Advanced Pediatric TB

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SANTA CLARA COUNTY TB CONTROLLER

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Objectives

1) Understand the nuances of diagnosing pediatric tuberculosis

2) Recognize the value of expeditious evaluation of pediatric contacts.

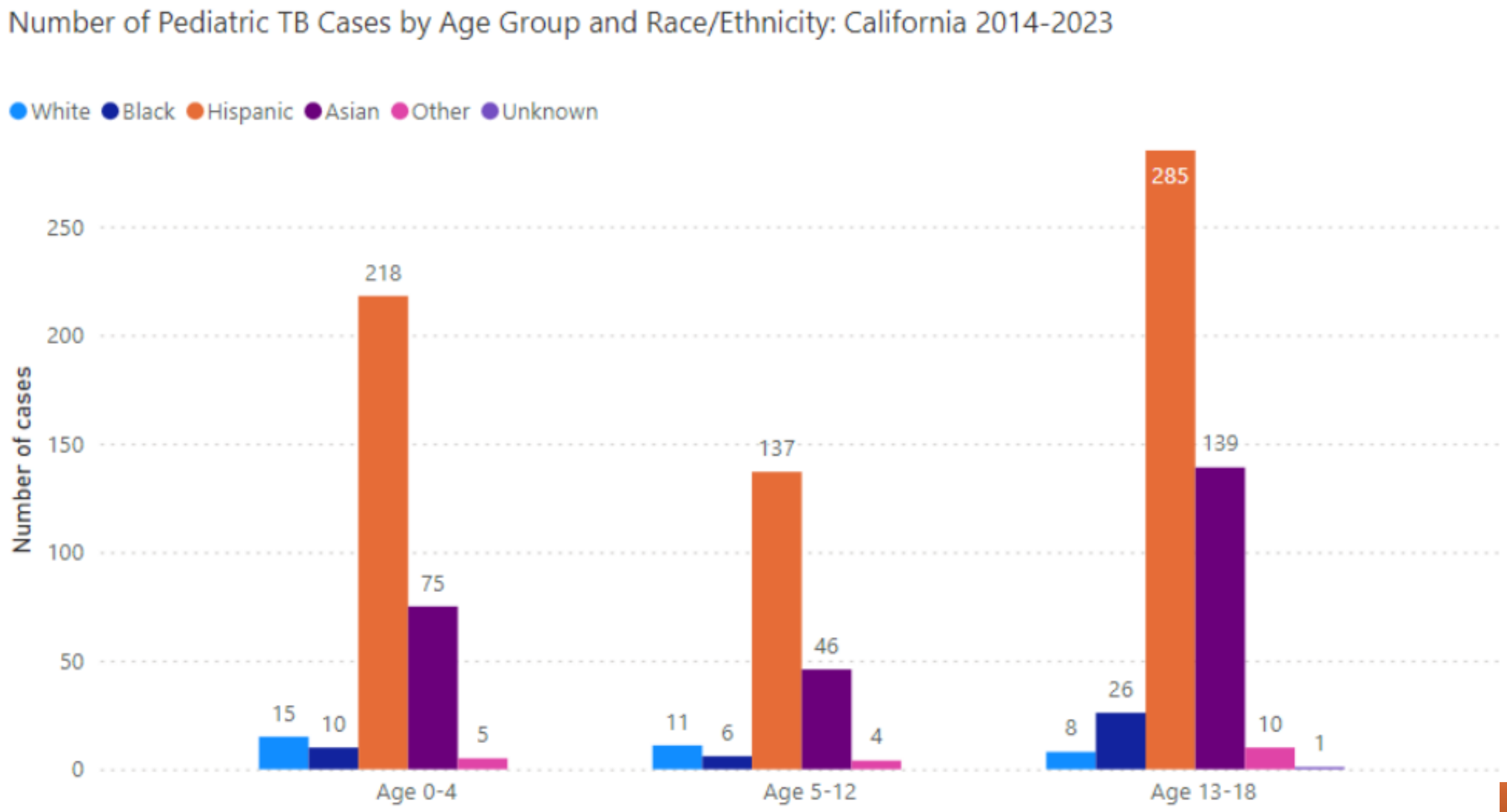
3) List options for TB treatment and drug administration in pediatric TB

4) Examine the possible causes of clinical or radiographic worsening in children with TB

Disclosures

I have no financial disclosures or conflicts of interest

Pediatric TB Basics



Spectrum of Clinical Features

- No symptoms
- Subclinical symptoms
  - Decreased appetite
  - Decreased energy / fatigue
  - Delayed development
  - Poor weight gain / weight loss
- Overt symptoms
  - Also cough, work of breathing, fever, irritability, stiff neck
  - Lymph node swelling
  - Pain: neck, belly, flank, bones, head
  - Neurologic changes

Other Clues

- Almost always more subtle progression of disease than bacterial infections
- Labs generally non-specific and don't look like a florid bacterial infection
- Classic CSF pattern (~ 200 WBC (lymph predom), glucose < ½ serum, high protein) often not present on the first LP

NB: LP recommended for young infants with TB and even toddlers who are the least bit irritable

- Usual demographics - family from parts of the world with more TB
- Teen or adult in the environment with symptoms suggestive of TB

Immune tests

TUBERCULIN SKIN TEST

- False negative tests:
  - early after infection / disease
  - Extensive disease
  - Young infants
  - Immunosuppressed
  - Incorrect handling

False positive tests

- Recent BCG
- NTM
- Incorrect placement

INTERFERON GAMMA RELEASE ASSAYS

Now “allowed” at any age.

Same limitations as TST

Plus - large blood volume

Trouble with blood draw

Journal of the Pediatric Infectious Diseases Society

PEDIATRIC ID CONSULTANT

Use of Interferon-Gamma Release Assays in Children <2 Years Old

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While interferon-gamma release assays (IGRAs) are widely used for detecting tuberculosis (TB) infection, tuberculin skin tests (TSTs) remain preferred for children under the age of 2 years. The preference for TST stems from concern over IGRA sensitivity in young children. However, TSTs are susceptible to false-positive results following Bacille Calmette-Guérin (BCG) vaccination, which is common in infancy, and exposure to nontuberculous mycobacteria. We reviewed available data for IGRA performance in children under age 2 years. Across four cohorts of high-risk children under age 2 (mostly case contacts or those born in tuberculosis endemic regions), 0 of 575 untreated children with negative IGRA test results progressed to tuberculosis disease—including 0 of 70 who were TST positive but IGRA negative. While neither TSTs nor IGRAs are perfectly sensitive for the diagnosis of tuberculosis infection, IGRAs are an acceptable alternative to TST in children <2 years of age.

