

CURRY
INTERNATIONAL
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CENTER

Pediatric Tuberculosis

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Introduction

- Basic situations in which children are evaluated
- Diagnosis and treatment of latent TB infection (LTBI)
- Tuberculosis (TB) treatment strategies



Reasons for complacency

- Pediatric TB is uncommon in the U.S.
 - In 2015, 440 pediatric TB cases in the U.S.
- Young children with TB are usually not contagious
- Adults with TB are relatively easy to identify
 - More symptomatic and can produce sputum
- Children with TB are difficult to diagnose

Reasons to learn about pediatric TB

- Worldwide, an estimated 1 million children annually become ill with TB
- Children represent up to 30% of TB cases globally, compared to 5% in U.S.
- Children age 0-4 years are more likely to develop TB once infected and are more vulnerable to disseminated TB
- Children serve as indicators of contagious adolescents or adults with TB

Three basic situations

1. General pediatric care for healthy children
 - Screen for TB risk factors
2. Child contacts to adults with potentially contagious TB
 - Evaluation and intervention required
3. Children with signs or symptoms of TB **or** radiographic changes
 - High index of suspicion required



Quiz question

Which situation yields the most cases of TB in children?

- Screening of healthy, asymptomatic children
- Screening of children exposed to contagious adults with TB
- Evaluation of children with symptoms concerning for TB



How are most cases found?

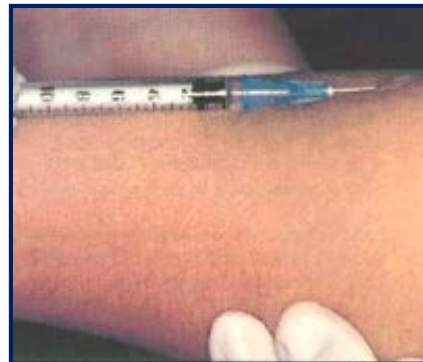
From various studies published in the U.S.:

- 26-80% of children with TB identified during contact investigations
- 3-25% of cases identified by routine screening
- 17-44% of cases presented because of symptoms

In developing countries, no screening of asymptomatic children.

Routine pediatric care: No more universal testing

- It is not cost-effective to routinely skin test healthy children without risk for TB infection or disease!
- Preferred strategy: “targeted testing”
 - Test only children more likely to be exposed to TB



Pediatric TB Risk Assessment Tool

- Developed by California TB Control Branch; released in 2016
- Tool for identifying asymptomatic children for LTBI testing

The image shows a screenshot of the 'California Tuberculosis Risk Assessment Pediatrics' form. At the top, it features the logos for the California Department of Public Health (CDPH) and the California Tuberculosis Control Branch (CTCB). The form includes a list of instructions for using the tool, such as 'Use this tool to identify asymptomatic children for whom TB infection (Tb) testing' and 'Do not repeat testing unless there are possible factors since the last negative test'. Below the instructions, there are three checkboxes for risk factors: 'Birth, travel, or residence in a country with an elevated TB risk for at least 1 month', 'Immunosuppression, current or planned', and 'Close contact to someone with infectious TB disease during lifetime'. A dark blue box contains the text 'Treat for LTBI if L-TbI test result is positive and active TB disease is ruled out.' At the bottom, there are fields for 'Provider Name', 'Patient Name', 'Assessment Date', and 'Date of Birth'. A QR code and a footer with the date 'May 2007' are also visible.

<https://www.cdph.ca.gov/programs/tb/Documents/TBCB-CA-Pediatric-TB-Risk-Assessment.pdf>

Advantages of targeted testing

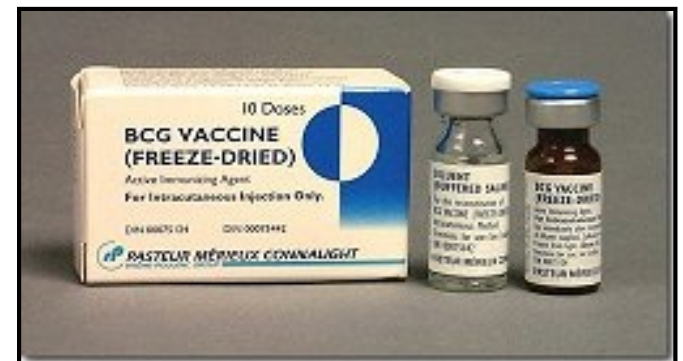
- Up to 85% of TST positive results will be FALSE positives in areas of low TB prevalence
 - More expense, anxiety, and unnecessary evaluations and treatment
- TST is not free, not without discomfort, and not so easy to place and interpret
- Families often do not return for TST reading

TST = tuberculin skin test

What about BCG?

