CURRY
INTERNATIONAL
TUBERCULOSIS
CENTER

Pediatric Tuberculosis

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Updated May 2025

Introduction

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

Reasons for complacence

- Pediatric TB is uncommon in the U.S.
  - In 2023, 466 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 1.3 million children annually become ill with TB
- Children represent up to 20% of TB cases in high-burden countries, 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?

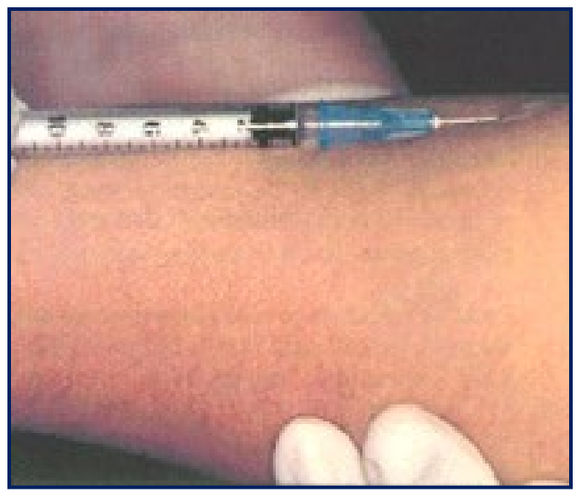
From various studies published in the U.S.:

- 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, often no screening of asymptomatic children.

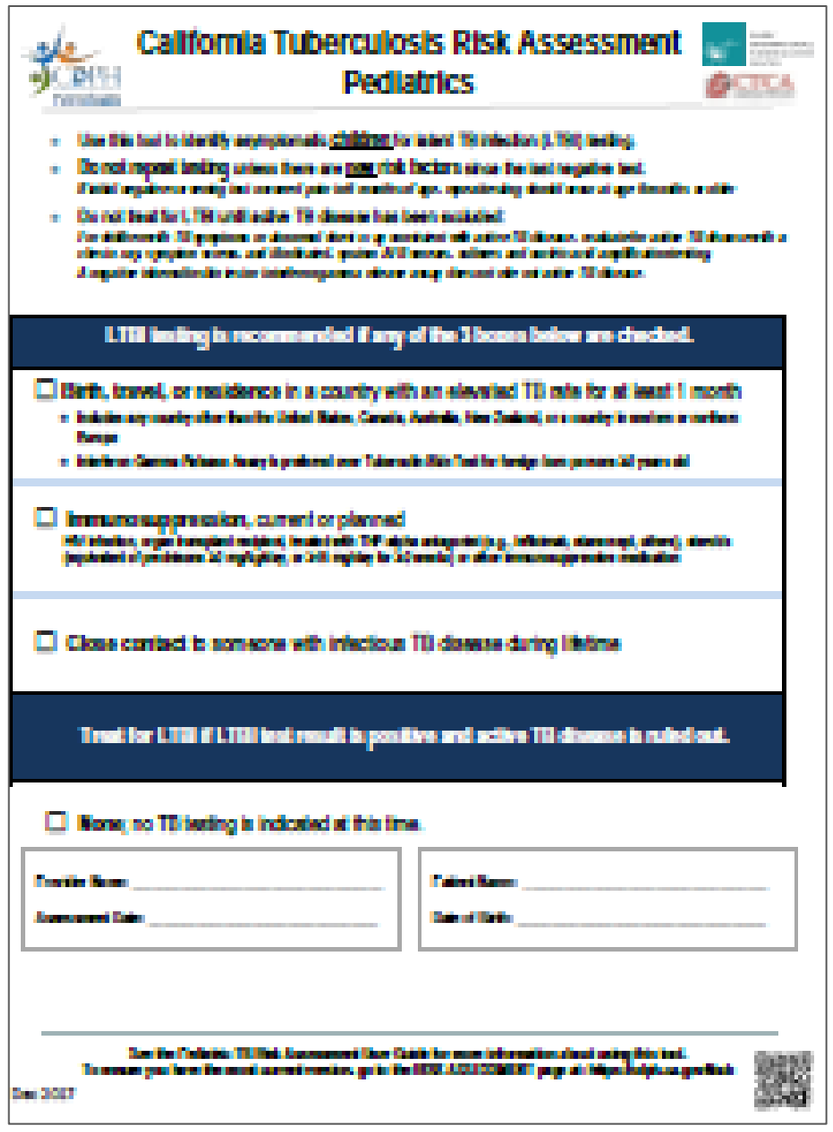
Routine pediatric care: No more universal testing