Key words. children <2 years; interferon-gamma release; tuberculosis; tuberculin skin tests.

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2024 AAP RedBook

Low-grade, false-positive IGRA results occur in some individuals. For children without specific TB risk factors other than foreign birth or travel who have an unexpected low-level positive IGRA result (QuantiFERON-TB Gold Plus <1.00 IU/mL, T-SPOT.TB with 5–7 spots), a second diagnostic test, either an IGRA or a TST, should be performed; the child is considered infected only if both tests are positive. Indeterminate or invalid IGRA results have several possible causes that could be related to the patient, the assay itself, or its performance; these results do not exclude *M tuberculosis* infection and may necessitate repeat testing, possibly with a different test. Indeterminate/invalid IGRA results should not be used to make clinical

QuantiFERON TB Gold Plus

Added TB2 tube intended to augment the test by adding CD8 response

- Hoped to improve sensitivity in early infection/ disease and in children
- In early studies, there is no improved sensitivity

I recommend TST and IGRA for sick children when you want evidence of mycobacterial infection

Imaging

Two view chest radiographs – especially for younger children

Chest radiographs

Characteristic:	Adults	Children
Location	Apical	Anywhere (25% multilobar)
Adenopathy	Rare (except HIV)	Usual (30-90%)
Cavitation	Common	Rare (except adolescents)
Signs and symptoms	Consistent	Relative paucity

Chest imaging

Considered LTBI:

Isolated pleural thickening

Tiny calcifications

Probably inactive:

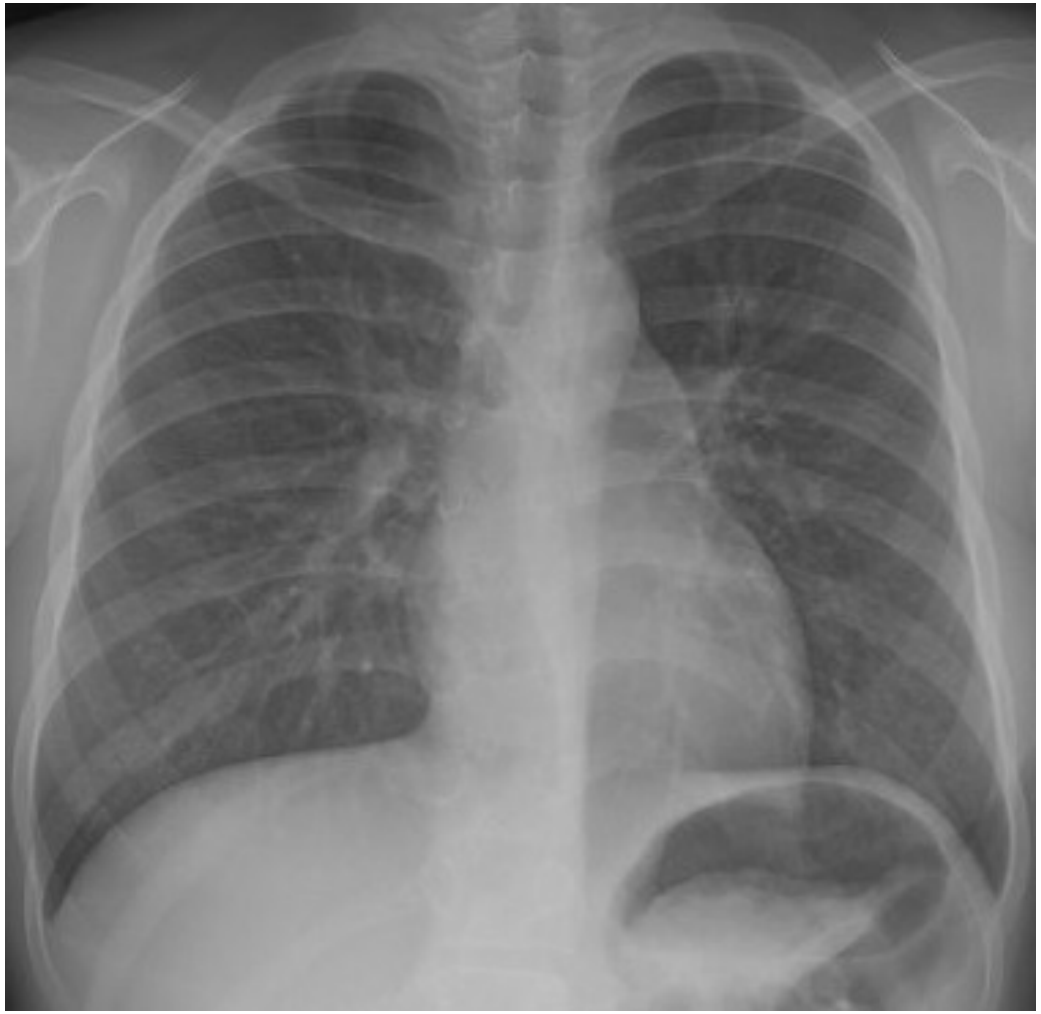
Discrete fibrotic changes / fibronodular changes without airspace opacity

