinvestigated
- On exam, she had crackles on right base.
- She was treated with oral amoxycillin with a diagnosis of Comm aq Pneumonia to rule out active TB
- Her Xray chest and GA for AFB were negative.
- TST was not repeated as it has no role in the diagnosis of a previously treated case.
- She improved on antibiotic therapy.
- Her mother is worried about her incomplete TB treatment

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S. No.	Duration of therapy	Duration of interruption	Decision
1.	Up to 4 weeks	<2 weeks	Resume original regimen
		>2 weeks	Reassess and start appropriate regimen
2.	4-7 weeks	<2 weeks	Resume original regimen
		>2-8 weeks	Extend intensive phase by 1month
		>8weeks (DR TB Suspect)	Re Treatment regimen
3.	> 8 weeks	<2 weeks	Resume therapy
		>2 weeks: Not active disease	Resume therapy
		>2 weeks:active disease	Category II

Khushboo

Module 13

Monitoring and management of treatment adverse effects

Monitoring of adverse effects of treatment

Clinical monitoring

No routine lab investigations

Enquire about symptoms at every visit

Forewarn care giver about the common adverse effects (anticipatory guidance) and changes like discolouration of urine with Rifampicin

Side effects of first line drugs

Drug	Side effects
Isoniazid	**Skin rash, Hepatotoxicity, Jaundice, Peripheral neuropathy** Rare: Toxic psychosis, Generalized epileptic convulsions, Pellagra, Arthralgia, Anaemia, Lupoid reactions (uncommon in children)
Rifampicin	**Orange-red discoloration** of secretions (urine, faeces, tears, sweat) **Hepatotoxicity** Cutaneous syndrome : Flushing and/or pruritus, with or without rash, involving particularly the face and scalp, often with redness and watering of the eyes. Abdominal syndrome: pain, nausea, vomiting or, less commonly, diarrhoea. "Flu" syndrome(uncommon), Purpura, acute haemolytic anaemia, shock, and renal damage with or without impaired kidney function or failure (rare)

Side effects of first line drugs

Drug	Side effects
Pyrazinamide	**Hepatotoxcity, Joint pain, Hypersensitivity** Rare: Gastrointestinal reactions, Sideroblastic anaemia.
Ethambutol	**Ocular toxicity** (dose dependent): (Impairment of vision, Red–green blindness, Central scotomas, and Peripheral field defects. *Rare:* Generalized cutaneous reactions, Arthralgia, Peripheral neuropathy
Streptomycin	**Vestibular damage and Ototoxicity** (Vertigo and ataxia, Tinnitus, and Loss of hearing) **Hypersensitivity reactions, Renal damage** Pain, rash, induration at injection site

ATT Drug induced liver injury (DILI)

Definition of Drug induced liver injury (DILI)

Presence of at least one of the following criteria:

- Rise of >5 times the upper limit of normal levels of ALT and /or AST, even when has no symptoms
- Rise in ALT and/or AST >3 times when has nausea, vomiting. diarrhoea
- Rise in level of serum total bilirubin above 1.5 mg/dl;

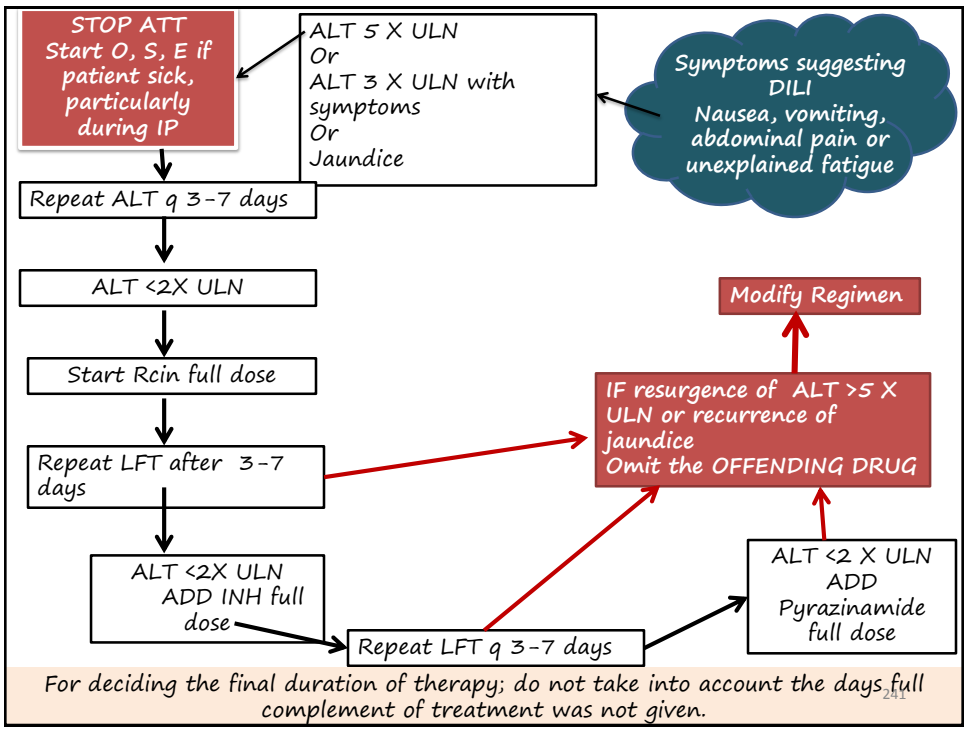
J Respir Crit Care Med 2002;166:916-9.

