Tuberculosis Case Studies:

Practical Applications in TB Management

Lisa Y. Armitige, MD, PhD
Co-Medical Director
Heartland National TB Center
San Antonio, Texas

Professor of Medicine/Pediatrics
UT-Health Northeast
Tyler, Texas

Case

- A 26 y/o man presents for panel physician evaluation but is found with a 2 month history of cough, fever, night sweats and 17 lb weight loss

- He has no health problems
  - smokes 1 ppd cigarettes, drinks 2 beers/week (Fridays), no illicit drug use
  - Immigrating to the US, no recent travel out of the country
  - Lives with his pregnant wife and 2 children (ages 10 months, 3 years) and his 14 years old brother

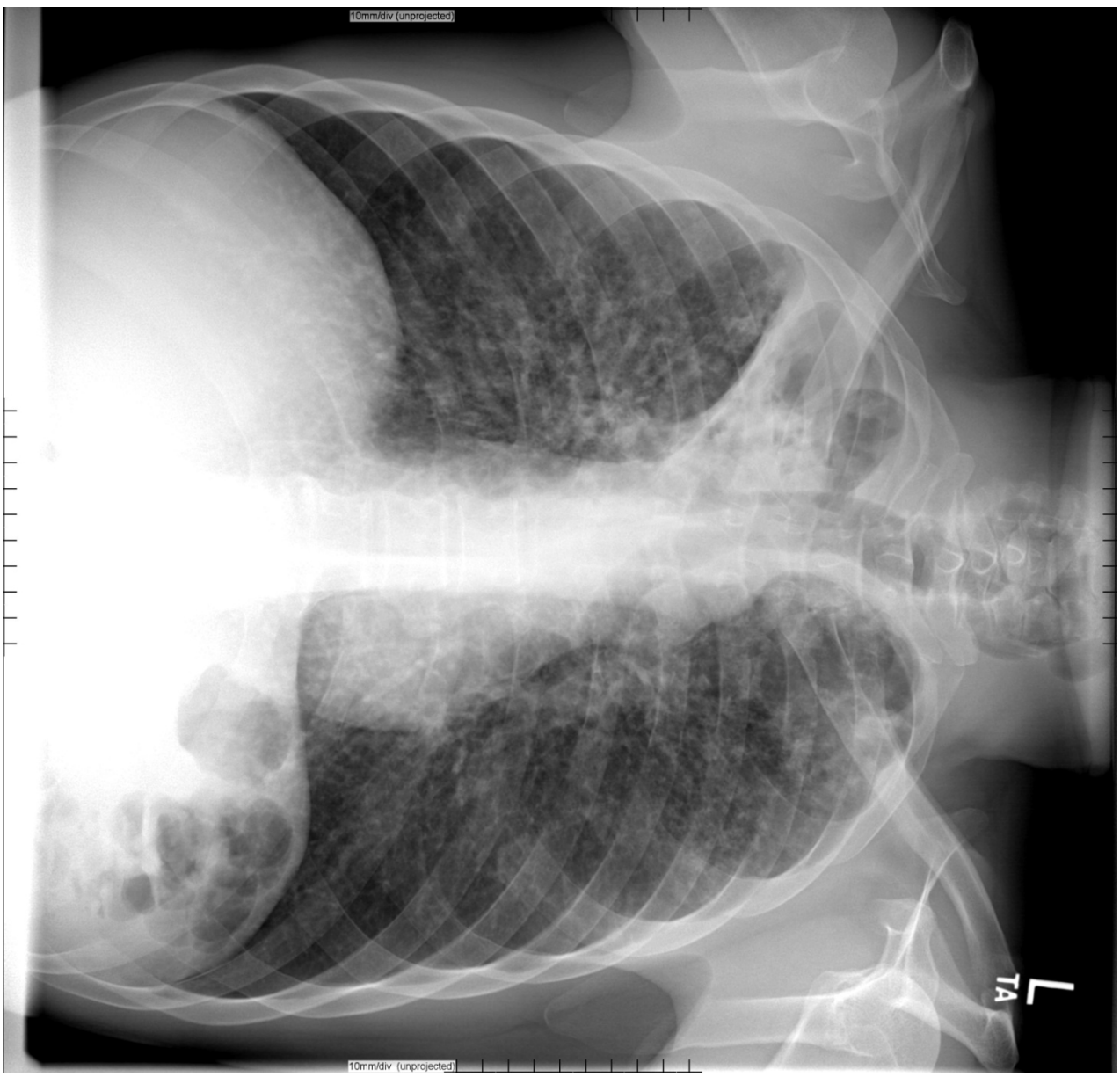
Case

- He has been seen at another clinic and treated with ‘medicine’ for a month without relief

- Physical exam
  - Thin man, mildly cachectic
  - Palpable right-sided supraclavicular LN
  - Egophony over his RUL, scattered crackles

What do you want to do next?

- Treat him with either levofloxacin or moxifloxacin as he has failed treatment for community acquired pneumonia
- Get a CXR
- Draw a CBC and CMP
- Send him home with a follow up appointment after you talk to his other doctor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What do you do next?

- Collect sputum and treat empirically for failed community acquired pneumonia
- Collect sputum for AFB and treat empirically for TB with 4 drugs
- Isolate the patient, collect sputum for routine culture and AFB and wait for a diagnosis

And now……

- The next day, you get a call that the AFB smear is positive.

- Do you…..?:
  - Tell the patient he has TB, give him prescriptions for 4 TB drugs, explain to him the importance of taking the meds and have him back in 1 month
  - Call the health authority
  - Carefully explain to the person on the phone that you are no longer rotating at that clinic and this is no longer your patient or problem

Next steps.....