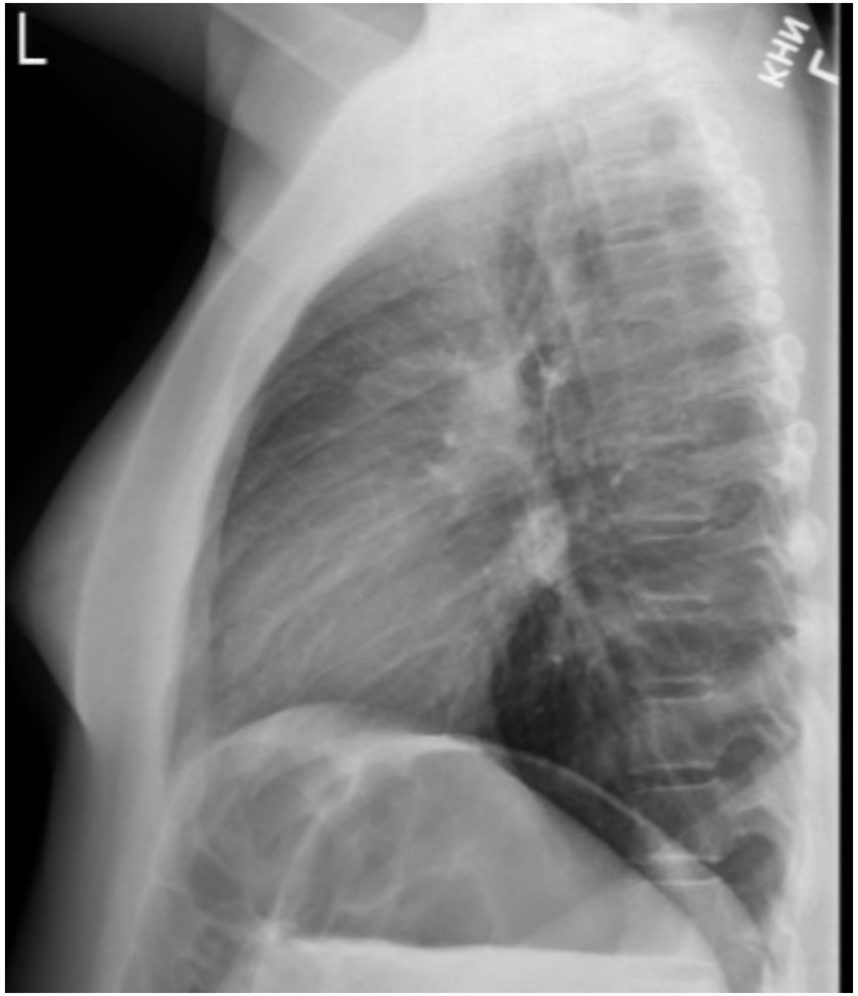
Small calcified nodules

Not TB:

Peribronchial thickening

Much of “perihilar fullness”





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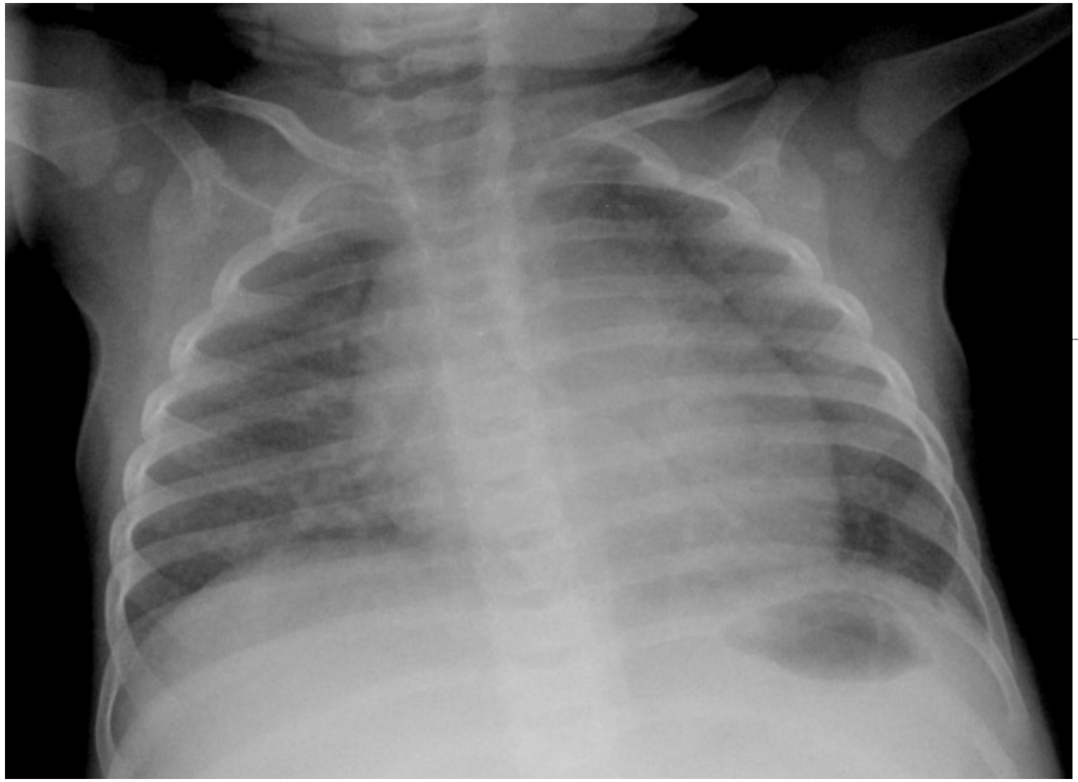
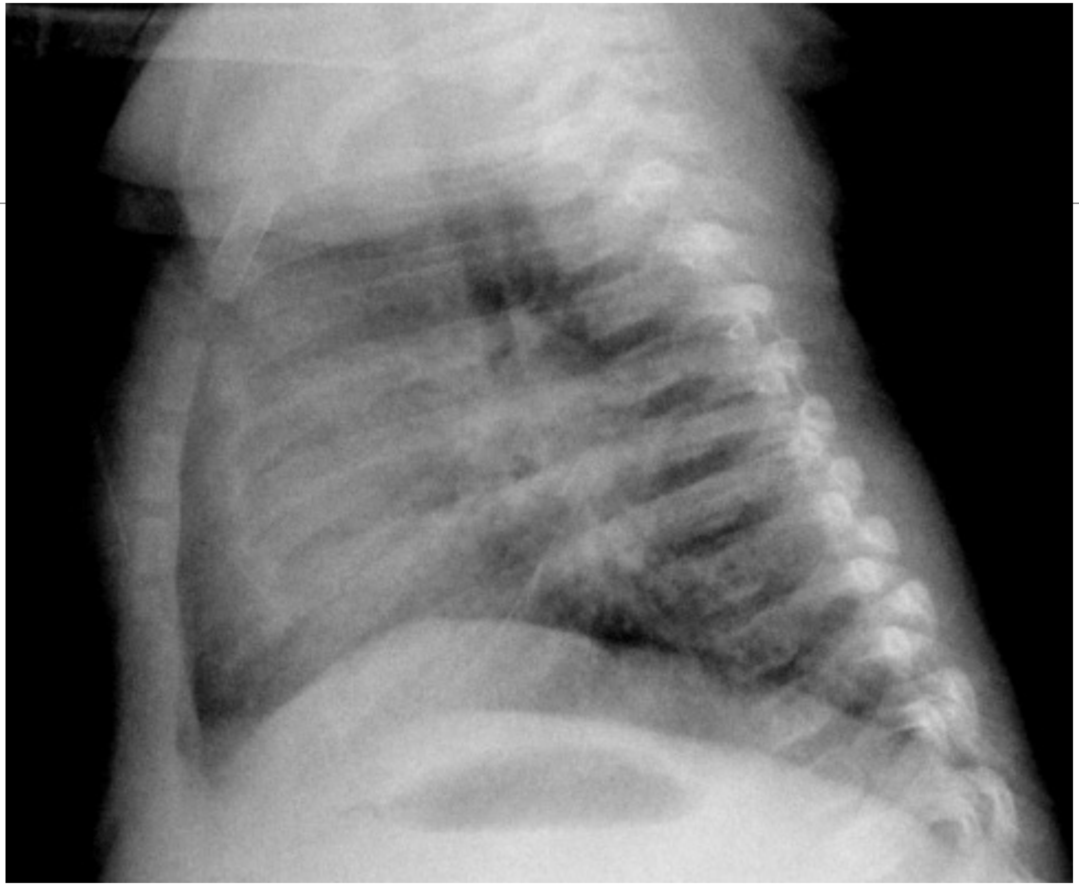


