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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 complacence

- Pediatric TB is uncommon in the U.S.
  - In 2008, 786 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, 500,000 children die annually from TB
- Children represent up to 30% of TB cases globally, compared to 6% in U.S.
- Children age 0-4 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

Advantages of targeted testing

- Up to 85% of 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

Statistics about TB risk in U.S. children

- 25% of children with TB are born outside U.S.
- 45% are Hispanic
- 16% are Asian
- 26-80% of 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, has child traveled outside the U.S.?
- Since last TST, has child been exposed to anyone with TB or with a (+) TST?

Questions to predict risk – local epidemiology

- Since last TST, has child consumed unpasteurized dairy products from Mexico?
- Since last TST, 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, 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!)

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
- Treat LTBI or TB based on breakpoints from last slide

BCG = **bacille Calmette-Guérin vaccine**
LTBI = latent TB infection

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

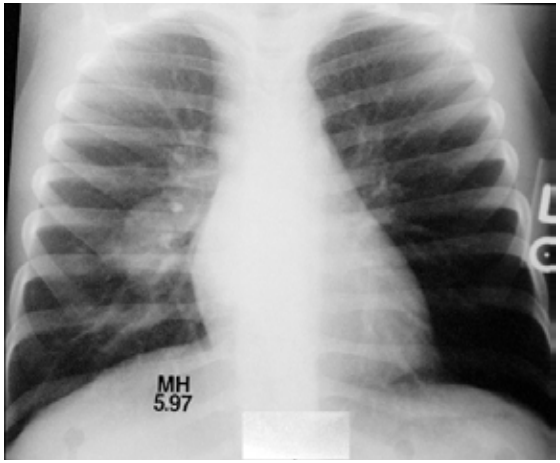
- Temperature and growth parameters
- Alertness and meningeal signs
- Peripheral lymph nodes
- Abdomen
- Palpate back and extremities

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)

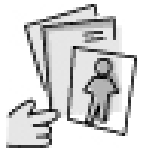
- Normal chest radiograph and physical exam,

  (+) TST = 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

Summary: Screening well children

- No more universal TB skin testing
- Targeted testing: Review TB exposure and population risk factors; TST only for children with new exposure risks since last TST
- If (+) TST, 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 result before performing evaluation on young child, immunocompromised or symptomatic individual

Treatment of contacts

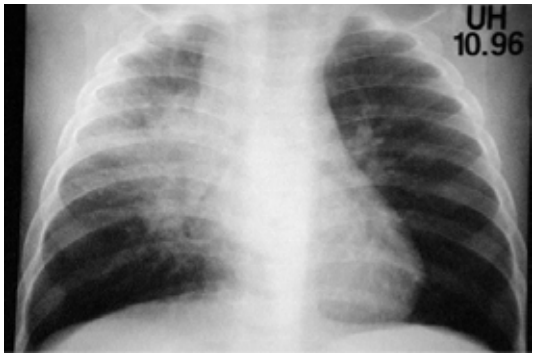
- If (+) TST, begin 9-month course of INH for LTBI
- If (-) TST, consider INH treatment as “window prophylaxis”
  - Repeat TST after 8-10 weeks of no further exposure to contagious case
  - If TST still (-), child is immunocompetent, and no new TB symptoms, stop INH
  - If exposure to contagious case has continued, or if another adult in proximity has TB, repeat evaluation and/or extend treatment
  - If (+) TST upon repeat testing, complete 9 months of INH

INH = isoniazid

Child contacts > 4 yr

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

Summary: Child contact



- Prompt TST and symptom review for all individuals with significant exposure to contagious TB case
- Children under 5
  - Chest radiograph even before TST is read
  - If no TB, start window prophylaxis, independent of TST result
- 8-10 weeks after exposure is ended, repeat TST. If (-) TST, 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 (-)