Clinical features

- Nausea,
- Vomiting,
- Anorexia
- Pain abdomen,

Present in 50-75%
Symptoms common to Gastritis – another adverse event

- Jaundice,
- Unexplained fatigue
- New onset hepatomegaly
- Bleeding manifestation



Module 14

Drug Resistant TB Including MDR

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Definitions

Mono Resistance

- Resistance to any first line ATT (HRZES)

MDR-TB

- Resistance to at least H & R

Poly Resistance

- Resistance to 2 first line drugs but not both H & R

XDR-TB

- MDR-TB + any fluoroquinolones + any second-line injectable drugs (Am/km/Cap)

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Who is a presumed case of DRTB (DR TB suspect)?

Treatment after lost to follow up (Defaulter)	Received ATT for ≥ 1 m from any source & not taken ATT consecutively for > 2 m & has active disease (clinical or bacteriological).
Recurrent TB (Relapse)	Child who was declared cured or treatment completed in past and now has a (clinical or bacteriological) evidence of recurrence.
Treatment after failure	A pediatric TB case who after 12 weeks of compliant intensive phase fails to have bacteriological conversion to negative status or fails to respond clinically / or deteriorates shall be deemed to have failed response

Since children usually have paucibacillary disease and are sputum negative, these definitions are to be used in conjunction with clinico-radiological picture

All of the above are DR TB suspects in addition to some other children who are at high risk of DR TB viz. contacts of MDR patients and/ or CLHA

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Approach to diagnose MDR TB in children

Careful history

- History of contact with MDR TB case is critical information
- Consider in child failing first-line TB treatment despite adherence

Clinical examination

Investigations relevant for suspected PTB or EPTB

- Important to try to get samples for culture and DST

HIV testing

- Failure to respond to TB treatment should consider HIV-related lung disease that is not TB as well as the possibility of MDR TB

Bacteriological confirmation and drug susceptibility testing whenever possible

- Sputum (or other relevant samples e.g. lymph node aspiration) should be collected in all children with suspected MDR TB for culture with drug sensitivity testing or LPA or CB NAAT (e.g. Xpert MTB/RIF)

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For MDR TB Diagnosis

Microbiological confirmation should always be done

- DST / LPA/ CBNAAT (e.g. Xpert Rif)
- Make all out efforts to get clinical samples from the affected site.
  - Pulmonary: Sputum, Gastric lavage, BAL, Lung Tap
  - Extra-Pulmonary: Lymphnode aspiration, excision
  - CSF
  - Laproscopic tissue biopsy

Diagnosis of drug resistant tuberculosis in the absence of bacteriological diagnosis must be thoroughly reviewed as it may often be untenable

Some times in DRTB suspect, if all other alternative causes for symptoms have been ruled out but there is no microbiological confirmation- bacteriologically Negative clinically diagnosed MDR TB can be considered

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Perform LPA /CBNAAT and Liquid cultures for every MDR Suspect at baseline

Molecular methods for every suspect

- For rapid detection of Rifampicin resistance to decide the treatment regimen.
- To decide whether only first line DST or both first Line and second line DST needs to be done additionally

Additional Liquid culture to detect baseline resistance to other drugs

- FLDs (S,H R E Z with level of INH resistance) if Rif sensitive. If any resistance to FLD, test for SLDs also
- FLD & SLD if Rif resistant (H E Z with level of INH resistance , Mfx,Lfx,Km,Am,Cm)

Facilities for these test available under RNTCP labs (free of cost) as well through a network of accredited private labs at a subsidised price through Initiative for Promoting Affordable Quality TB Tests (IPAQT).

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Principles of treatment of Drug resistance TB

Always be treated in consultation with an expert

Include at least 4-6 bactericidal medications to which the strain is known or likely to be susceptible

Don't a single drug to a failing regimen

Treatment should be given for at least 12 months after *M. tuberculosis* cultures have converted to negative

With HIV infection or cavitatory lesions it is extended to 24 months

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Treatment phase	Duration	Characteristics
Intensive phase: Km Lfx Eto Cs Z E	At least 6m & until sputum smears & cultures are continuously Negative	• Close monitoring for side-effects • At least five drugs • Includes injectable
Continuation Phase: Lfx Eto Cs E	18 months [12 mo in paucibacillary ds]	• Fewer side-effects • Usually only oral drugs

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MODULE 15

HIV and TB

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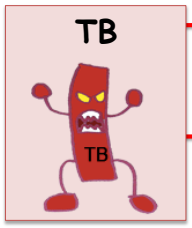
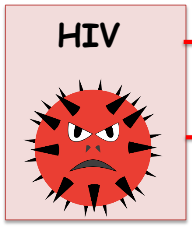
TB:HIV

How they work hand-in-hand



→ Can hasten disease progression in HIV – more OIs

→ Can increase mortality in HIV



→ Promotes progression of TB infection to active TB disease

→ Can drive MDR TB

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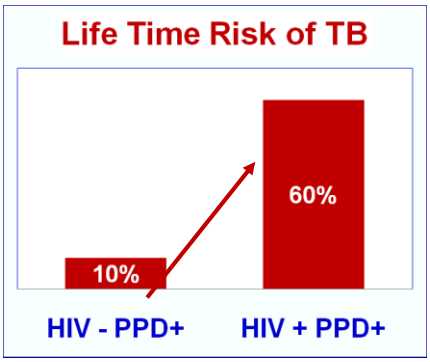
Risk of TB in HIV-infected children