- It is not cost-effective to routinely 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 2016, updated 2024
- Tool for identifying asymptomatic children for LTBI testing


California Tuberculosis Risk Assessment
Pediatrics

https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/TB-Risk-Assessment.aspx

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
- IGRA blood tests are expensive, uncomfortable, and have risk for false positive/negative results

TST = tuberculin skin test **IGRA = Interferon gamma release assay**

What about BCG?

- BCG vaccine is routinely given to newborns/infants in most areas of the world
- National guidelines suggest using IGRA (not TST) to test children with history of BCG vaccine
- 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)

- Alternative to TST for dx of TB infection
- QFT 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

QFT = QuantiFERON®-TB Gold Plus **NTM = nontuberculous mycobacteria**

Are IGRAs recommended for children?

- IGRA can be used in children of any age; preferred to TST when hx of BCG or unlikely to return for TST reading
- IGRA useful when parents are skeptical
- Use both TST and IGRA if high concern for TB disease (not for screening)
- Negative IGRA or TST never rules out TB

2023 statistics about TB risk in U.S. children

- 28% of children with TB are born outside U.S.
- 45% are Hispanic
- 15% are Asian
- Many pediatric cases are identified during evaluation of contacts of adults with TB

Questions validated to predict risk

- Was 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 ?
- Is child on current (or planned) immunosuppressive therapy?

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 testing

- Don’t test someone you won’t treat if TST/IGRA is positive
- If child has no TB exposure risks, don’t 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!)

Interpreting low-grade IGRA (+) results (1)

- Some low-grade positive IGRA results may be “false (+)”
- Early after infection and in the context of TB disease, a low-grade (+) IGRA should not be dismissed
- After any (+) TB test (TST or IGRA):
  - Perform a chest radiograph
  - Evaluate for disease by H&P
- Some low-grade (+) IGRA may be repeated by TST or IGRA
  - No specific TB risk factors or exposures (other than travel, residence or birth in area of high TB rates)
  - Normal chest radiograph
  - No signs or symptoms of TB disease
  - No immunocompromising conditions

Interpreting low-grade IGRA (+) results **(2)**

2024 AAP *Red Book*:

- Low-grade, false (+) IGRA results occur in some individuals
- For children without specific TB risk factors other than foreign birth or travel
- Unexpected low-level (+) IGRA result
  - QuantiFERON-TB Gold Plus <1.00 IU/mL
  - T-SPOT.TB with 5–7 spots
- Perform a second diagnostic test, either an IGRA or a TST
- The child is considered infected only if both the original and repeated tests are positive

If TST/IGRA is negative

- Document TST 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/IGRA only if child has new risk factor

TB or LTBI?

- TB disease: 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

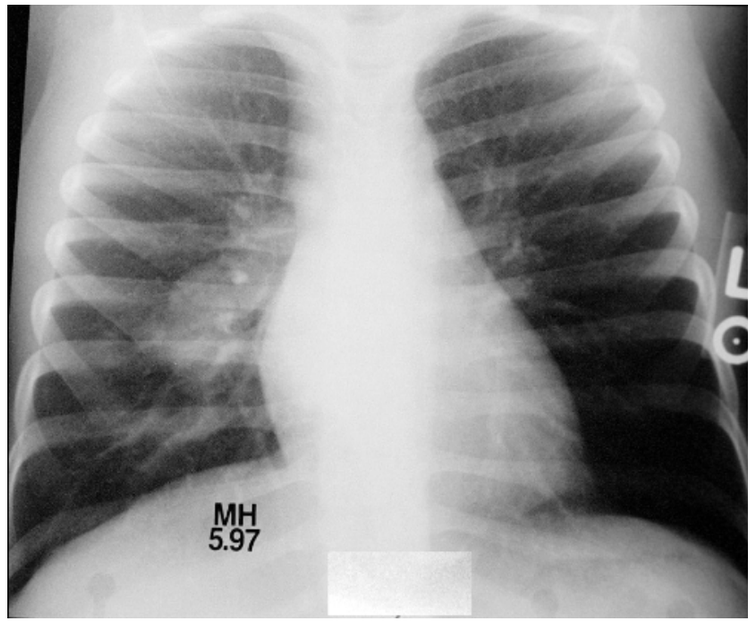
- Temperature and growth parameters
- Alertness and meningeal signs
- Peripheral lymph nodes
- Abdomen
- Palpate back and extremities