- BCG vaccine is routinely given to newborns/infants in most areas of the world
- Ignore history of BCG when placing or interpreting TST
- Increased risk of positive TST results being caused by BCG
 - BCG received as an older infant or child (>1 month of age)
 - Multiple BCG doses
 - BCG in recent past

BCG = bacille Calmette-Guérin vaccine



Interferon Gamma Release Assays (IGRAs)

- Newer option for clarifying dx of TB infection
- QFT-G and T-SPOT[®].TB are licensed in U.S.
- Both incubate patient's blood with TB-specific proteins and controls
- Test is (+) if lymphocytes have recognized TB proteins and produced gamma-interferon well above the level in control tube
- IGRAs are better than TSTs at distinguishing true TB infections from those caused by NTM or BCG exposure

Are IGRAs recommended for children?

- IGRA preferred for age 2+ years w/ BCG hx or unlikely to return for TST reading
- IGRA useful when parents are skeptical
- Some experts do not use IGRA in children < 2 years
- Use both TST and IGRA if high concern for TB disease (not for screening)
- Negative IGRA or TST never rules out TB

Statistics about TB risk in U.S. children

- 20% of children with TB are born outside U.S.
- 43% are Hispanic
- 20% are Asian
- Many pediatric cases are identified during evaluation of contacts of adults with TB



Questions validated to predict risk

- Was your child born in Latin America, Asia, Eastern Europe, or Africa?
- Since last TST / IGRA, has child traveled outside the U.S.?
- Since last TST / IGRA, has child been exposed to anyone with TB or with a (+) TST / IGRA ?



Questions to predict risk – local epidemiology

- Since last TST / IGRA, has child consumed unpasteurized dairy products from Mexico?
- Since last TST / IGRA, has child been around people who have been incarcerated, homeless or in shelters, or people who have HIV, or use illegal drugs?
- Since last TST / IGRA, has child lived with new person who was born or traveled outside U.S.?

Targeted TB skin testing

- Don't skin test someone you won't treat if TST is positive
- If child has no TB exposure risks, don't skin test!
- “A decision to test is a decision to treat.”



TST basics

- Store PPD in the bottle, clearly labeled in refrigerator; discard open bottles after 1 month
- Providers who administer TST should be trained and evaluated on TST technique
- Inject 0.1 ml of PPD material intradermally into volar aspect of forearm
 - Correct placement yields pale, distinct wheal, raised for several minutes

PPD = purified protein derivative

Reading TST results

- A trained professional should read TST results 48 to 72 hours after placement
- A positive test has distinct induration, not just erythema:
 - Bend arm at elbow; look with indirect light
 - Feel gently with your non-dominant hand or run pen across the induration
 - Measure and record result in millimeters of induration perpendicular to long axis of arm

TST interpretation

- ≥ 5 mm is (+) only if child is:
 - immunocompromised
 - a contact to a known or suspected case of TB
 - has clinical or radiographic evidence of TB or old TB
- ≥ 10 mm is (+) for child with intermediate risk:
 - age <4 years
 - medical conditions predisposing them to TB or increased risk of TB exposure
- ≥ 15 mm is (+) if child has no risk (should not be skin tested!)



If TST is negative

- Document results as millimeters of induration in the chart and vaccine record
- Advise family to return to clinic if induration increases in next few days
 - A (+) TST can be read up to 7 days after placement
- Repeat questionnaire procedure at next well-child visit
- Repeat TST only if child has new risk factor

TB or LTBI?

- TB: child has metabolically active *M. tuberculosis* bacteria in some part of the body
 - Many children are asymptomatic at time of TB diagnosis in U.S.
- LTBI: organism is dormant; physical exam and radiograph are normal
- To decide, perform focused history, physical exam, and chest radiograph

TB = tuberculosis disease

LTBI = latent TB infection

Focused physical exam

- Temperature and growth parameters
- Alertness and meningeal signs
- Peripheral lymph nodes
- Abdomen
- Palpate back and extremities