HIV patients are at an increased risk of developing TB disease



- Developing active TB, once infected with *M. tb*
- Becoming re-infected with a second strain of TB
- Relapsing after stopping treatment

Estimated burden of HIV among TB patients: 4.78% in India

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Implications of TB-HIV Co-infection

- Need to screen all HIV patients for TB
  - New WHO algorithm
- Need to screen all TB patients for HIV
  - Active promotion and routine offering of **Voluntary Counseling and Testing**

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When to suspect TB?

Screen all HIV patients for TB with signs and symptoms

- Cough (for any duration)
- Cough with blood in sputum
- Unexplained fever
- Unexplained weight loss (>10% in 6 months)/excessive fatigue, night sweats, loss of appetite
- Pleuritic chest pain
- Swelling in the neck, armpits, groin, abdomen, joints etc

Source: TB/HIV module NACO 2010

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Diagnosis: microbiology

Sample specimen

- sputum, gastric aspirate, induced sputum, lymph node tissue.

Microbiology

- Smear
- Culture
- PCR-based (CB-NAAT, LPA)

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Specific Problems in Diagnosis of TB in children infected with HIV

Overlapping Symptoms

- Chronic pulmonary symptoms due to other HIV related condition eg. GERD, bronchiectasis frequently coexist
- Weight loss and failure to thrive are both features of HIV and tuberculosis

Radiology

- CXR interpretation- difficult with presence of other HIV related conditions pneumonia, LIP, bronchiectasis
- HIV infected patients with active TB proven on sputum culture can have normal chest radiographs

Tuberculin Sensitivity Test (TST)

- Induration >5 mm is read as positive TST
- Extremely low sensitivity in culture confirmed TB with HIV cases despite taking cut-offs of 5 mm

Madhi S et al. Pediatr Infect Dis J 1999
Iriso R et al, Int J Tuberc Lung Dis 2005

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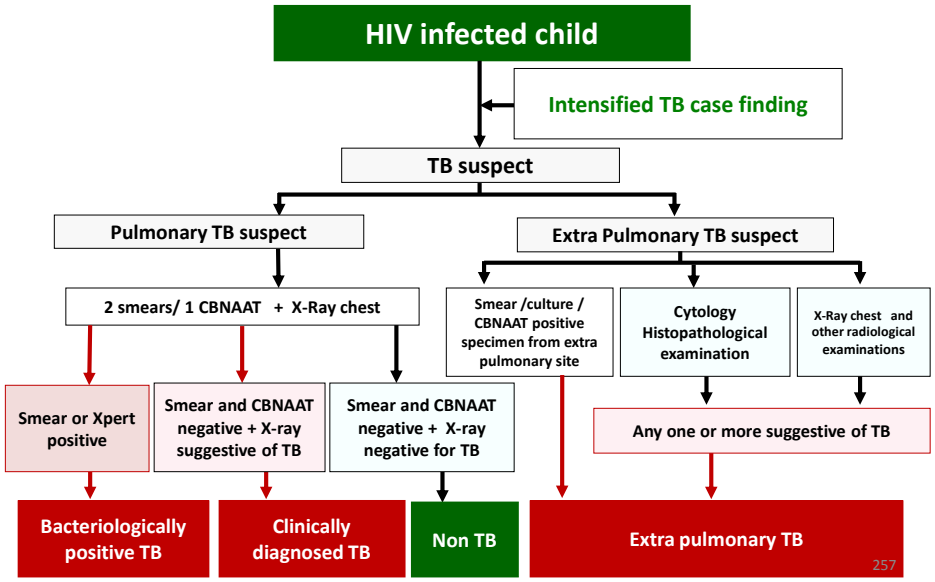
Diagnostic Algorithm of TB in CLHIV



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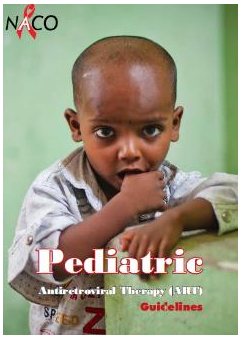

NACO Pediatric ART Guidelines 2014

- Start ATT immediately.
- Start ART 2-8 weeks later.
- **Short course ATT (6 months) followed by 6 months IPT.**
- Daily ATT: intensive and continuation phase.
- TB meningitis/osteo-articular TB: 12 months.
- Nevirapine is no longer used as first-line ART.