Lung findings

- Lung findings are often 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 LTBI 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 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

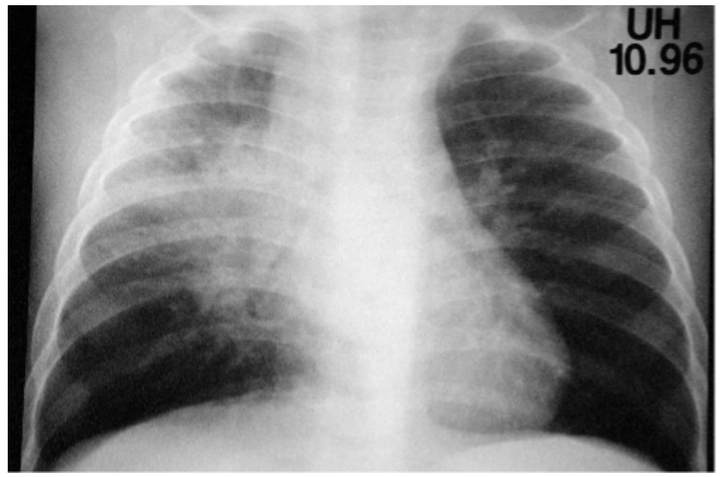
Treatment of contacts

- If (+) TST / IGRA, begin a course of LTBI treatment
- If (-) TST / IGRA, consider treatment as “window prophylaxis” for exposed children <5 yrs of age
  - 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 (now or on 2nd round of testing) obtain chest radiograph if not performed initially

Summary: Child contact



- Prompt TST / IGRA 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 / IGRA results
  - If no TB, start window prophylaxis, independent of TST / IGRA result
- 8-10 weeks after exposure is ended, repeat TST / IGRA. If (-) TST / IGRA , 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 almost always smear (-)