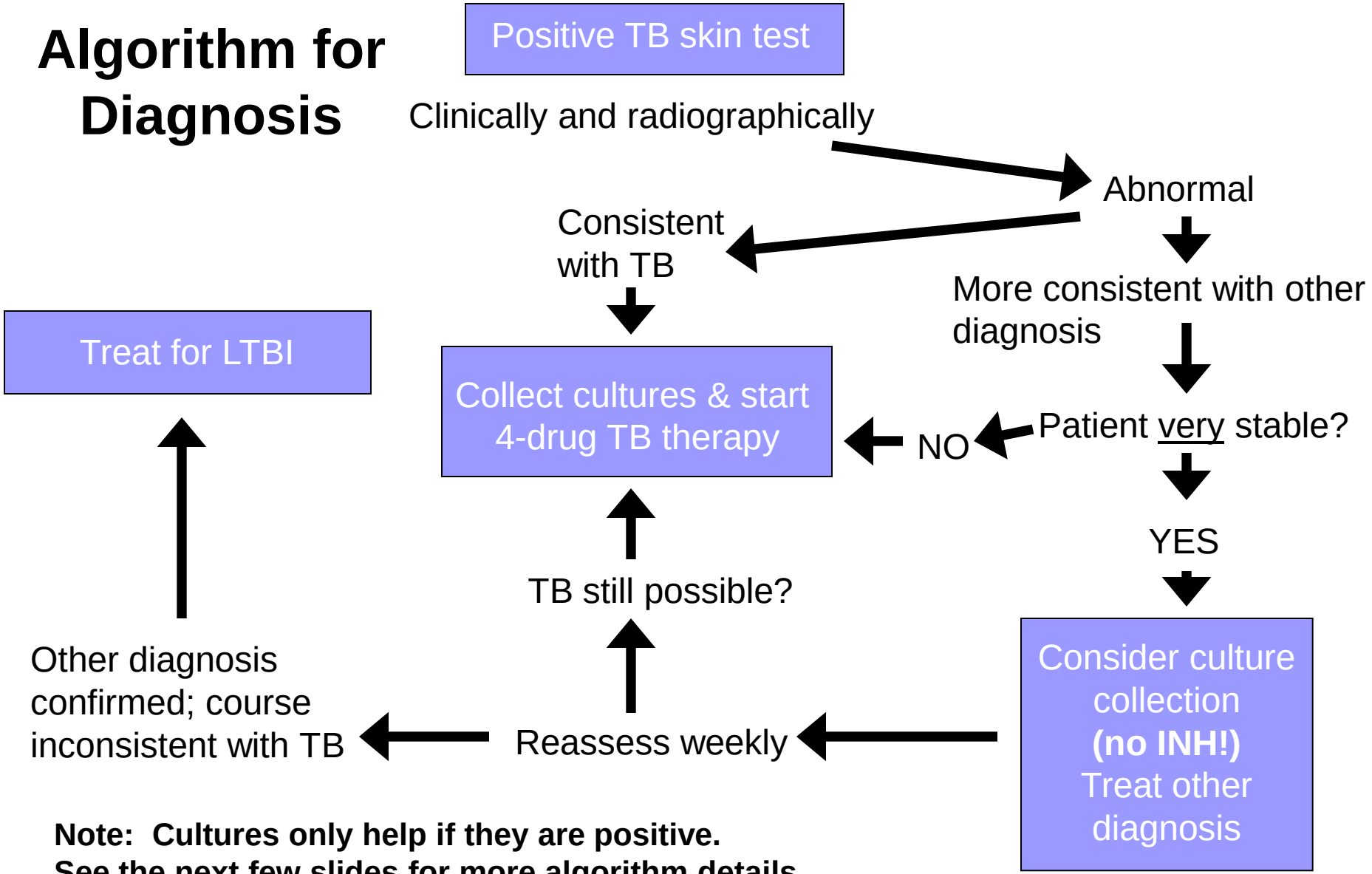
Circumstances that increase TB suspicion