- The patient visits the health authority for evaluation and reveals he has small children in his family at home
- He asks you if you will see the rest of the family or if you can tell him how they should be evaluated
- You say yes!..... But what are you looking for with his contacts?

Treatment of Patients with *Drug Susceptible* TB Disease

- Initiation phase of therapy
  - 2 months
  - INH, Rifampin and PZA +/-EMB
- Continuation phase of therapy
  - 4-7 months
  - INH and Rifampin

Treatment of Culture-Positive Drug Susceptible Pulmonary TB

- General conclusions from the literature
  - 6 mo (26 wk) is the MINIMUM duration of RX
  - 6 mo regimens require rifampin and INH throughout and PZA for the first 2 months
  - 6 mo regimens are effective without INH if PZA given throughout
    - rifampin, ethambutol and PZA for the entire course + a fluoroquinolone
  - Intermittent regimens (2-3x/wk): DOT ONLY!
    - Drug susceptible isolate
    - Regimen contains INH and rifampin

Treatment of Culture-Positive Drug Susceptible Pulmonary TB

- General conclusions from the literature:
  - Without PZA - minimum duration is 9 months
  - Without rifampin - minimum duration is 12 months (up to 18 months)
  - Streptomycin and ethambutol (EMB) are approximately equivalent in effect
    - concern about increasing Streptomycin resistance among foreign born leads to preference of EMB for initial therapy

Adult Dosing Pearls

- INH 5 mg/kg/day (max 300 mg)
- Rifampin 10 mg/kg/day (max 600 mg)
  - If they weigh over 100 lb, give the max
- PZA and EMB look at CDC table

TABLE 4. Suggested pyrazinamide doses, using whole tablets, for adults weighing 40–90 kilograms

	Weight (kg)*		
	40–55	56–75	76–90
Daily, mg (mg/kg)	1,000 (18.2–25.0)	1,500 (20.0–26.8)	2,000† (22.2–26.3)
Thrice weekly, mg (mg/kg)	1,500 (27.3–37.5)	2,500 (33.3–44.6)	3,000† (33.3–39.5)
Twice weekly, mg (mg/kg)	2,000 (36.4–50.0)	3,000 (40.0–53.6)	4,000† (44.4–52.6)

*Based on estimated lean body weight.
†Maximum dose regardless of weight.