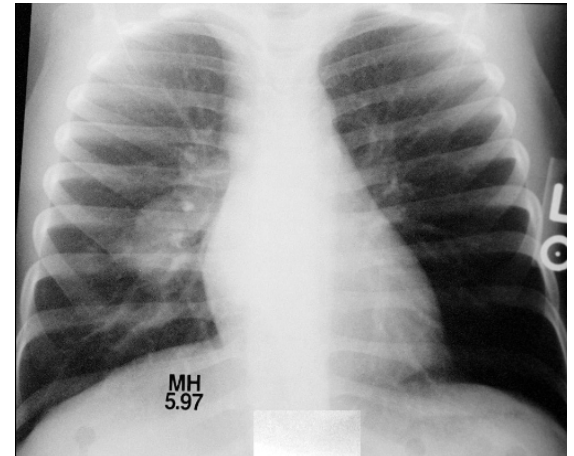
Lung findings

- Lung findings are relatively modest, even with abnormal chest radiograph
- Infants and adolescents most likely to have rales, decreased breath sounds, and increased work of breathing



Chest radiograph

- Two-view chest radiograph helps identify common abnormality: Intrathoracic lymphadenopathy
- Mention symptoms and possibility of TB on radiology order form
- Same-day interpretation by radiologist experienced with pediatric TB is ideal
- Wait until TB is ruled out before starting treatment



LTBI (latent TB infection)

- Normal chest radiograph and physical exam, (+) TST / IGRA = diagnosis of LTBI
- Why treat all children who have LTBI?
 - LTBI treatment is less toxic in children than in adults
 - Young children are more likely to develop TB once infected than are adults
 - Young children were infected recently, increasing risk of progression to TB

When there's doubt...

- After TB disease is ruled out, offer LTBI treatment to all children with positive TST or IGRA
- If parents are reluctant to accept positive TST results, IGRA can be offered; ask parents to agree to LTBI treatment if IGRA is positive
- If IGRA negative, advise parents to watch for symptoms and seek care if they occur

Summary:

Screening well children



- No more universal TB skin testing
- Targeted testing: Review TB exposure and population risk factors; TST / IGRA, only for children with new exposure risks since last TST / IGRA
- If (+) TST / IGRA, conduct focused history and physical exam to discern TB from LTBI

Child contact to a TB case

- Contact investigation: Evaluation of contacts to a contagious TB case
- Young children are high priority for evaluation
 - More likely to develop TB
 - May develop TB within weeks of infection
- Contacts < age 5: immediate chest radiographs, history, and physical exam
- Do not wait for (+) TST / IGRA result before performing evaluation on young child, immunocompromised or symptomatic individual

Treatment of contacts

- If (+) TST / IGRA, , begin a course of LTBI treatment
- If (-) TST / IGRA, , consider treatment as “window prophylaxis”
 - Repeat TST / IGRA after 8-10 weeks of no further exposure to contagious case
 - If TST / IGRA still (-), child is immunocompetent, and no new TB symptoms, stop LTBI treatment
 - If exposure to contagious case has continued, or if another adult in proximity has TB, repeat evaluation and/or extend treatment
 - If (+) TST / IGRA upon repeat testing, complete an LTBI treatment regimen

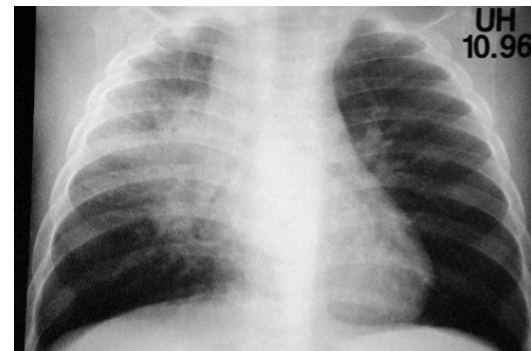
Child contacts > 4 yr

- TST / IGRA and symptom review
- If (-) TST / IGRA and no symptoms, chest radiograph not imperative
- Individualize use of window prophylaxis; local health department can advise you
- Repeat TST / IGRA 8-10 weeks after contact is broken or source case is deemed non-contagious
- If (+) TST / IGRA obtain chest radiograph if not performed initially



Summary:

Child contact



- Prompt TST / IGRAs and symptom review for all individuals with significant exposure to contagious TB case
- Children under 5 yrs or immunocompromised
 - Chest radiograph and physical exam even before TST / IGRAs results
 - If no TB, start window prophylaxis, independent of TST / IGRAs result
- 8-10 weeks after exposure is ended, repeat TST / IGRAs. If (-) TST / IGRAs, stop window prophylaxis (assuming immunocompetence)

Symptoms and abnormal radiographs

- Difficult to distinguish community-acquired pneumonia or asthma from TB on radiographic findings
- Symptoms often subtle or even absent
- Difficult to confirm microbiologically
 - Children cannot produce sputa easily
 - Sputa from young children usually smear (-)