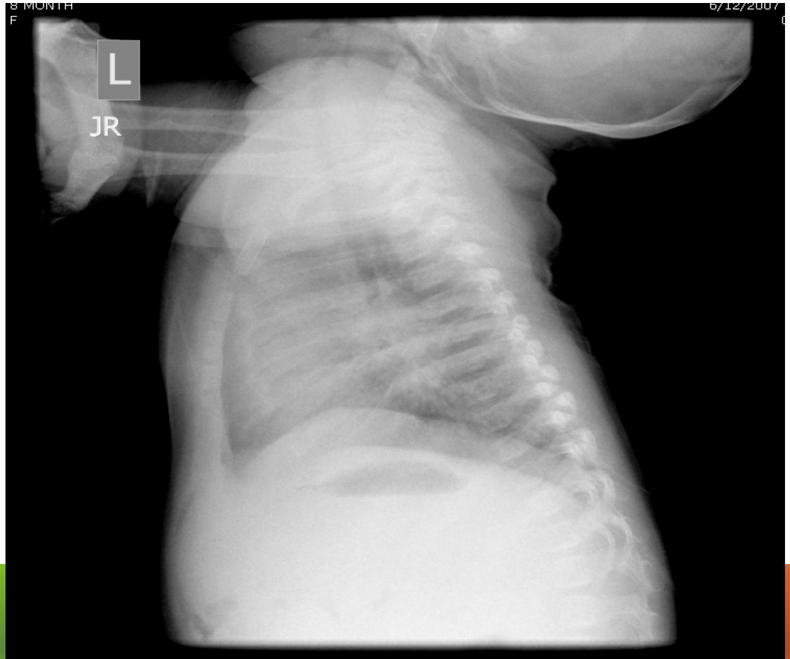


10 month old Ethiopian adoptee, growing and thriving in her new home, TST positive s/p BCG

10 year old Ethiopian adoptee MDR-TB

Extrapulmonary tuberculosis

- >25% of children have extrapulmonary TB
  - 67% lymphatic – mediastinal and scrofula
  - 13% meningeal
  - 6% pleural
  - 5% miliary
  - 4% bone and joint
  - 5% others
    - intra-abdominal
    - ears and mastoids
    - skin, laryngeal, kidneys, etc.



Scrofula

- Enlarging nodes
- Not particularly painful
- Skin becomes dusky and thin / flaky over time
- May eventually suppurate and drain
- Differential diagnosis: bacterial; cat scratch disease, non-tuberculous mycobacteria

Bacteriologic diagnosis

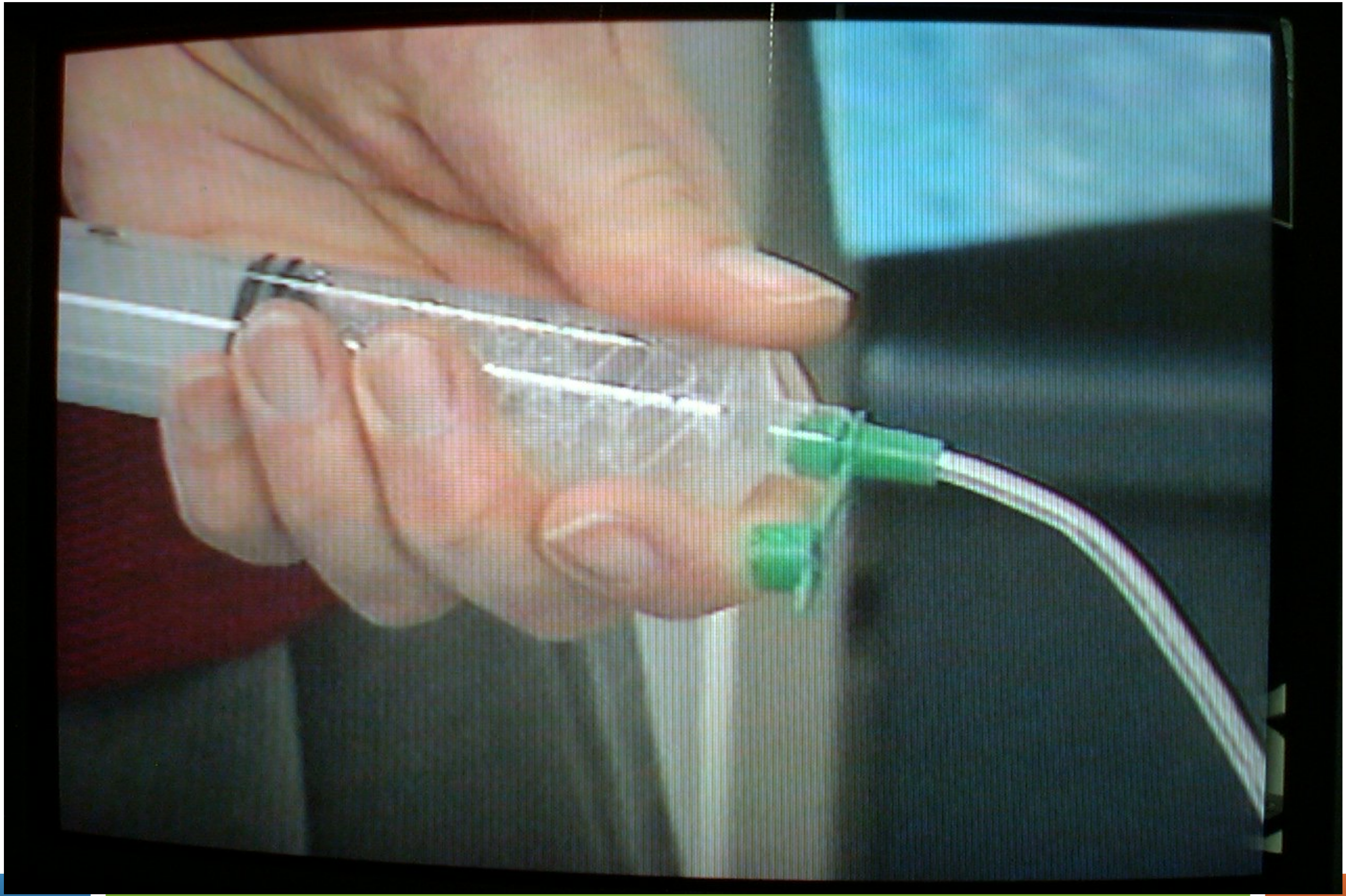
- Sputum can rarely be collected from children
- Can try sputum induction in older children
- South African protocol for sputum induction in younger kids
- Bronchoalveolar lavage is invasive, expensive and should be reserved for situations where the diagnosis is in question