- Exposure to person with TB
- Several people in child's environment with (+) TSTs
- 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 results are not definitive

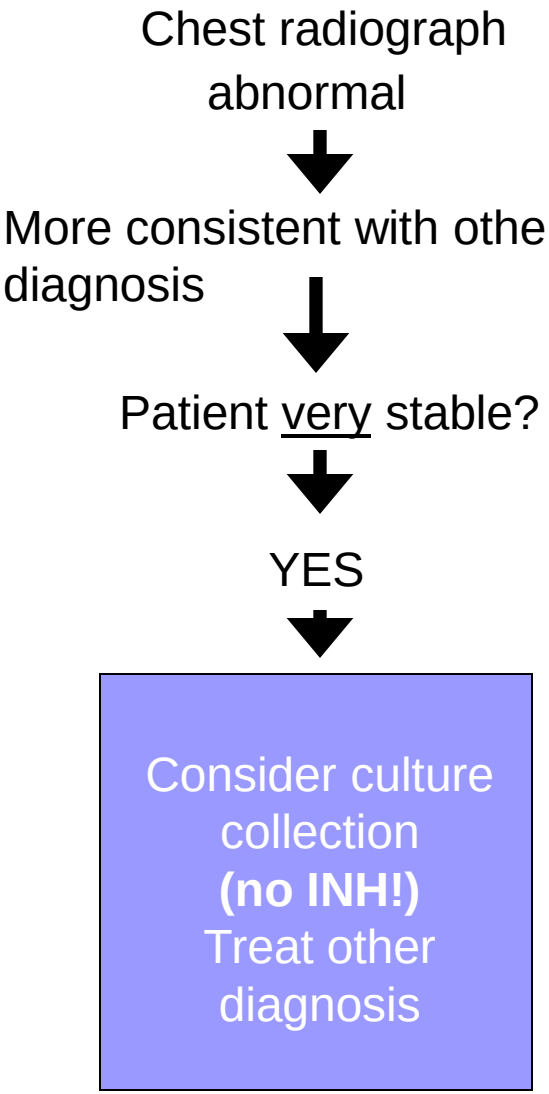
- A positive TST does not confirm the diagnosis of TB
- A negative TST does not exclude TB
- TST results are merely one factor in the equation

Algorithm for Diagnosis

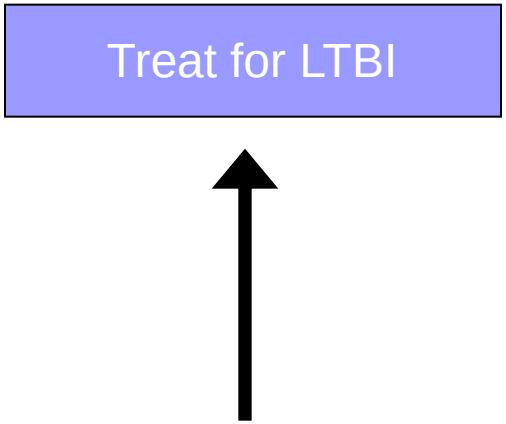


Note: Cultures only help if they are positive.
See the next few slides for more algorithm details.