Circumstances that increase TB suspicion

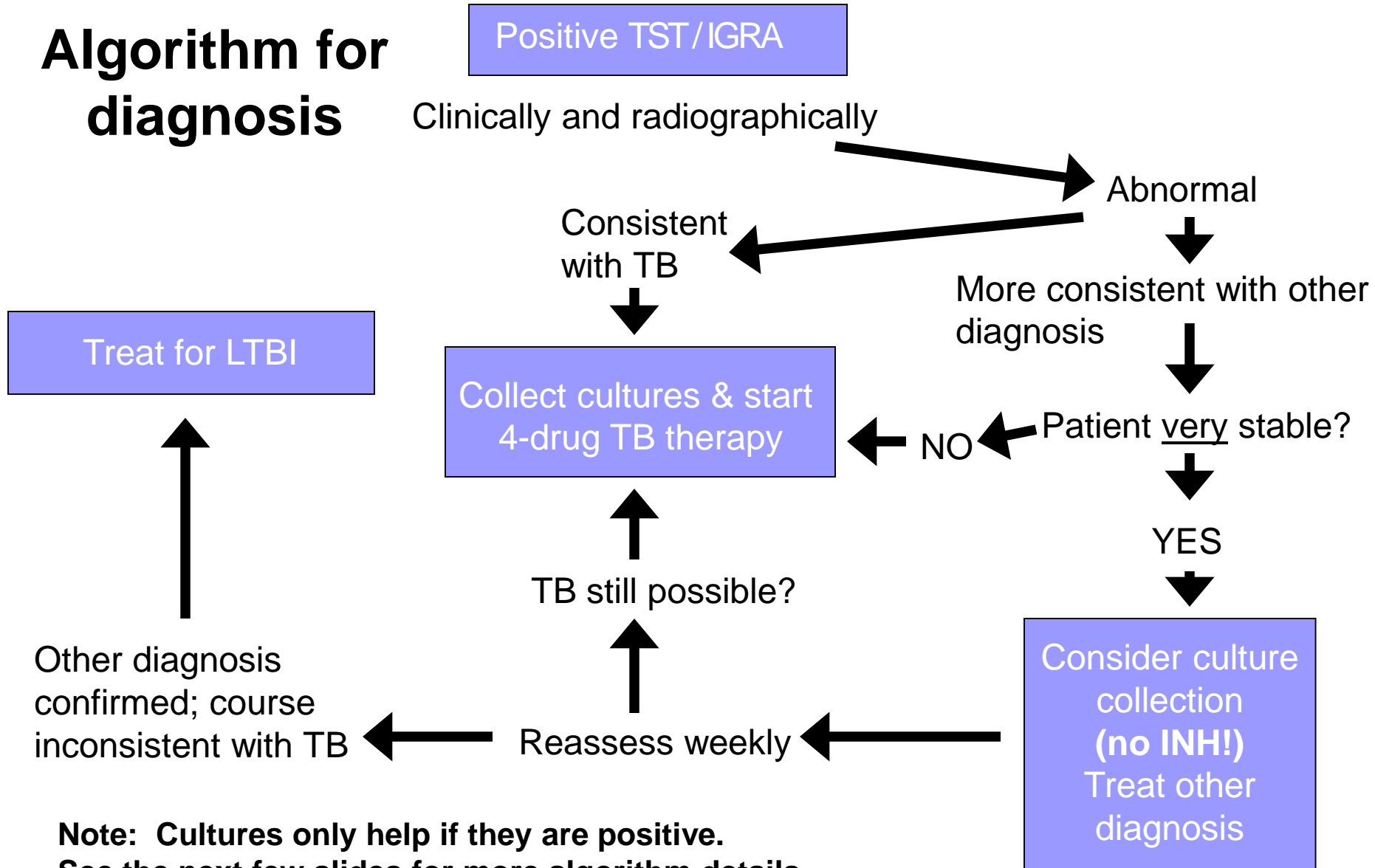
- Exposure to person with TB
- Several people in child's environment with (+) TSTs / IGRAs
- Radiographic changes common in pediatric TB, including intrathoracic adenopathy and calcified granulomata
- A relative paucity or chronicity of symptoms in comparison to radiographic changes

TST / IGRA results are not definitive

- A positive TST / IGRA does not confirm the diagnosis of TB
- A negative TST / IGRA does not exclude TB
- TST / IGRA results are merely one factor in the equation