	ART	ATT
Child < 3 years	ZDV (or ABC) + Lam + Lop/r + superboosting of ritonavir	2HRZE/ 4HRE
If< 3 years and < 10 kg	Triple NRTI (ZDV + Lam + ABC)	2HRZE/ 4HRE
≥ 3 years	Tenofovir + Lam + EFV	2HRZE/ 4HRE

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Considerations of concomitant ART and ATT

Drug interaction: Rifampicin is a potent inducer of cytochrome P450

- increasing metabolism of NNRTI and protease inhibitors
- reducing their therapeutic drug level

Increased hepato-toxicity

Increased incidence of adverse effects

Possible development of IRIS

High Pill count

- May affect patient's acceptance

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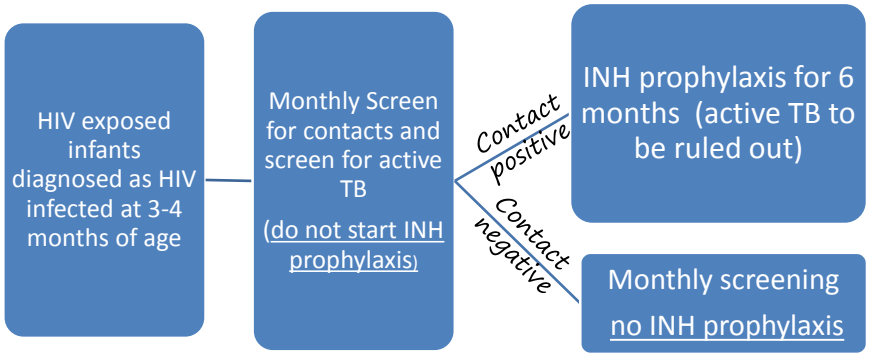
What to do in HIV exposed infants?



Source- WHO 2010 guideline for HIV

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How to introduce INH prophylaxis?

10 mg/kg of INH should be given orally every day

6 months of duration is currently recommended

Hepatitis and peripheral neuropathy are the only contraindications

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MODULE 16

Neonate Born To Mother With TB

Neonate exposed to TB- Likely Clinical situations

Mother has Active TB when baby is born

- Pulmonary:
  - Undiagnosed
  - On treatment: CAT I, CAT II, MDR (for variable duration)
- Extra Pulmonary

Mother has completed treatment but was having disease while carrying this baby

Neonate exposed to a Health care worker/other contact with Pulmonary TB

Evaluation of the neonate for presence of disease

Clinical examination:

- Vitals signs: HR, RR, signs of respiratory distress
- Chest examination
- Abdomen for hepato-splenomegaly
- CNS

Xray Chest – where ever facilities are available

Other investigations as required in case neonate has suggestive clinical history or examination

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Preventive therapy to the neonate

Recommended for whom

- if mother has any form of active TB detected in pregnancy or after birth
- If exposed to any infectious case of TB after birth

Rule out active disease in neonate

Drug: INH preventive therapy (IPT)

- Only INH, 10 mg/kg
- Pyridoxine
  - Usually not needed in neonates
- **No prophylaxis in case of MDR contacts**

Duration

- 6 months

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Isolation and breastfeeding

No Isolation

- If baby is on IPT then separation is not required.
- Consideration need to be to sick Mother's health, nutrition and rest
- Mother's Cough hygiene and etiquette are important
- Required when
  - Mother not adhering to treatment
  - Infectious -XDR /MDRTB
  - Expressed breast milk can be used in such situations

Breast feeding is safe and should be continued

- ATT in small amounts are present in breast milk but are of no consequence

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	Mother with active infection	Contact Sputum Positive	Mother completed treatment or currently sputum negative	Mother with active disease - EP TB
Breastfeeding	Yes	Yes	Yes	Yes
Separation of mother & neonate	No. Only if MDR	No.	No	No
INH prophylaxis	Yes	Yes	Yes	Yes
BCG	Yes	Yes	Yes	Yes

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Perinatal Tuberculosis

- Tubercular infection acquired during intrauterine life or before complete passage through the birth canal

Two main infectious routes

- Transplacental route, forming a primary complex in liver of infant with secondary hematogenous spread.
- By aspiration or ingestion of infected amniotic fluid, leads to primary focus in lungs or GIT

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Perinatal TB: Preferred term

Preferred which encompasses true congenital and neonatal forms of disease

Distinction between true congenital cases & those acquired postnatally is purely of epidemiological significance

Modes of presentation, treatment, and immediate prognosis do not differ between two groups and may be difficult to differentiate at times

Singh M, et al. Perinatal Tuberculosis: a Case Series. J Trop Pediatr 2006; 53 (2): 135-138.