Bacteriologic diagnosis (2)

- Gastric aspirates
  - people swallow mucus in their sleep
  - collect gastric contents before the stomach empties
  - https://www.currytbcenter.ucsf.edu/products/pediatric-tuberculosis-guide-gastric-aspirate-procedure
    - Pediatric on-line course: resources

Gastric aspirate collection

- Have everything ready
- Have helper if possible
- Restrain the child well (or not)
  - mark tube length to stomach with pen
  - insert at least 10 French catheter through nose
  - stay away from septum
  - aim straight at the bed



Gastric aspirate collection (2)

- If insignificant yield:
  - put any yield in sterile container
  - check tube position in stomach by instilling air and listening with stethoscope
  - instill 20 ml sterile water
  - re-aspirate
  - if no good mucous – advance and withdraw tube, roll the child, etc. looking for mucous
  - continue to aspirate syringe as you withdraw tube

Gastric aspirate collection (3)

- Put all yield in sterile cup or tube
- Immediately transport to lab for neutralize ***OR***
- Neutralize at bedside
- Order AFB smear and culture

(Bicarbonate for neutralization – 2.5 grams $NaHCO_3$ dissolved in 100 cc deionized water. Filter the solution through a 45um filter. Use 1.5 cc for each specimen. Lab should monitor and correct the pH)

Gastric aspirate yield

- A negative culture does not rule out TB
- **First** specimen is the very highest yield
- Nearly 100% yield for <3-month-olds
  - smear rarely positive after 3 months
- Literature for 3 gastric aspirates: 40%

Non-respiratory specimens

Smear / culture / NAAT (usually Xpert MTB/RIF)

Cerebrospinal fluid / pleural or pericardial fluid

Fine needle aspirate

Biopsy or Resection

Do not put these specimens in formalin!!!

Do not put these on a swab

Sterile specimen tube or cup

Paraffin imbedded tissue

A few labs will extract Mtb DNA from paraffin impeded tissue

- Univ of Washington
- Stanford (also looks for rpoB mutation)

- CDC - takes many weeks, but if Mtb DNA extracted, they will try look for many resistance mutations.

Pediatric contacts

- Infants less than 1 year of age have a 40% chance of developing TB disease if infected
- They can rapidly progress to disseminated disease
- Risk gradually declines in the first four years