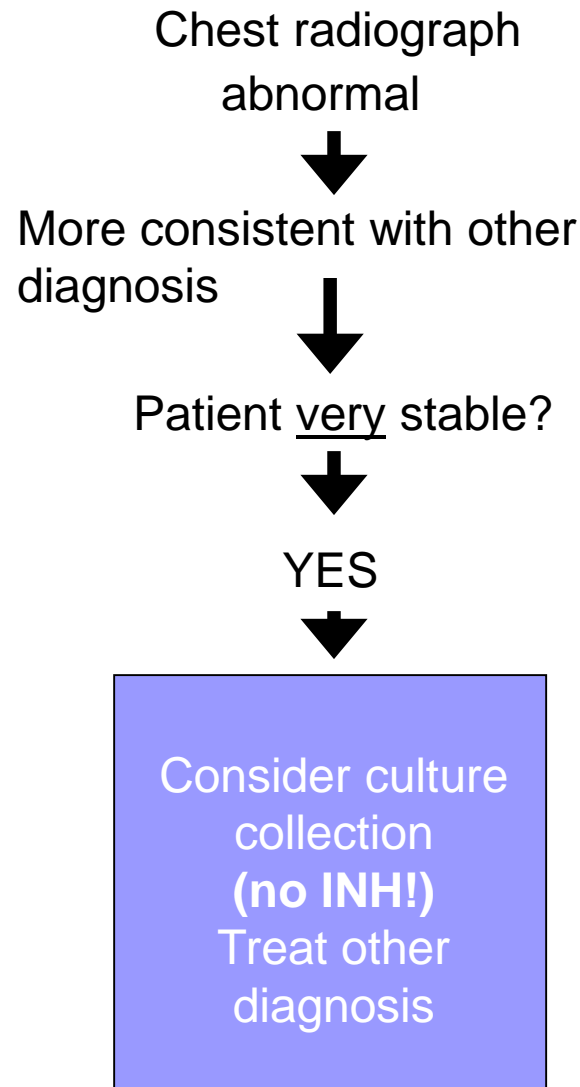


Algorithm for diagnosis



**Note: Cultures only help if they are positive.
See the next few slides for more algorithm details.**

Findings more consistent with another diagnosis...



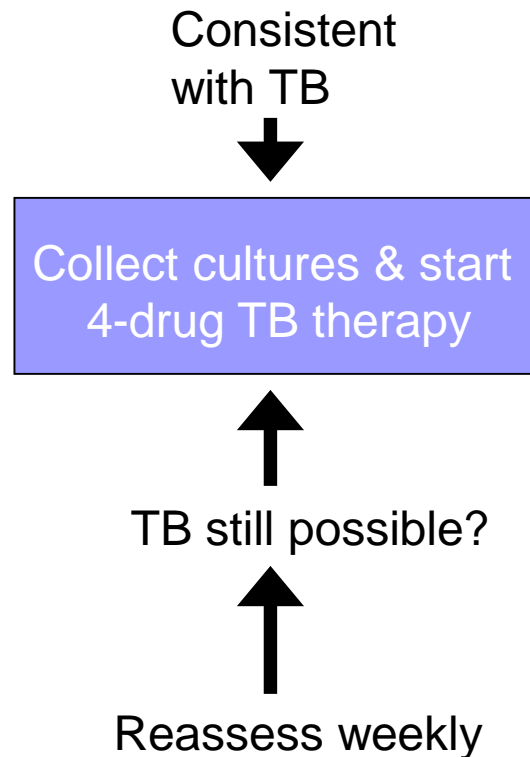
If radiograph normalizes without TB treatment...

Treat for LTBI



Other diagnosis confirmed; course inconsistent with TB

If findings do not normalize...



OK to overtreat in uncertain situations

- If patient is not stable: Submit specimens for cultures and start TB therapy; sometimes diagnosis becomes clear over time
- Sometimes diagnosis doesn't become certain; complete treatment for TB
- Weigh all likely diagnoses, consider risks and benefits, and make best judgment after discussion with family and expert resources

When TB is most likely diagnosis...