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Treatment

Treatment regime

2 HRZE + 4 HRE

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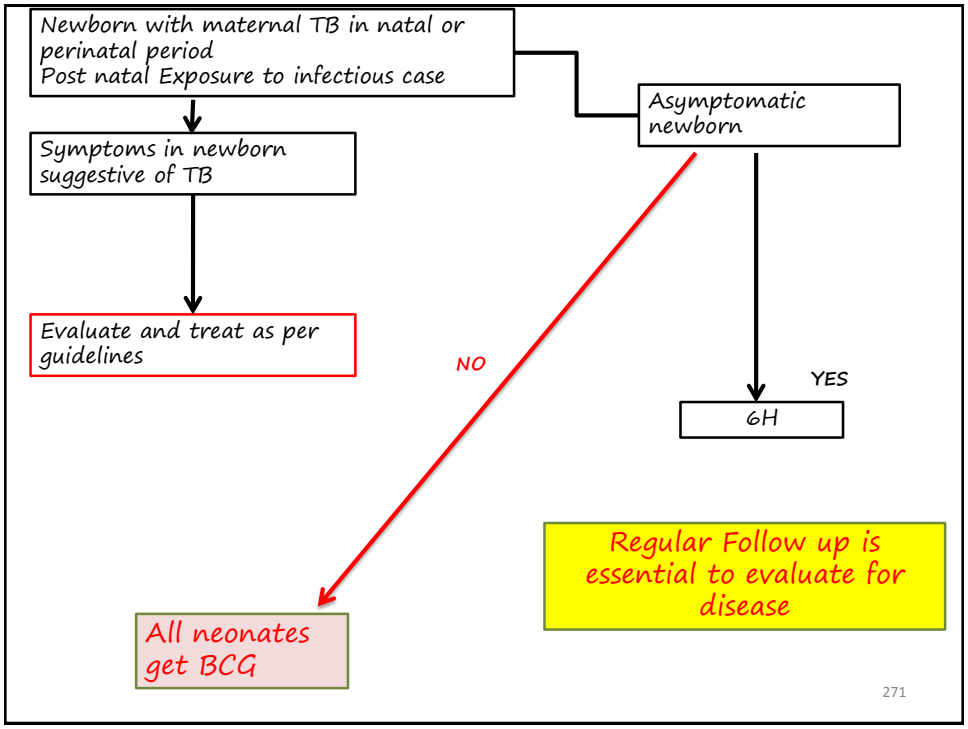

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MODULE 17

Prevention of TB

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Risk factors for TB infection and disease in children

For TB infection

- Contact with source case
  - Closeness of contact
  - Duration of contact
- **Source case**
  - Smear positivity
  - Cavities on CXR
- **Increased exposure**
  - Living in high TB endemic communities
  - Children of families living with HIV

For TB disease

- Young age
  - Especially 0-2 years
- **HIV infection**
  - Risk of infection and disease
- **Other immunosuppression**
  - Malnutrition
  - Post-measles
- **Not BCG vaccinated**
  - Risk of disseminated disease

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Factors that Predict Likely Transmission of TB

Anatomical site of the disease
Positive sputum bacteriology
Radiographic findings
Behaviors that increase aerosolization of respiratory secretions
Age
HIV status
Administration of effective treatment

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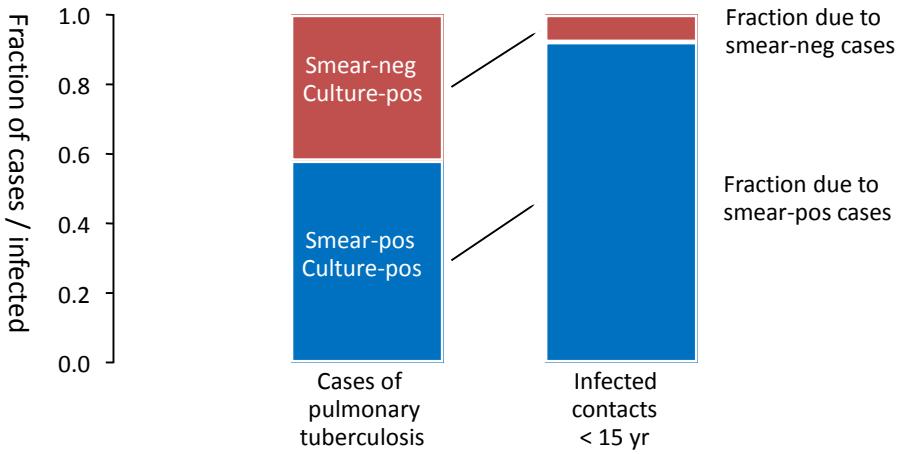
Yield for all TB (bacteriologically confirmed & clinically diagnosed) was 4·5% of contacts investigated; for cases with bacteriological confirmation the yield was 2·3%

Latent tuberculosis infection was found in 51·4% (95% CI 50·6–52·2) of contacts investigated

Morrison J. Lancet Infect Dis 2008; 8: 359–68

Infection with TB can occur from contact with a sputum smear-negative source case but it is less common than from smear-positive cases



Grzybowski S, et al. Bull Int Union Tuberc Lung Dis 1975

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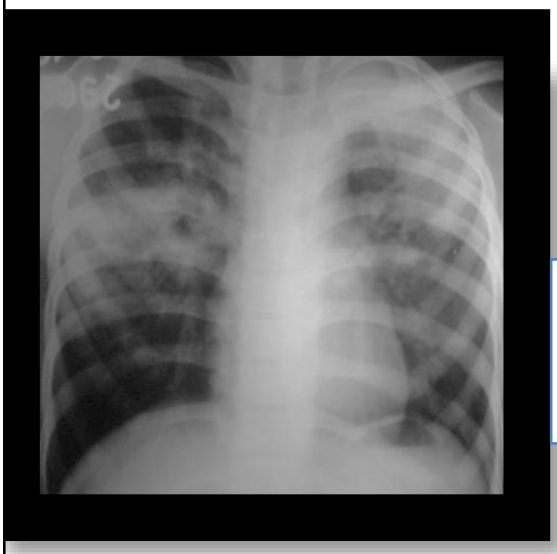

16y male
Sputum positive
Pulmonary TB

Contacts screening:
6 m old boy
3 y old boy
7 y old girl

Which of these need chemoprophylaxis?