Findings more consistent with another diagnosis…

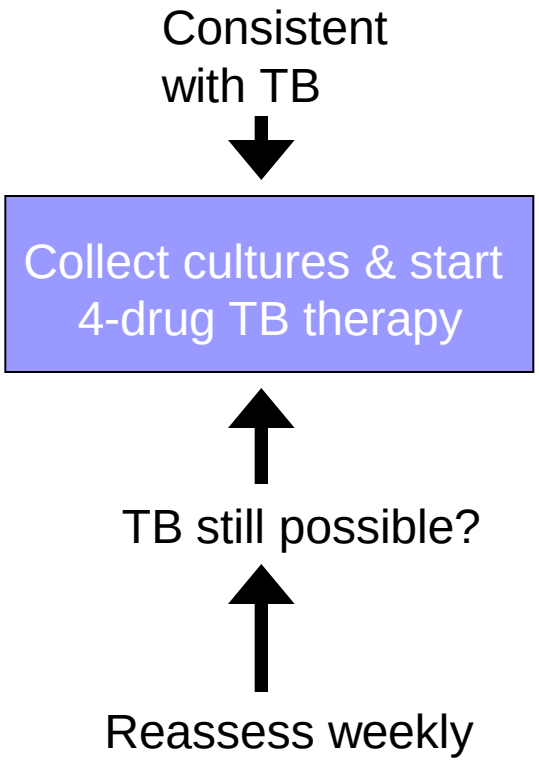


If radiograph normalizes without TB treatment…



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…

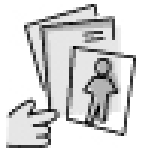
Positive TB skin test

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

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

- A negative TST 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

Interferon Gamma Release Assays (IGRAs)

- New 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

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

Are IGRAs recommended for children?

1. IGRAs can be used in place of TST for immunocompetent children 5 years and older
2. Negative IGRA cannot rule out TB infection or disease
3. IGRAs are better than TST at distinguishing true infections from those caused by NTM or BCG exposure
4. IGRAs cannot be recommended routinely for children younger than 5 years of age or immunocompromised children

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

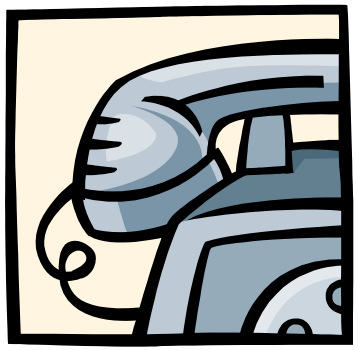
- Other specimens: Cerebrospinal fluid, lymph node tissue, blood, urine, bone biopsy, synovial fluid
- Submit large volume specimens in sterile container without formalin

Summary: Diagnosis

- Not everyone with (+) TST has TB
- Not everyone with TB has (+) TST
- Consider TB exposure, TST 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

- All children with LTBI should be treated
- 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
- Use INH 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

TB MEDICATION MANAGEMENT RECORD

- Ensure adherence
- Monitor for toxicity
- Arrange for quick nurse visits
- Only dispense bottles of 30 INH doses; no refills
- When child has finished 9 bottles, course is done
- Provide toy or incentive to keep child engaged
- Or offer incentive at end of therapy (movie tickets, fast food voucher, toy, etc.)

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 270 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