Positive TST/IGRA

Clinically and radiographically

Consistent
with TB



Collect cultures & start
4-drug TB therapy

Scrofula

- Scrofula: peripheral mycobacterial lymph nodes
- Typically enlarge over several weeks; not tender unless they enlarge quickly
- Overlying skin discolors, first pink, then dusky or purplish
 - Different from pyogenic lymph nodes
- Children with TB scrofula
 - often have (+) TST/IGRA



Scrofula in brief



■ TB scrofula

- Tends to occur in children over 5
- Associated with TB exposure or risk factors: Travel to endemic areas and consumption of unpasteurized dairy products (*M. bovis*)
- Most often in cervical chains (could be anywhere)
- Associated with larger TST induration

■ Non-tuberculous or atypical mycobacterial scrofula

- More likely in children < 5
- More frequently in submandibular and submental chains.

■ Cat Scratch Disease

- More common in axilla and groin
- Exposure to kittens and history of scratches common

Clinical suspicion, negative TST / IGRA

- A negative TST / IGRA never rules out TB
- 20% of culture-proven pediatric TB cases are TST (-) when initially evaluated
- Pursue diagnosis and treatment of TB:
 - Known source case
 - Radiographic abnormalities most consistent with TB
 - Clinical findings are subtle or more modest than radiographic findings
 - Intrathoracic lymphadenopathy

Culture collection

- Sputum: Older children can collect sputum by induction or in shower
- Gastric aspirate
 - Highest yield specimen for infants
 - ~ 50% yield in children with TB
- Other specimens: Cerebrospinal fluid, lymph node tissue, blood, urine, bone biopsy, synovial fluid
- Submit large volume specimens in sterile container without formalin

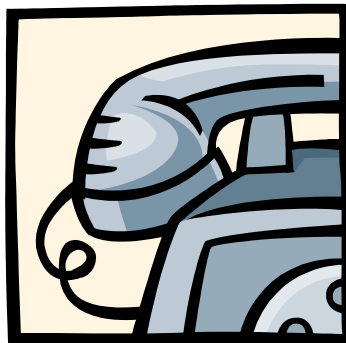


Summary: Diagnosis

- Not everyone with (+) TST / IGRAs has TB
- Not everyone with TB has (+) TST / IGRAs
- Consider TB exposure, TST / IGRAs results, signs/symptoms, and radiographic features
- Test for other likely diagnoses
- Consider a therapeutic trial of bronchodilator therapy or single course of antibiotics
- Utilize dedicated TB clinic or expert pediatric TB consultants

Reporting cases

- Determine local requirements for reporting patients to local health department (LHD)
- Report suspected cases of TB to LHD within 1 working day
- No universal reporting requirement for LTBI



LTBI = latent TB infection

Treatment of LTBI: INH option

- 270 doses of isoniazid (INH)
- Minimum 9 months
- Goal is to finish 270 doses within 12 months



Treatment of LTBI: RIF option

- 4 months of daily Rifampin (15-20 mg/kg/dose)
- 3x per week (15-20 mg/kg/dose) via DOT also probably effective
- Better adherence
- May have fewer side effects than INH

Treatment of LTBI: INH/RPT option

- 12-week course of once-weekly doses of INH and Rifapentine (3HP)
- Administer via DOT
- Strong adherence and efficacy

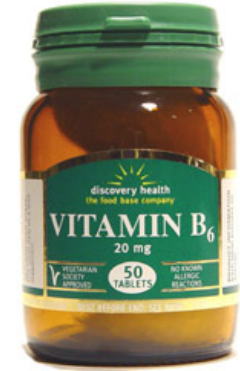
Tips for completing therapy

- Give a big pep talk at beginning of therapy
- Explain:
 - Benefit of treatment
 - Consequences if child were to activate the TB
- If using INH, use tablets, not liquid, to avoid abdominal pain and diarrhea
- Minimize GI side effects by giving drug with snack and/or at bedtime
- Provide calendar and stickers

Liver toxicity

- Liver function testing (LFT) is no longer standard
- Most children tolerate therapy well
- LFT's only for children with:
 - Underlying liver disease
 - Taking other hepatotoxic meds
 - Symptoms of hepatotoxicity
- Watch for anorexia, malaise, abdominal pain
- Make sure family stops treatment and returns for evaluation if symptoms develop

B6 table



Vitamin B6 (pyridoxine) dosing in children

AGE OF CHILD	PYRIDOXINE DOSE	
Infant	6.25 mg	¼ of 25 mg tablet
Toddler	12.5 mg	½ of 25 mg tablet
School-aged	25 mg	25 mg tablet

Tablet can be crushed or fragmented into liquid or soft vehicles.