TABLE 5. Suggested ethambutol doses, using whole tablets, for adults weighing 40–90 kilograms

	Weight (kg)*		
	40–55	56–75	76–90
Daily, mg (mg/kg)	800 (14.5–20.0)	1,200 (16.0–21.4)	1,600† (17.8–21.1)
Thrice weekly, mg (mg/kg)	1,200 (21.8–30.0)	2,000 (26.7–35.7)	2,400† (26.7–31.6)
Twice weekly, mg (mg/kg)	2,000 (36.4–50.0)	2,800 (37.3–50.0)	4,000† (44.4–52.6)

The patient wants to go back to work….when can he go?

- The CDC recommendations state if:
  - Low likelihood of MDR
  - Received 2-3 weeks of standard 4 drug tx by DOT or equivalent (5-7 days if AFB smear negative)
  - Clinical improvement
  - Contacts have been assessed and are not high-risk
  - Hospitalized patients or returning to a congregative setting
    - Are receiving 4 drug treatment
    - Have demonstrated clinical improvement
    - Have THREE consecutive AFB smear-negative sputums

What about his family?

Contacts of Active TB Case

- Among close contacts approximately 30% have LTBI and 1-3% have active TB disease
- Without treatment, approximately 5% of contacts with newly acquired LTBI progress to TB disease within 2 years
- Examination of contacts is one of the most important activities for identifying persons with disease and with LTBI

Risk of Progression from TB Infection to Disease by Age

Age at Primary Infection (yr)	No Disease (%)	Pulmonary Disease (%)	Miliary or Central Nervous System TB (%)
<1	50	30 to 40	10 to 20
1 to 2	75 to 80	10 to 20	2.5
2 to 5	95	5	0.5
5 to 10	98	2	<0.5
>10	80 to 90	10 to 20	<0.5

Adapted from Marais, et al. Childhood pulmonary tuberculosis: old wisdom and new challenges. *Am J Resp Crit Care Med*. 2006;173:1078–1090.

Peds in Review 2010;31:13

The Best Approach to Contacts

- Get an organism out of the source case
  - Rule out resistance
    (INH resistance is 10-15%, rifampin resistance is about 2% in worldwide)
  - This will dictate how you 'treat' the others
- Start with those most at risk
  - Children, elderly, immunocompromised
  - Screen for HIV when indicated
- Rule out active disease in all TB screening test (TST/IGRA) before you go any further

Proper Evaluation of a Contact to a Case of Tuberculosis

- History and Physical
  - Current medical problems (HIV, diabetes, TNF-α agents)
  - Previous exposure
  - Previous TST or IGRA result
  - Previous Treatment for LTBI or TB