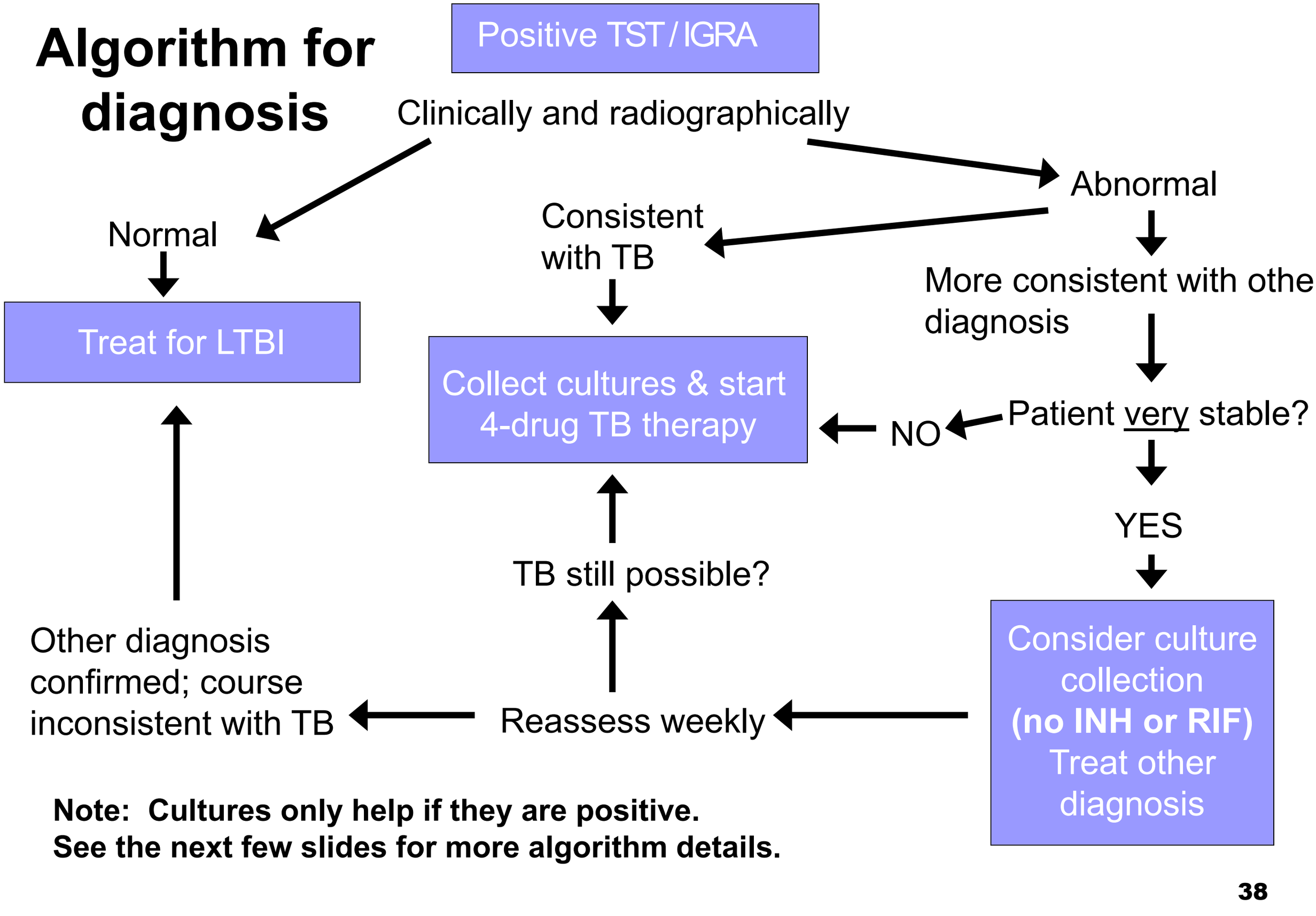
Circumstances that increase TB suspicion

- 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…

Chest radiograph abnormal

↓

More consistent with other diagnosis

↓

Patient very stable?

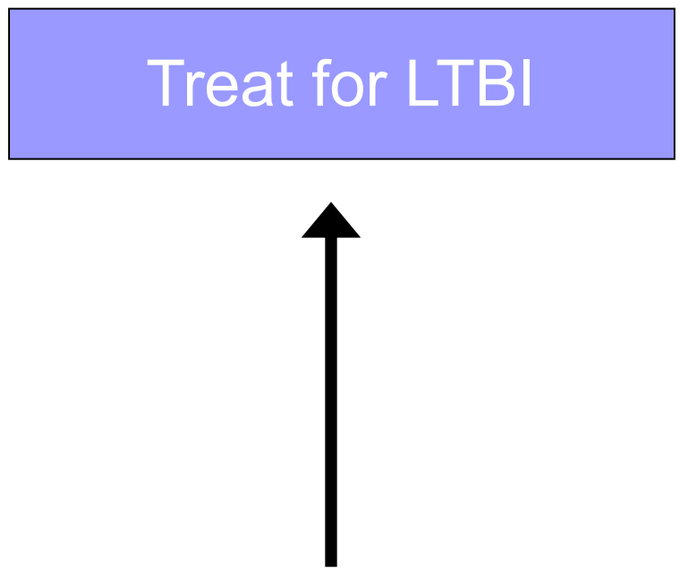
↓

YES

↓

Consider culture collection **(no INH or RIF)** Treat other diagnosis

If radiograph normalizes without TB treatment…



Other diagnosis confirmed; course inconsistent with TB

If findings do not normalize…

Consistent with TB

↓

Collect cultures & start 4-drug TB therapy

↑

TB still possible?