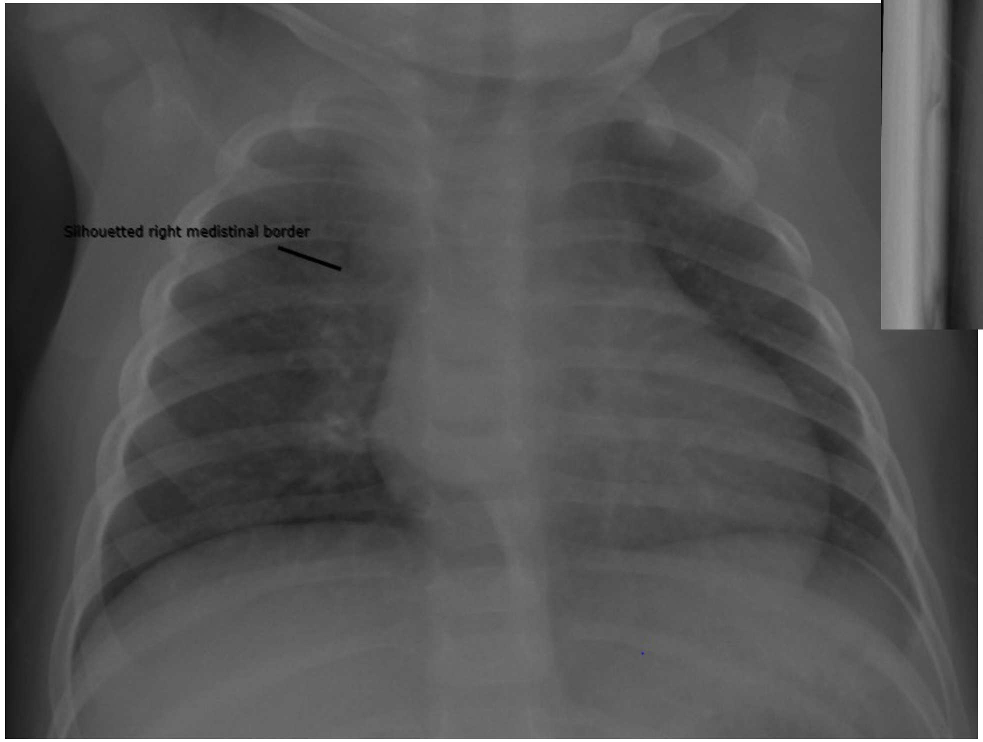
DAA

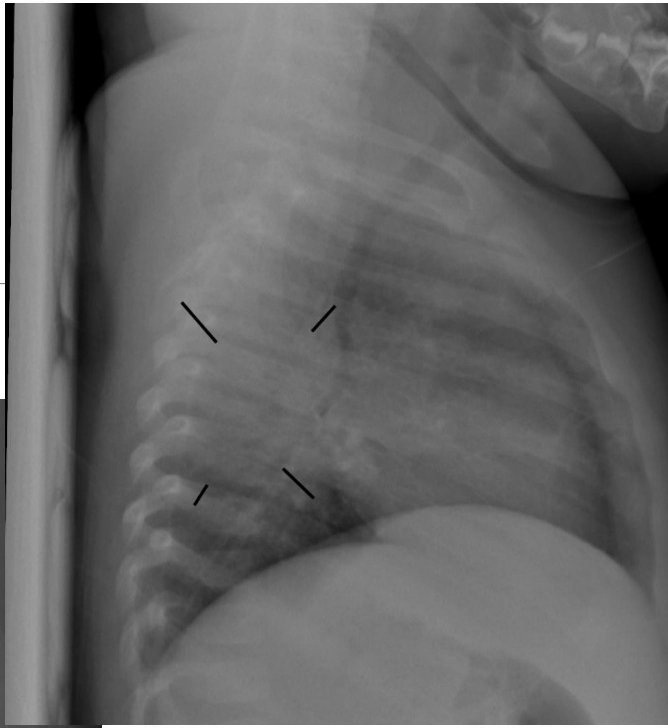
- ~ 20 yo son of SMEAR + Congtagious lady is not answering calls and texts from public health
- He and young family living in central valley.
- Mom gets message that they need to be tested
- She takes 10 mo child to community clinic and they both have negative IGRA

- Subsequently, she is seen at a local ED for respiratory symptoms. No CXR or TB testing is done.

DAA

Eventually, the 12 mo old child was admitted to a children's hospital for fever and vomiting and developed recurrence of cough. **QFT is now positive**, pt is symptomatic with abnormal CXR and GA grew MTb





Class 1 exposure

- Exposure to an adult or adolescent / teen with TB disease:
  - TST placement or IGRA; chest radiograph (PA and lateral) - best reading
  - physical exam to rule out extrapulmonary TB
  - if no evidence of TB disease,
    initiate “window prophylaxis”

Window prophylaxis

- The practice of treating high-risk individuals
  - with negative TST / IGRA no evidence of TB disease
  - exposed to a likely contagious case of TB
  - with RIF or INH (unless source case resistant)

Window prophylaxis (2)

- Repeat TST / IGRA 8-10 weeks
  - after source case non-contagious OR
  - contact with source case broken
  - if TST / IGRA reliable (4-6-12 months of age/immunocompetent)
- Stop prophylaxis if TST / IGRA negative and no other source case!!

Window prophylaxis (3)

- Pediatricians and pediatric providers do not consistently know about urgency to test and treat young child contacts

- Refer them to the AAP RedBook 2024 page 918

Therapy for Contacts. Children and adolescents recently exposed to a contagious person with TB disease should have a TST or IGRA test performed and should be evaluated for TB disease (history and physical examination, as well as chest radiography if symptomatic or positive TST or IGRA results). For exposed contacts with impaired immunity (eg, HIV infection) and all contacts younger than 5 years, treatment for presumptive TBI should be initiated with either isoniazid or rifampin, even if the initial TST or IGRA result is negative, once TB disease is excluded (see Treatment Regimens for TBI, p 898). Children with TBI can have a negative TST or IGRA result because a cellular immune response has not yet developed or because of anergy. Children with a negative TST or IGRA result should be retested 8 to 10 weeks after the last exposure to a source of infection. If the TST or IGRA result still is negative in an immunocompetent person, treatment can be discontinued. If the contact is immunocompromised and TBI cannot be excluded, after an evaluation for TB disease, treatment should be continued to the completion of the regimen. If a TST or IGRA result of a contact becomes positive, the regimen for TBI should be completed after an evaluation for TB disease.

Treatment of latent TB infection

Regimen	Adults	Children
INH and rifapentine	Weekly X 12 doses	>2yrs, ideally observed, weekly x 12 doses
Rifampin	4 months	4 months
INH and rifampin	3 months	3 months
Isoniazid	6-9 months	9 months

Drug/regimen	Children
Isoniazid – daily	10-20 mg/kg/dose up to 300 mg
Isoniazid – thrice weekly DOPT (rarely used)	20-30 mg/kg/dose up to 900 mg
Isoniazid – weekly with rifapentine	25 mg/kg in patients 2-11 yrs up to 900 mg; 15 mg/kg for $\geq$ 12 yrs
Rifapentine	Wt: 10 – 14 .0 kg = 300 mg 14.1 – 25.0 kg = 450 mg 25.1 – 32.0 kg = 600 mg 32.1 – 49.9 kg = 750 mg Up to 900 mg
Rifampin – daily or Thrice weekly DOPT	15-20 mg/kg/dose older kids up to 600 mg (higher end for infants and toddlers)