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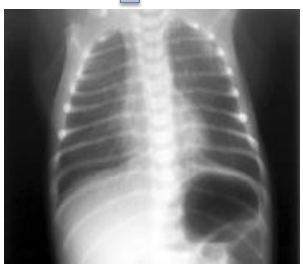
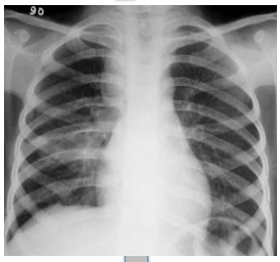
6m old
Thriving well
Asymptomatic
TST Negative

3y old
Thriving well
Asymptomatic
TST 12mm

7y old
Thriving well
Asymptomatic
TST 8 mm
CXR NAD





NO ATT
INH Preventive therapy
Follow up

ATT

NO ATT
Follow up
NO Chemoprophylaxis

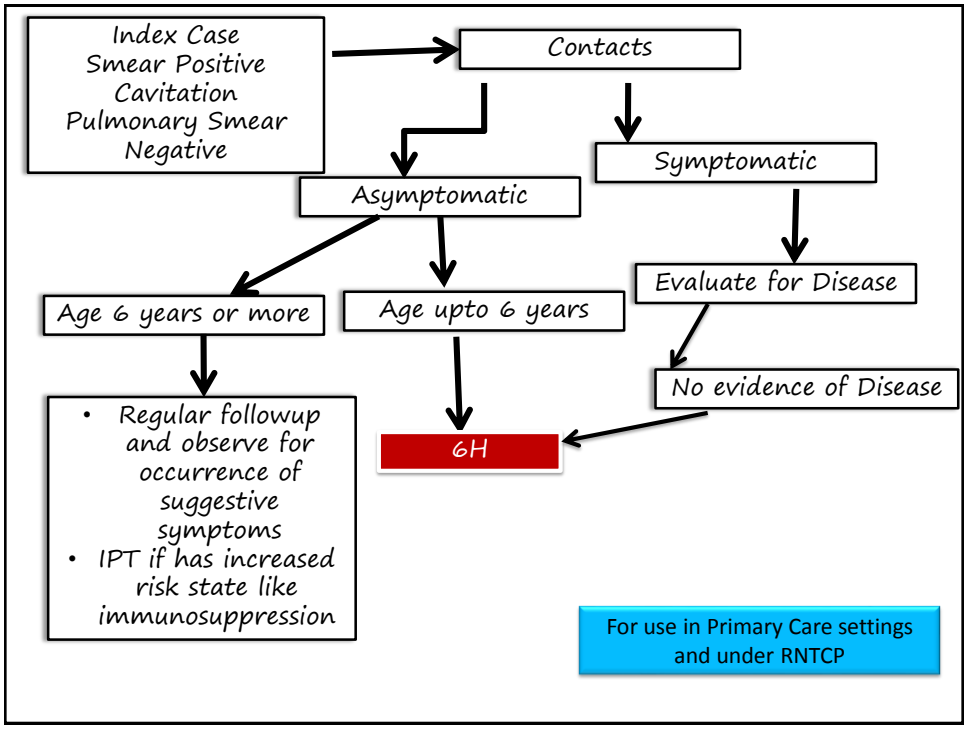
Initiating a Contact Investigation

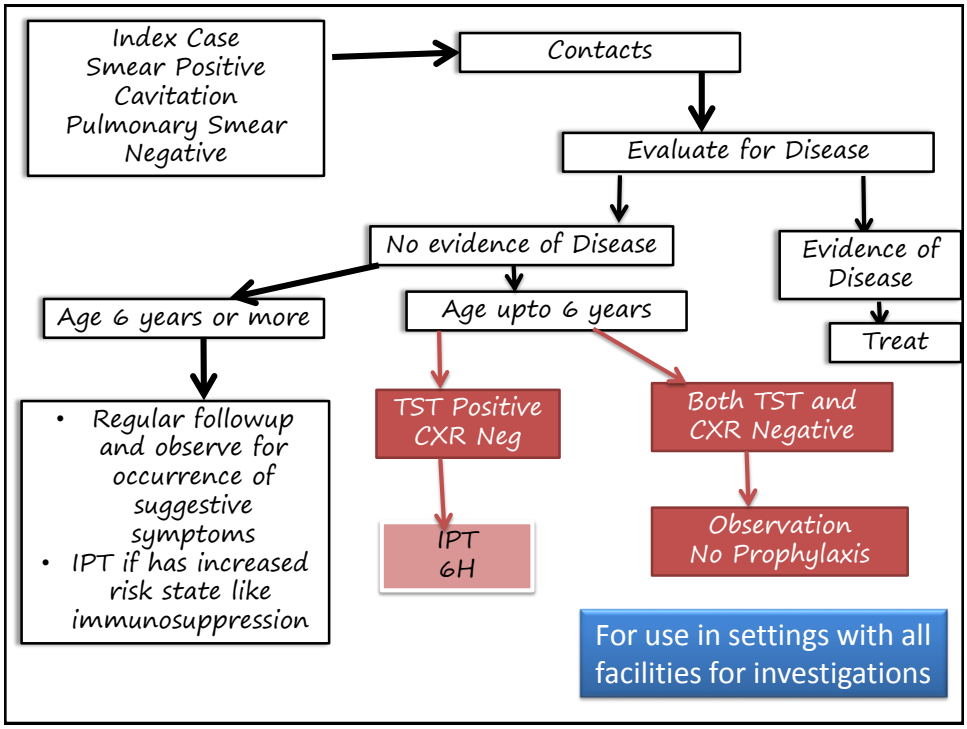
Whose contacts- Source case?