↑

Reassess weekly

OK to overtreat in uncertain situations

- If patient is not medically 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

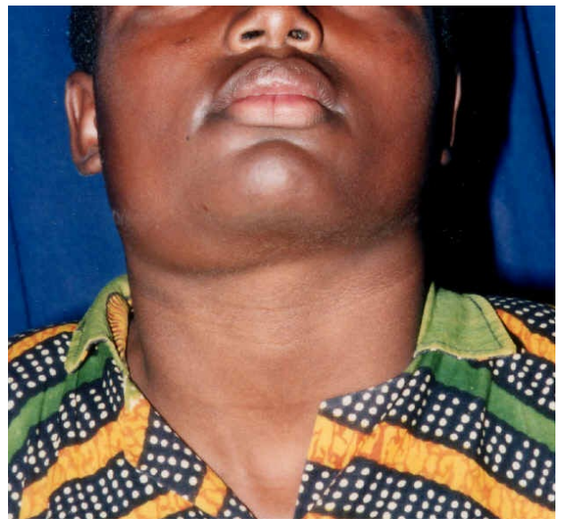
↓

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 yrs of age
  - 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 yrs of age
  - 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 / IGRA negative 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

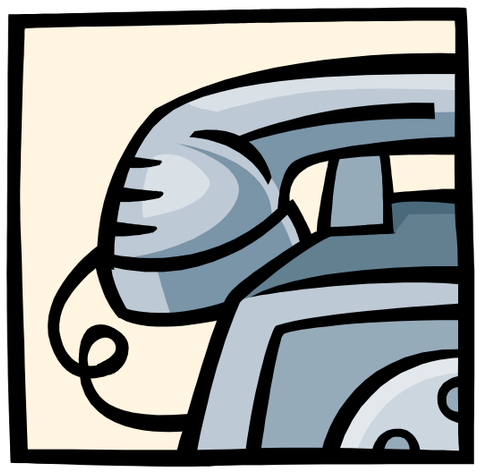
- Other specimens: Cerebrospinal fluid, lymph node tissue, blood, urine, bone biopsy, synovial fluid
- Submit large volume specimens in sterile container without formalin

Summary: Diagnosis

- Not everyone with (+) TST / IGRA has TB
- Not everyone with TB has (+) TST / IGRA
- Consider TB exposure, TST / IGRA 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
Option 1: RIF

- 4 months of daily rifampin (RIF)
  - 15-20 mg/kg/dose
- Better adherence; may have fewer side effects than INH
- RIF interacts with many other meds; review child's med list; alert any other provider if new medications prescribed

Treatment of LTBI
Option 2: INH/RPT

- 12-week course of once-weekly doses of isoniazid and rifapentine (3HP) for children ≥ 2 years of age
- Strong adherence and efficacy
- Administer via DOT or with some sort of support/monitoring
- RPT interacts with other meds; check home med list for drug interactions

Treatment of LTBI
Option 3: INH/RIF

- 3 months of daily isoniazid and rifampin
  - INH child doses: 10–15 mg/kg (max 300 mg)
  - RIF child doses: 15–20 mg/kg (max 600 mg)
  - See weight-based dosing tables in resource material
- Good adherence, shorter regimen but pill burden more than other regimens
- RIF interacts with many other meds; review child's med list; alert any other provider if new meds prescribed
- Lab tests not required until signs or symptoms hepatotoxicity or underlying liver disease

Treatment of LTBI
Option 4: INH

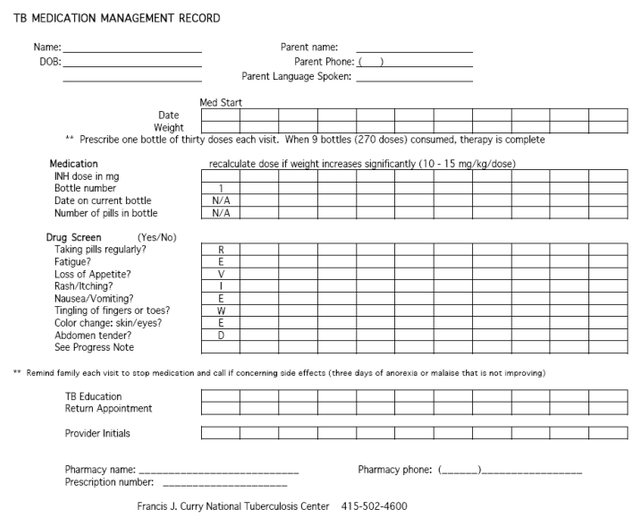
- 270 doses of isoniazid (INH)
- Minimum 9 months
- Goal is to finish 270 doses within 12 months