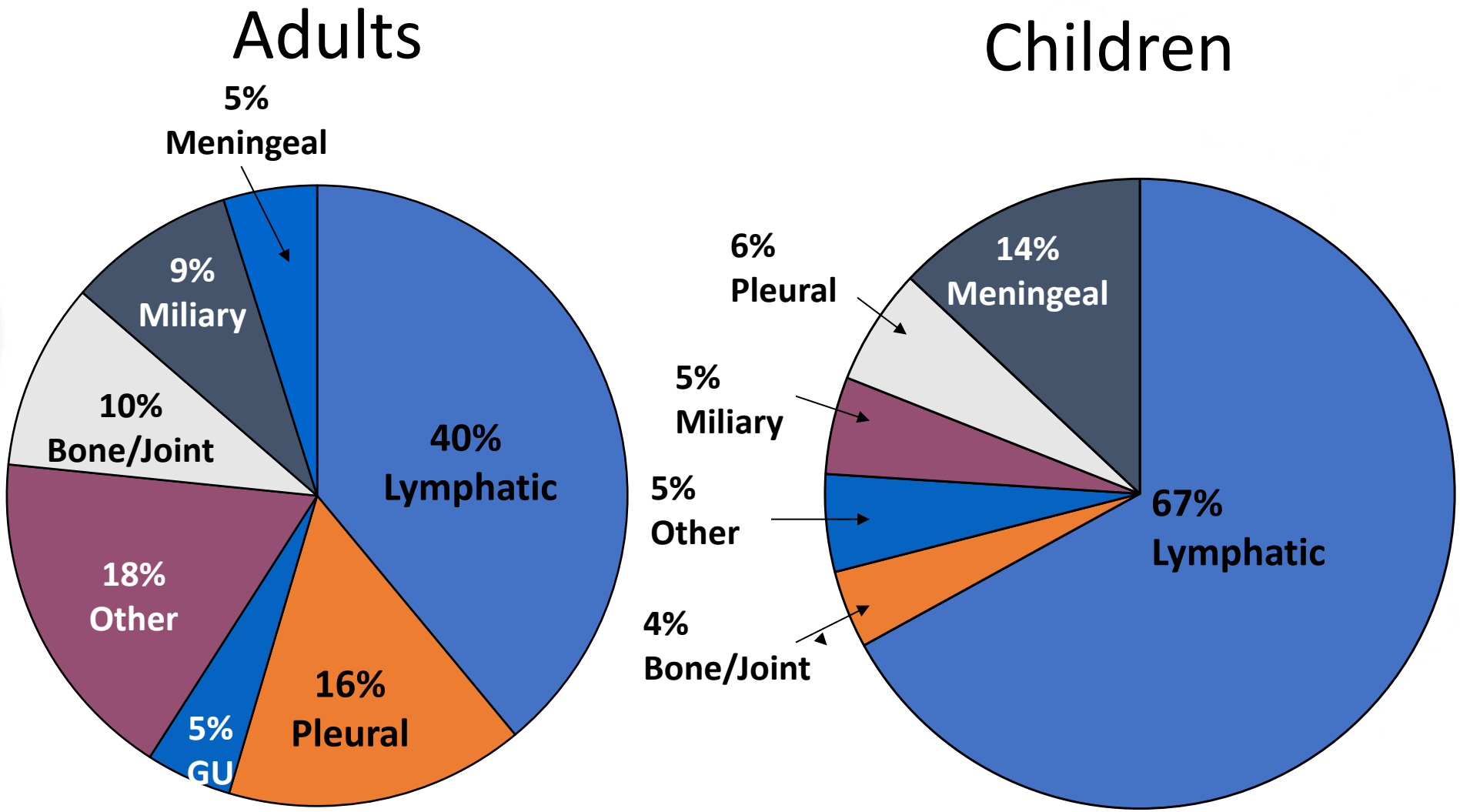
- Should you do a TST or an IGRA?

TST Limitations

- Technical problems in administration and reading
- >1 visit needed
- False-negative responses
  - Anergy (compromised immunity)
  - TST reversion at old age
- Repeated TSTs boost the immune response
  - Need 2-step approach in serial testing
- False positives
  - Nontuberculous mycobacteria (NTM)
  - Bacille Calmette-Guerin vaccination (BCG)

Physical Examination

Extrapulmonary TB Disease



Proper Evaluation of a Contact to a Case of Tuberculosis

- Should you get a CXR?
  - TST/IGRA result positive
  - Symptoms present
  - HIV positive
  - Child < 5 y/o
- Should you get cultures ?
  - Symptoms present
  - Abnormal CXR
  - If you do, wait for the results

The Contacts

How do you approach…..?