Summary: LTBI treatment

- Most difficult thing: getting child to take all the doses
- Let family know what to expect
- Teach good tricks for dosing
- Provide incentives
- Ensure families understand symptoms of drug toxicity
- Monthly visits are important; keep them quick



Treatment of TB

- Send child to TB clinic with pediatric expertise
- Confer with local health department and pediatric TB consultant
- Four-drug empiric therapy using directly observed therapy (DOT)
 - DOT: Non-family member observes patient taking medication
 - DOT can increase completion rates to 90% range
 - Can take place at home, work, school, clinic, or street corner

Electronic DOT

- For select families, video or facetime DOT allows for less expensive, more flexible, less intrusive support and monitoring.
- The family doesn't have to wait at home for an outreach worker.
- For families with hard-to-dose children, meds can be given at odd hours, and video files submitted electronically to public health department.

Four-drug treatment table

Adapted from American Academy of Pediatrics (AAP)

DRUG	DAILY dose in mg/kg/dose (maximum dose)	3 TIMES WEEKLY dose in mg/kg/dose (maximum dose)
Isoniazid	10-15 (300 mg)*	20-30 (900 mg)
Rifampin	15-20 (600 mg)**	15-20 (600 mg) ⁺
Pyrazinamide	30-40 (2 grams)	50 (2 grams)
Ethambutol [#]	15-25 (1 gram ^{##})	50 (2.5 grams)

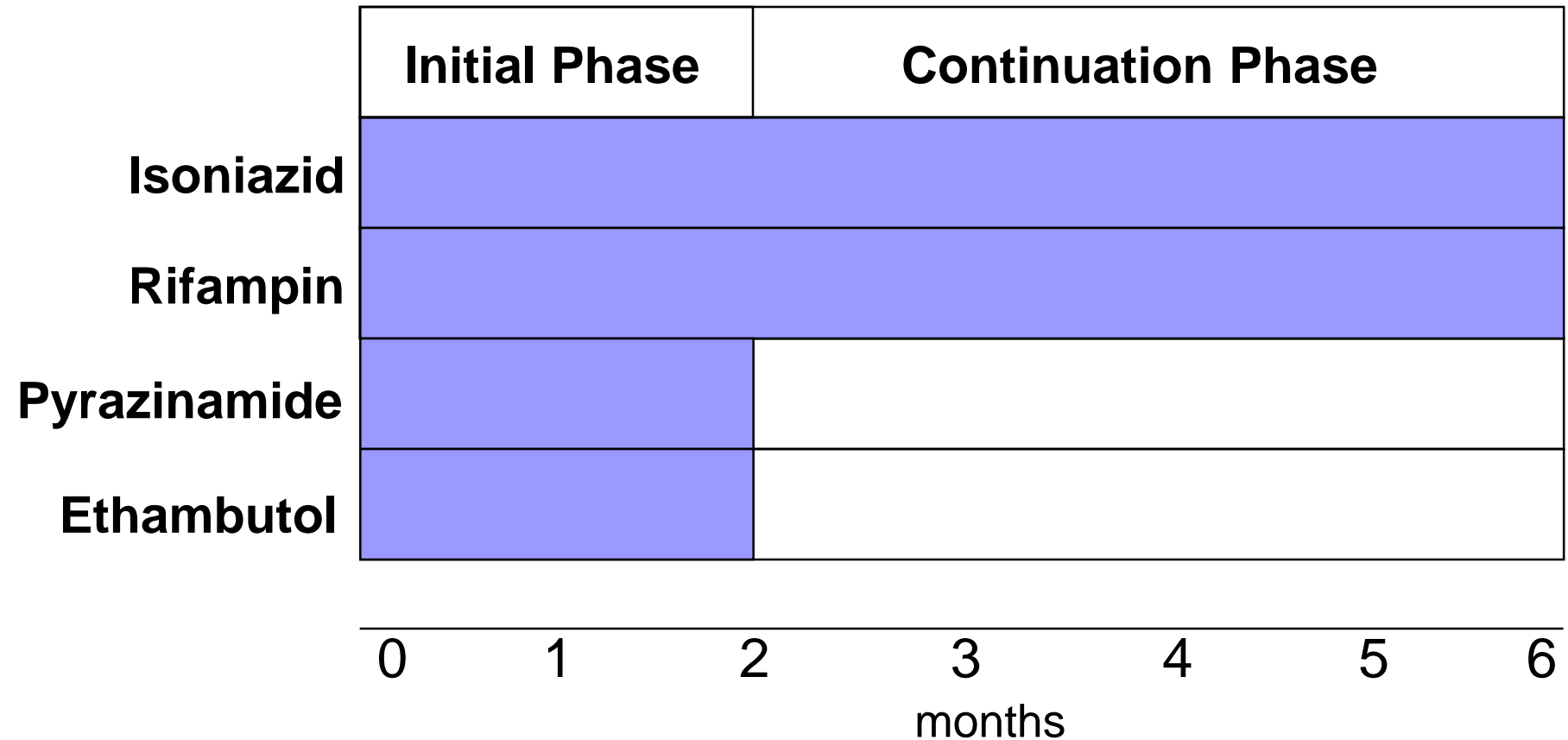
* When isoniazid in a dosage exceeding 10/mg/kg/dose is used in combination with rifampin, the incidence of hepatotoxic effects may be increased.