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

Monthly visits during therapy

- Ensure adherence
- Monitor for toxicity
- Arrange for quick nurse visits



TB MEDICATION MANAGEMENT RECORD

Name: _____ Parent name: _____
DOB: _____ Parent Phone: (___) _____
_____ Parent Language Spoken: _____

	Med Start										
Date											
Weight											

** Prescribe one bottle of thirty doses each visit. When 9 bottles (270 doses) consumed, therapy is complete

recalculate dose if weight increases significantly (10 - 15 mg/kg/dose)

Medication											
INH dose in mg											
Bottle number	1										
Date on current bottle	N/A										
Number of pills in bottle	N/A										

Drug Screen (Yes/No)											
Taking pills regularly?	R										
Fatigue?	E										
Loss of Appetite?	V										
Rash/Itching?	I										
Nausea/Vomiting?	E										
Tingling of fingers or toes?	W										
Color change: skin/eyes?	E										
Abdomen tender?	D										
See Progress Note											

** Remind family each visit to stop medication and call if concerning side effects (three days of anorexia or malaise that is not improving)

TB Education											
Return Appointment											
Provider Initials											

Pharmacy name: _____ Pharmacy phone: (_____)_____
Prescription number: _____

Francis J. Curry National Tuberculosis Center 415-502-4600

- For INH or RIF, dispense only 1-month supply; no refills
- Provide toy or incentive to keep child engaged
- Or offer incentive at end of therapy (movie tickets, fast food voucher, toy, etc.)

General med toxicity

- Transient upset stomach, loose stools
- Over time, children get back to normal and have no symptoms
- Rashes
- Allergies
- Peripheral neuropathy, other CNS side effects
- Severe systemic/dermatologic side effects
- Hepatotoxicity

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, vomiting
- Make sure family stops treatment and returns for evaluation if symptoms develop

Drug interactions

- RIF and RPT interact with many other meds by inducing cytochrome p450 metabolism
- Most common profound drug interactions are with oral contraceptives, warfarin, some HIV antiretrovirals, some antifungals, and GERD meds
- Advise families to let future providers know if new meds are prescribed
- Helpful resource: *Rifamycin Drug-Drug Interactions: A Guide for Primary Care Providers Treating LTBI*

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 (preferred)** **dose in mg/kg/dose (maximum dose)**	**3 TIMES WEEKLY (used infrequently)** **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)