- **Recommended if**
  - Sputum smear positive Pulmonary TB
- **Consider if index patient has**
  - Cavitatory Pulmonary TB on Chest radiograph (AFB sputum smear negative)
  - Sputum smear negative Pulmonary TB

Which Contact?

- **High Priority:**
  - <6 years
  - Immuno-compromised/HIV
  - House-hold contacts


Index Case
Smear Positive
Cavitation
Pulmonary Smear
Negative
Contacts
Asymptomatic
Symptomatic
Age 6 years or more
Age upto 6 years
Evaluate for Disease
No evidence of Disease
• Regular followup and observe for occurrence of suggestive symptoms
• IPT if has increased risk state like immunosuppression
6H
For use in Primary Care settings and under RNTCP


Index Case
Smear Positive
Cavitation
Pulmonary Smear
Negative
Contacts
Evaluate for Disease
No evidence of Disease
Evidence of Disease
Treat
Age 6 years or more
Age upto 6 years
• Regular followup and observe for occurrence of suggestive symptoms
• IPT if has increased risk state like immunosuppression
TST Positive CXR Neg
Both TST and CXR Negative
IPT 6H
Observation No Prophylaxis
For use in settings with all facilities for investigations

IAP and RNTCP Recommendation for preventive therapy

- Recommended preventive therapy
  - INH 10 mg/kg daily for 6 months

Indications

- All asymptomatic contacts (under 6 years of age) of a smear positive case, after ruling out active disease and irrespective of their BCG or nutritional status
- All HIV infected children who either had a known exposure to an infectious TB case or are Tuberculin skin test (TST) positive but have no active TB disease
- All TST positive children who are receiving immunosuppressive therapy (*e.g.* Children with nephrotic syndrome, acute leukemia, *etc.*)
- A child born to mother who was diagnosed to have TB in pregnancy
  - INH prophylaxis for 6 months, provided congenital TB has been ruled out.

Are there any issues with IPT ?

Long duration treatment to an asymptomatic subject

Low completion rates

Hepatotoxicity

Then why Isoniazid?

Best understood and proven

Combination with RH not much shorter for same efficacy and increases cost

Infection to disease is a continuum in children and given the state of diagnostics available, there is a possibility of mistaking disease for infection in few, where RH will be a poorer therapy and may increase the risk for amplification of Rifampicin resistance

How to deal with contacts of DRTB cases?

The sputum cultures of the index case are Resistant to H and R

All household contacts should be screened for disease as discussed before as suggested by many studies about 5-10% cases are likely among close contacts

- A recent study reported a high pooled yield
  - for active tuberculosis 7.8% (95% CI, 5.6%–10.0%)
  - for latent tuberculosis 47.2% (95% CI, 30.0%–61.4%)

Clinical Infectious Diseases 2014;58(3):381–91

Chemoprophylaxis of MDR Contacts

- Controversy:
  - No Drugs vs Combination of E+Z+F
- Recent Systematic Review found insufficient evidence for the use of the above mentioned drugs
- At Present
  - No Drugs. Follow up for next 2 years.

VanderWerf etal. Lack of evidence to support policy development for management of contacts of multidrug-resistant tuberculosis patients: two systematic reviews. INT J TUBERC LUNG DIS 16(3):288–296

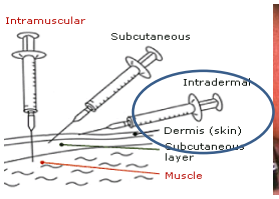
MODULE 17

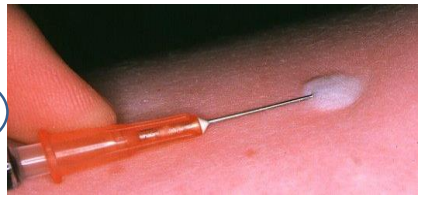
BCG Vaccination And Its Complications

BCG: Mycobacterium bovis BCG; live, attenuated vaccine

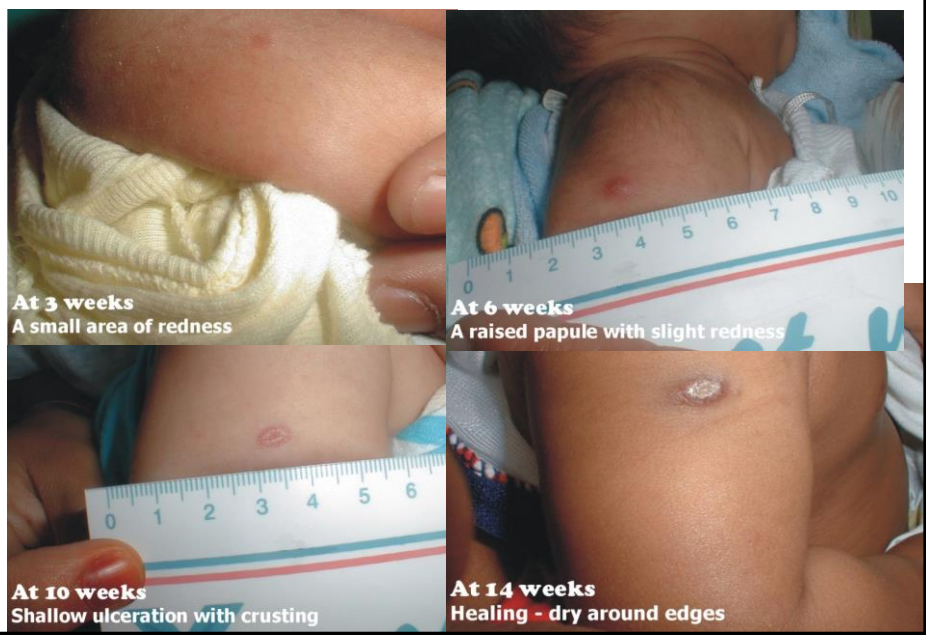
Routinely given at birth or soon thereafter based on tuberculosis risk