+ Many experts recommend using a daily rifampin dose of 20–30 mg/kg/day for infants and toddlers, and for serious forms of tuberculosis such as meningitis and disseminated disease.

Consider risk and benefit of ethambutol in children whose visual acuity cannot be monitored.

AAP recommended max dose for daily ethambutol for a child is 1 gram. TB pharmacologists suggest dosing based on lean weight. Max daily dose might exceed 1 gram in a muscular teen.

Course of treatment



Ethambutol can be stopped if the patient or source case isolate is INH/RIF susceptible.

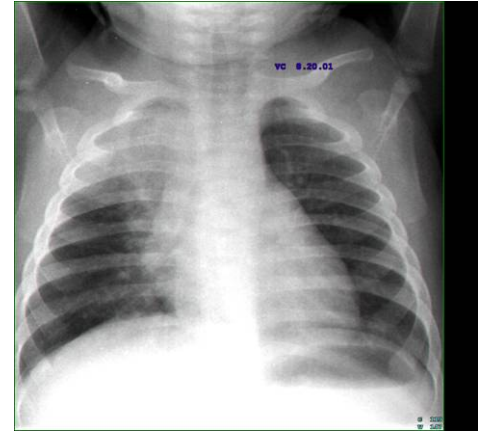
After 2 months of therapy

After two months, regimen can be changed to INH and RIF by DOT 3 times weekly **if:**

- Patient is doing well (gaining weight and not worsening clinically or radiographically)
- Patient is taking and retaining each DOT dose, and appears to be absorbing the drugs
- And there is no concern for drug resistance

Assess the course of treatment

- At two months:
 - Repeat chest radiograph and assess the situation.
 - If adherence and response are good and no particular concern for resistance, treat with INH and RIF for remainder of course
- Total duration of therapy for uncomplicated pulmonary TB is six months, measured by number of doses observed
- Patients receiving a typical regimen receive 40 daily doses and 54 3x-per-week observed doses.



Challenges of treating children

1. Microbiologic confirmation is less common. Monitoring success by serial sputum is nearly impossible
2. Monitoring for toxicity is more difficult. Children tolerate regimens better than adults.
3. INH liquid is poorly tolerated. Need to open capsules, crush tablets, hide drug into soft foods or liquids.

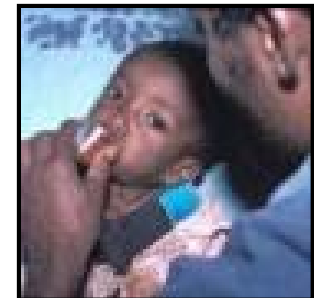


Dosing tips

- Anticipate trial-and-error period for 1-2 weeks
- Don't alienate child while figuring out a good system
- Possible vehicles: Maple syrup, chili, nutella, spinach baby food, chocolate whipped cream
- Layer vehicle and drug on a spoon
- Teach child to take contents of spoon without chewing
- Be prepared to try new tricks or incentives
- Never let child think the dose is optional

Circumstances for prolonged therapy

- If disease is extensive or slow to respond
- If patient has TB meningitis or osteomyelitis (treated for 12 mo)
- If TB isolate is drug-resistant
 - Includes treatment of *M. bovis* (inherently resistant to PZA and often sluggishly responsive to therapy)
- If patient has been poorly adherent



Conclusion

- Pediatric TB is relatively uncommon in U.S. and sometimes missed
- Screen healthy children with risk factor questionnaires and reserve TST / IGRA for those at risk of exposure
- Evaluate children exposed to active cases of TB promptly and thoroughly; they are at highest risk of infection and disease
- Not all children with TB have (+) TST / IGRA and not all children with (+) TST / IGRA and radiographic abnormalities have TB

Next steps

- Peruse course resource materials
- Share the resources with friends and colleagues
- Call a pediatric TB expert for assistance

**Thank you for your care
of the children.**