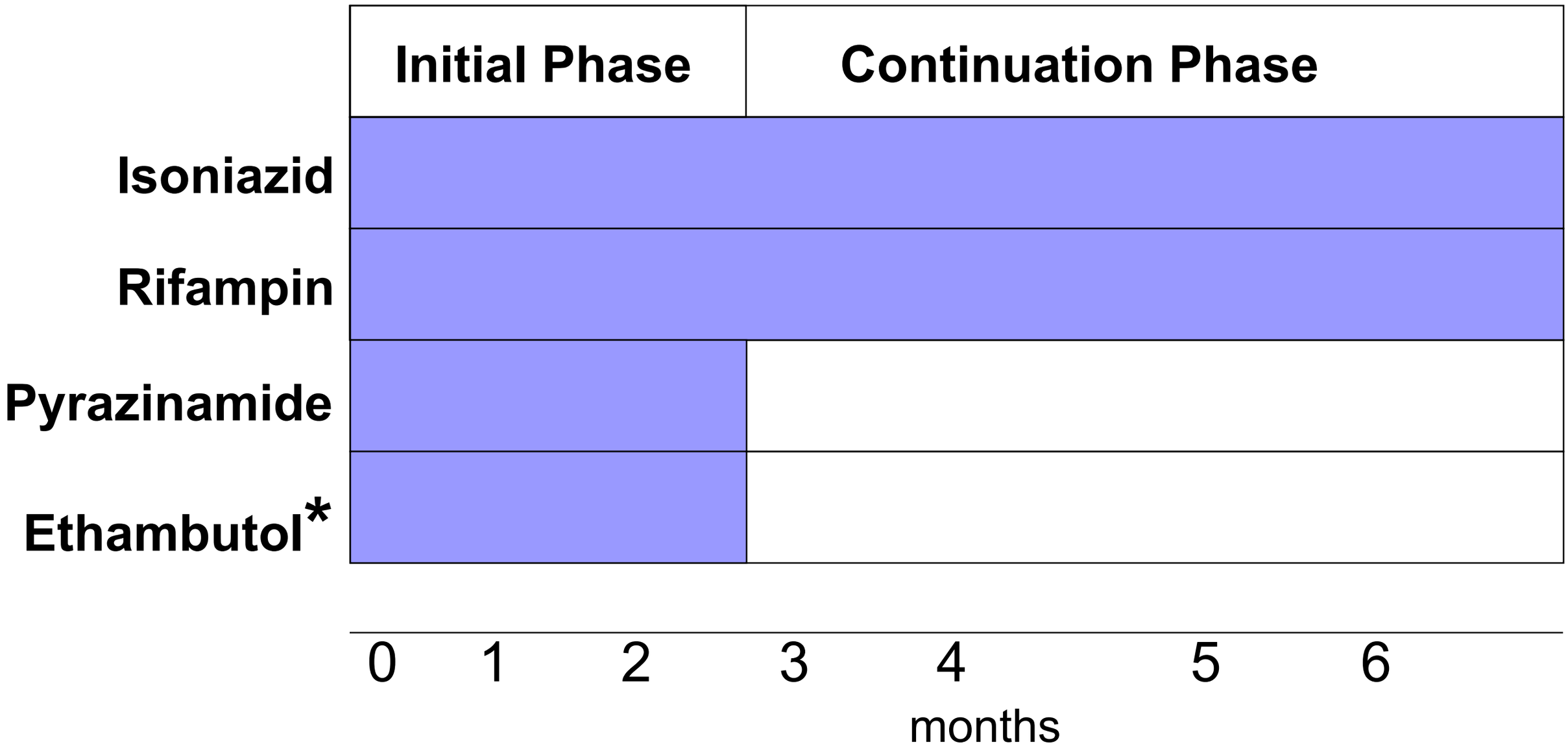
***** When isoniazid in a dosage exceeding10/mg/kg/dose is used in combination with rifampin, the incidence of hepatotoxic effects may be increased.

+ 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 **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

Shorter treatment for nonsevere TB

- Children are known to usually have relative paucibacillary TB
- Some studies of presumed paucibacillary TB in adults have shown success with 4 mos of TB tx
- 1200 children in India and Africa were studied to compare 4 vs 6 months of nonsevere TB disease tx
- Initial therapy was standard INH, RIF, PZA & EMB (optional per local guidelines) x 2 mo -> INH & RIF
- 3% of children in each group had “unfavorable outcome”
- 4 mos is non-inferior to 6 mos for nonsevere pediatric TB

Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children

“Nonsevere TB” definition for this study

- Peripheral lymph node TB
- Pulmonary/intrathoracic TB
  - Sputum smear-negative
  - Presumed drug susceptible
  - Chest findings:
    - Single lung lobe, no cavities
    - Not miliary; no complex pleural effusion
    - Intrathoracic lymph node TB without significant airway obstruction or bilateral airway narrowing

Challenges of treating children

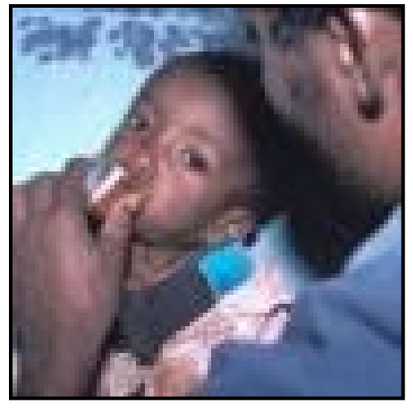
1. Microbiologic confirmation is less common. Monitoring success by serial sputum is nearly impossible
2. Monitoring for toxicity is more difficult. Children tolerate regimens better than adults.
3. INH liquid is poorly tolerated. to open capsules, crush drug into soft foo

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 or disease
- 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.