TABLE 5. **Rifampin (RIF, R): Standard dose RIF**

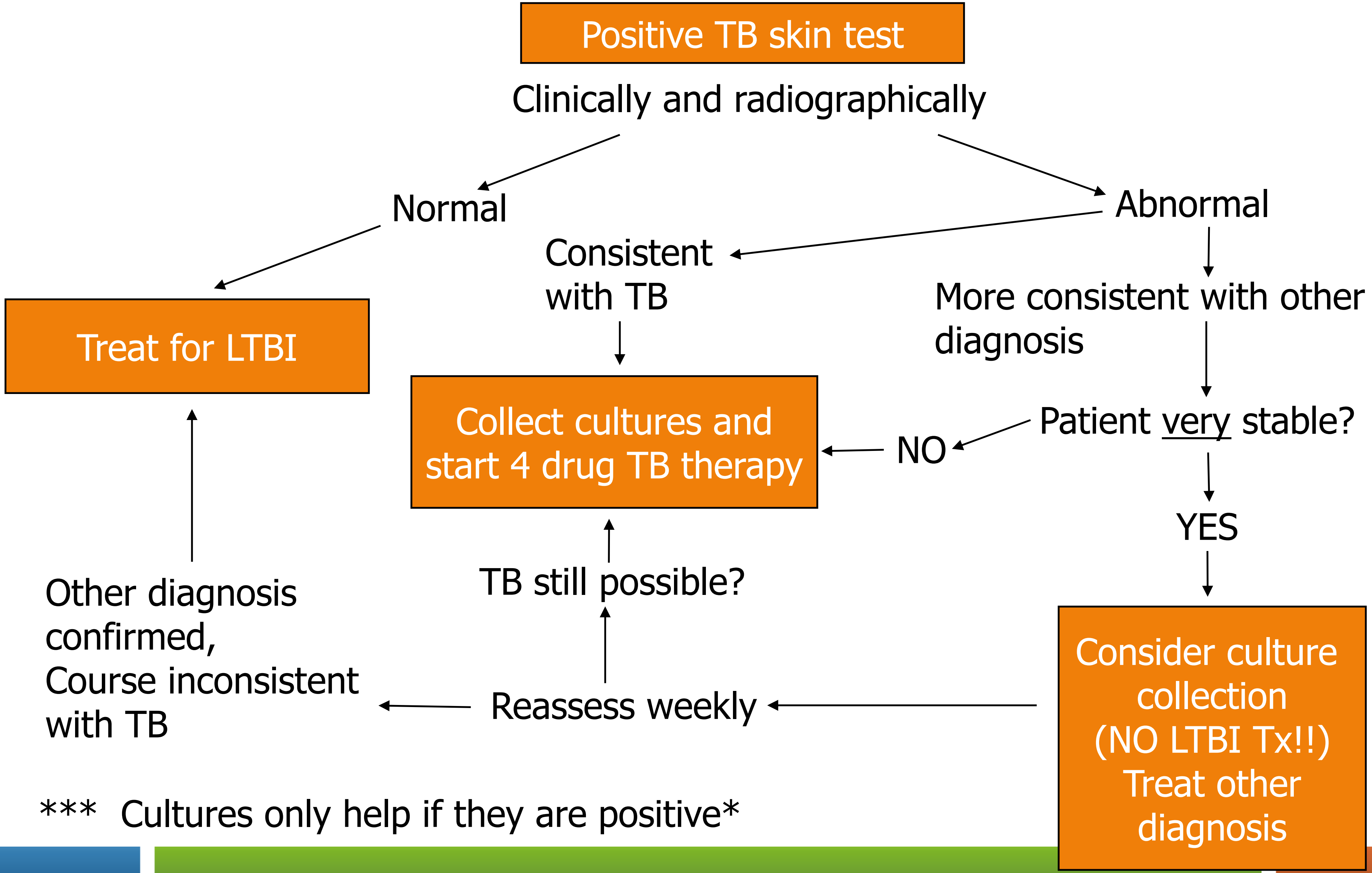
Standard RIF dosing for RIF-susceptible LTBI in children of all ages and non-severe/non-extensive TB disease in older children (outside the infant/toddler age group). See **Table 6** for high-dose RIF.

Child's weight		**Daily rifampin dose:** 15 - 20 mg/kg/dose			
KILOGRAMS	POUNDS	MILLIGRAMS	SUSPENSION 125 mg / 5 ml	150 mg CAP	300 mg CAP
Neonates < 28 days of age		10 mg/kg: use suspension		–	–
Infants >28 days and <3.75 kg		Use suspension			
3.75 – 6	Up to 13.2	75 mg	Weight in kg x 18 mg/kg = mg dose. Divide mg dose by 25 mg/ml and **round** to the nearest ml or 0.5 ml dose up to 600 mg or 24 ml	½	0
6.1 – 10	13.3.1– 22	150 mg		1	0
10.1 – 15	22.1 – 33	225 mg		1 ½	0
15.1 – 20	33.1 – 44	300 mg		0	1
20.1 – 30	44.1 – 66	450 mg		1	1
Over 30 kg	Over 66 lbs	600 mg		0	2
Maximum daily rifampin dose: 600 mg					

SG3_2022_Chapter6_Pediatrics.pdf (ucsf.edu)

Pediatric TB:

- A decision to treat is a decision to treat
- Most often, once TB treatment is begun, it must be completed
- Unlike adults – positive cultures often not available
- Clinical or radiographic improvement on treatment may be attribute to TB treatment or spontaneous resolution of another process



*** Cultures only help if they are positive*

Treatment regimens

- TB disease
  - four drugs for two months
  - if chest radiograph is not worse, compliance good, and isolate presumed sensitive, two drugs for **two to four more months**
  - miliary or CNS disease – one year
  - Daily (or rarely, three times weekly) dosing in the continuation phase

RESEARCH SUMMARY

Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children

Turkova A et al. DOI: 10.1056/NEJMoa2104535

CLINICAL PROBLEM

Most children with tuberculosis (TB) have nonsevere disease, which probably could be treated with shorter regimens than the currently recommended 6 months. However, data from randomized trials of this approach in children are limited.

CLINICAL TRIAL

Design: An open-label, parallel-group, randomized, controlled trial examined whether 4 months of treatment would be noninferior to 6 months of treatment in children with nonsevere, symptomatic, presumably drug-susceptible, smear-negative TB in sub-Saharan Africa and India.

Intervention: 1204 children younger than 16 years of age were randomly assigned to 4 or 6 months of standard first-line anti-TB treatment with World Health Organization–recommended pediatric doses. The primary efficacy outcome was unfavorable status — defined as treatment failure or change, loss to follow-up during treatment, TB recurrence, or death — by 72 weeks.

RESULTS

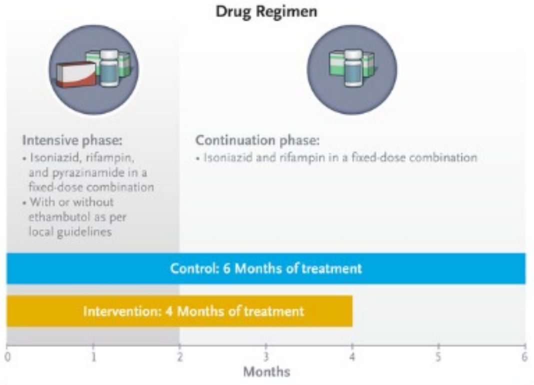
Efficacy: The percentage of children with an unfavorable status by week 72 did not differ significantly between the groups, showing noninferiority of the shorter regimen.