Four-drug treatment table

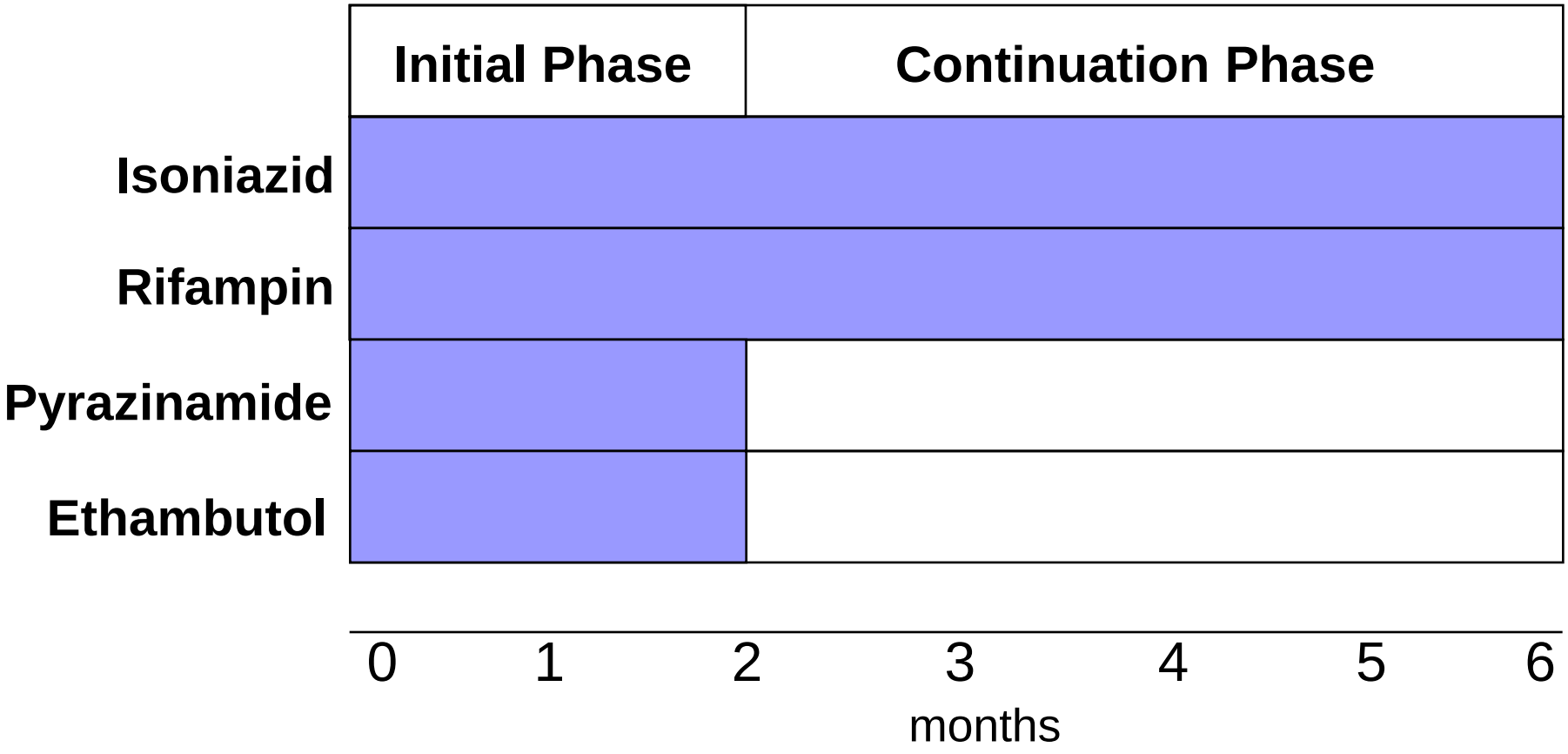
American Academy of Pediatrics

DRUG	**DAILY dose in mg/kg/dose (maximum dose)**	**TWICE WEEKLY dose in mg/kg/dose (maximum dose)**
Isoniazid	10-15 (300 mg)*	20-30 (900 mg)
Rifampin	10-20 (600 mg)*	10-20 (600 mg)
Pyrazinamide	20-40 (2 grams)	50 (2 grams)
Ethambutol#	15-25 (2.5 grams)	50 (2.5 grams)

***** When using **both** INH and Rifampin DAILY, dose INH at 10/mg/kg/dose and Rifampin no more than 15 mg/kg

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

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 2 to 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 is six months, measured by number of doses observed
- Patients receiving a typical regimen receive 40 daily doses and 36 twice-weekly doses

Challenges of treating children

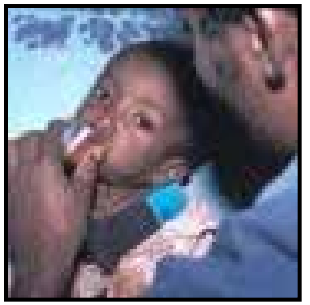
1. Microbiologic confirmation is less common. Monitoring success by serial sputum is nearly impossible
2. Monitoring for toxicity is more difficult. Children tolerate regimens better than adults.
3. INH liquid is poorly tolerated. Need to open capsules, crush tablets, hide drug into soft foods or liquids.

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 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 and not all children with (+) TSTs 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.