Multiple BCG strains





Natural history of BCG vaccination

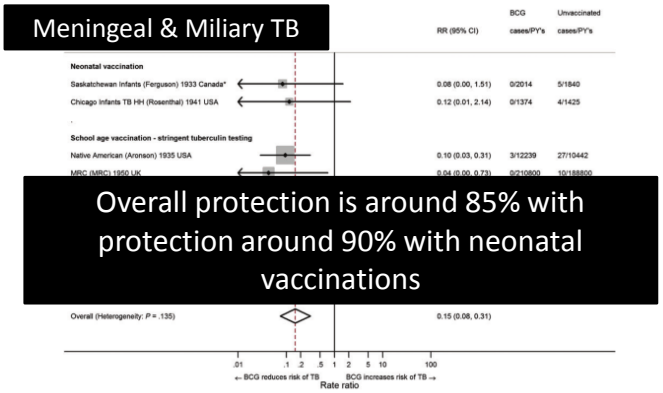


BCG Protection: Pulmonary TB

- Efficacy variable:
  - ranged from substantial protection, in UK MRC trial (RR 0.22; 95% CI, .16–.31) to
  - absence of clinically important benefit (Chingleput trial)
- Efficacy better in school age with prior testing (74%) and neonatal vaccination (60%)
- Estimated efficacy varied according to latitude. Greater efficacy in trials conducted at latitudes farthest from the equator.

Protection by BCG Vaccine Against Tuberculosis: A Systematic Review of Randomized Controlled Trials. Clinical Infectious Diseases 2014;58(4):470–80

Meningeal & Miliary TB



Overall protection is around 85% with protection around 90% with neonatal vaccinations

Figure 5. Rate ratios and 95% confidence intervals for meningeal and/or miliary tuberculosis, stratified by age at vaccination and tuberculin testing stringency. Pooled results from fixed effects meta-analysis only as the numbers of studies were small, ordered by year of study start. *Outcome is miliary tuberculosis only. Abbreviations: BCG, Bacille de Calmette et Guérin; CI, confidence interval; MRC, Medical Research Council; PY, person-years; RR, rate ratio; TB, tuberculosis; TB HH, tuberculosis households.

Protection by BCG Vaccine Against Tuberculosis: A Systematic Review of Randomized Controlled Trials. Clinical Infectious Diseases 2014;58(4):470–80

BCG lymphadenitis: diagnosis

Isolated axillary (or supraclavicular/cervical) lymph node enlargement

History of BCG vaccination on same side

Absence of tenderness & raised temperature over swelling (except in impending rupture state)

Absence of fever & other constitutional symptoms

BCG lymphadenitis: diagnosis

TST not helpful in distinguishing BCG lymphadenitis from TB LN

FNAC cytology and presence of AFB does not distinguish between BCG or TB adenitis as the pattern is similar

Clinical Differentiation from TB lymphadenitis may not be difficult, as cases of isolated axillary glandular TB are very rare

- Preceding history of vaccination on the same side
- Can appear anytime with in first year
- More often with subcutaneous or injection high up on shoulder
- Injection given high up on the shoulder can cause ipsilateral cervical adenopathy
- Never has associated systemic issues in healthy children

BCG lymphadenitis: Types

- Simple or non-suppurative
- Suppurative:
  - Distinguished by development of fluctuations in swelling, with erythema & oedema of overlying skin
- Disseminated BCGiosis (seen in immunosuppressed HIV infected children)

Untreated lymphadenitis: Course

Non suppurative Lymphadenitis

- Regresses spontaneously over a period of few weeks to months
  - Can take upto 6-8 months
- In few, progressive enlargement & evolution into abscess formation can occur
- Suppuration may develop in 30% to 80% of cases of BCG lymphadenitis

Suppurative lymphadenitis

- spontaneous regression can occur
- most likely outcome in these cases is development of spontaneous rupture and sinus formation.
- Ultimate healing occurs by healing of sinus through cicatrisation, but process usually takes several months.

BCG lymphadenitis: Management

Non-suppurative BCG lymphadenitis is allowed to regress spontaneously

If suppuration develops,

needle aspiration may be done to prevent rupture and subsequent large ulceration

Surgical excision is resorted to if needle aspiration fails, as in cases with multiloculated or matted glands

Erythromycin and ATT are ineffective in hastening regression or preventing suppuration in BCG lymphadenitis and should not be used

Thanks to Contributors

Core Group

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