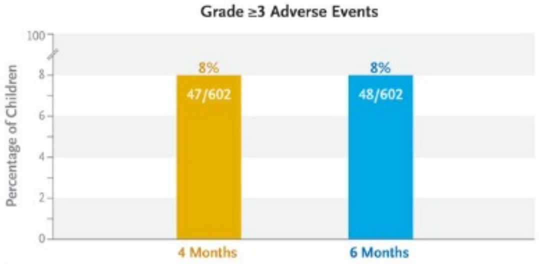
Safety: The percentage of children with an adverse event of grade 3 or higher during treatment or in the 30 days after treatment did not differ significantly between the groups. Pneumonia or other chest infections were the most common such events.

LIMITATIONS AND REMAINING QUESTIONS

- The open-label design of the trial may have led to more treatment extensions with the 4-month regimen.
- It is unknown whether the results would apply to sites without radiographic capabilities to confirm nonsevere TB.

Links: Full Article | NEJM Quick Take | Editorial





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The NEW ENGLAND JOURNAL of MEDICINE

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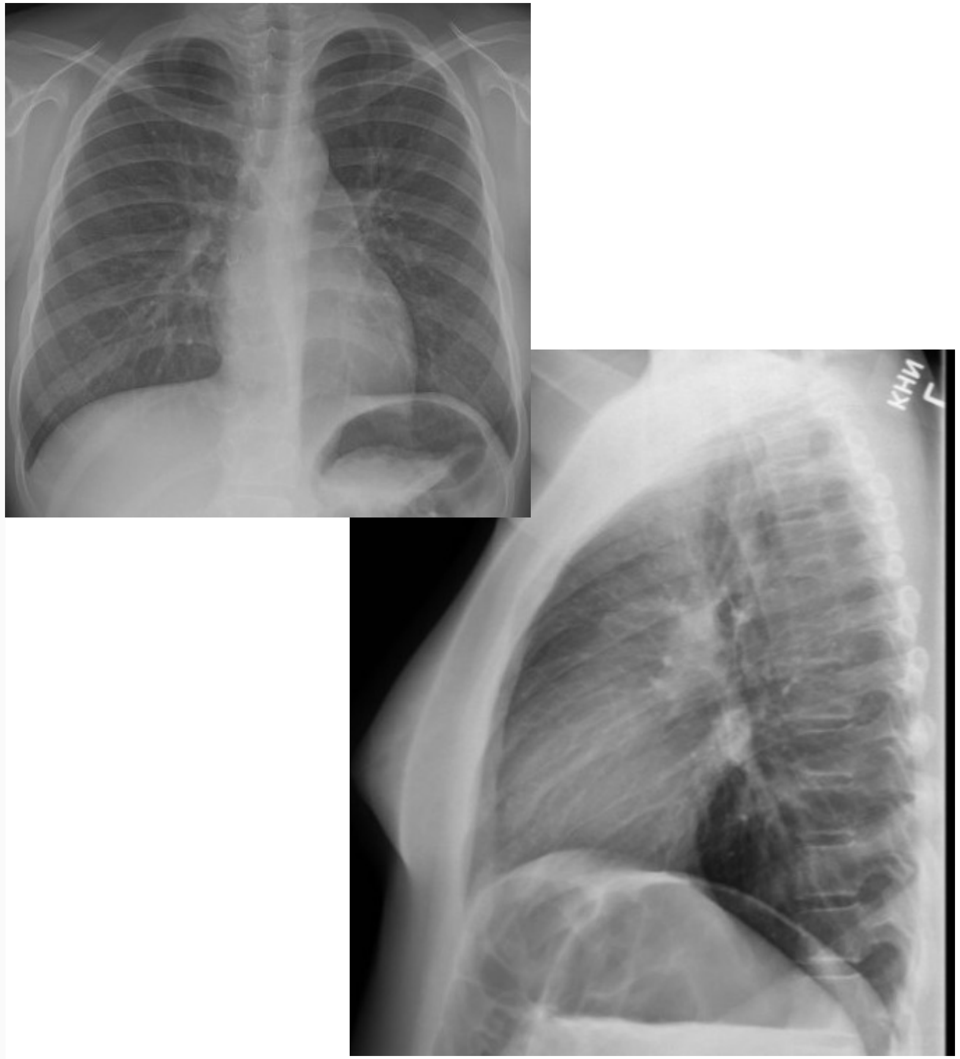

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Dosing difficulties

- Avoid liquid suspensions
  - INH is only commercially available. High osmotic load, stomach upset
  - Babies tolerate it better
  - Increasing data for rifampin. Ok to use compounded suspension and add powder from other meds just before use

Dosing difficulties (2)

- Crush or fragment tablets, open capsules onto vehicle and layer with a topping of the food

Dosing difficulties (3)

- Use thick, strong flavored vehicles:
  - jelly
  - Nutella
  - chocolate whipped cream
  - syrup
  - chocolate sauce
  - baby foods
- Give a spoonful of vehicle before and after drug dose

Dosing difficulties (4)

- Small amounts of non-sugary liquids
- Rarely, dose infants in their sleep

Not always smooth sailing

Running the list

- How is the child doing clinically?
  - Cough, fever, affect, energy, appetite, weight, work of breathing
- Are we sure we have the right diagnosis?   Or the only diagnosis?
- Could there be drug resistance? Alternate source case?
- Are the doses all perfect?
- Is the child taking and retaining every drop?

Common issues

It just takes a long time for lymph node disease / immune response to improve

Paradoxical reaction – clinical / radiographic worsening, usually after TB meds started.

- Usually lymph node / tuberculoma effect
- Most dramatic in CNS disease

Immune reconstitution - (IRIS) – usually reserved for PL HIV / ART

Airway compression

- Endobronchial TB
- Bronchogenic spread
- Ball valve phenomenon – air trapping

Conclusion

- Children are not always easy to diagnose or treat with TB
- Collaboration between TB nurses / providers / pediatric experts is key
- The biggest challenge is often in dosing the meds
  - Allow a period of adjustment and anticipate need for changes in regimen dosinmg

- The question of clinical or radiographic worsesning OFTEN arises
- Most images are not better at two months into therapy
- "Run the list" and seek input from the most experienced clinician