Pregnant wife

14 year old

3 year old

10 month old

History

- Wife
  - 25 y/o, 8 months pregnant, no health problems, no symptoms, previously TST+ (contact to her mom with TB)
- 14 year old brother
  - No health problems, no symptoms
- 3 year old boy
  - Born full term, immunizations up to date, no daycare, currently has a ‘cold’ with cough
- 10 month old girl
  - Born full term, immunizations up to date, has older brother’s ‘cold’

Physical Exam

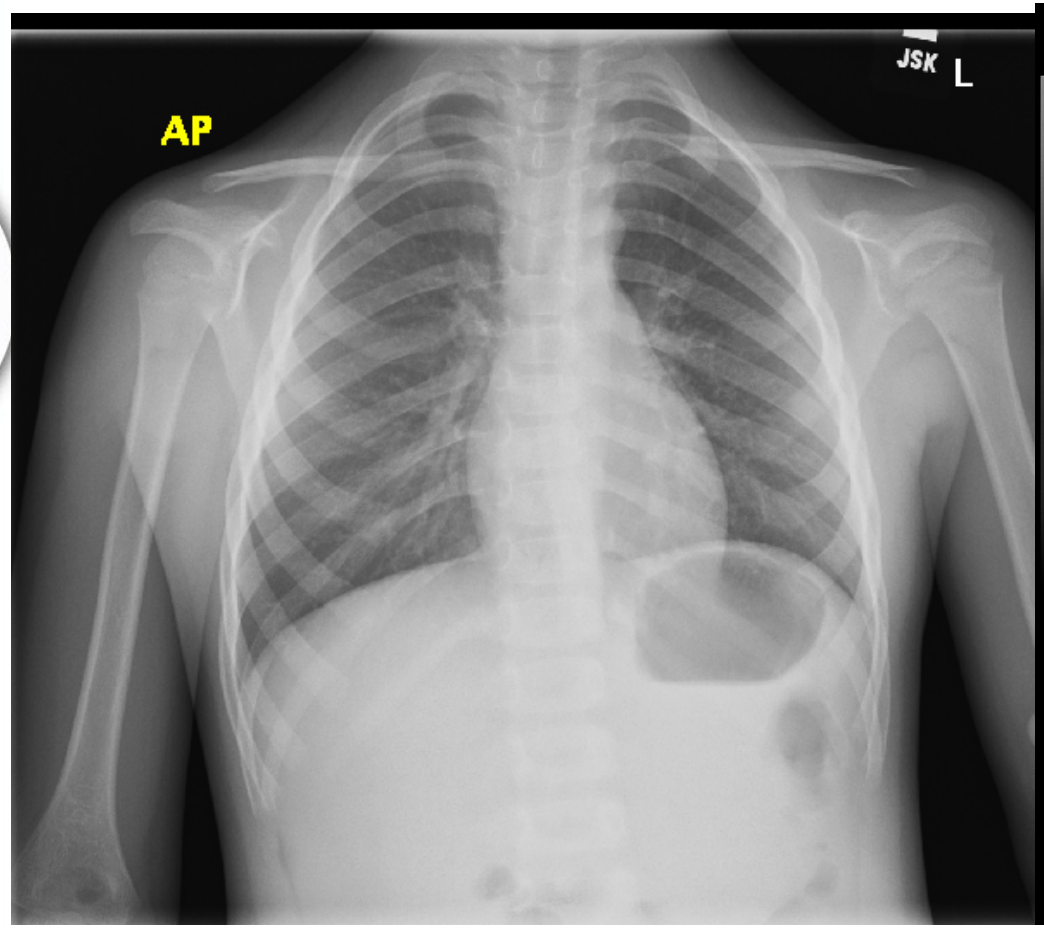
- Wife
  - Gravid abdomen, lungs clear, no palpable LAD
- 14 year old boy
  - Healthy teen, normal exam
- 3 year old boy
  - 75th percentile, URI symptoms, lungs clear, no LAD
- 10 month old girl
  - 55th percentile, no URI symptoms, rare cough, diffuse crackles, no LAD

TB Test Results

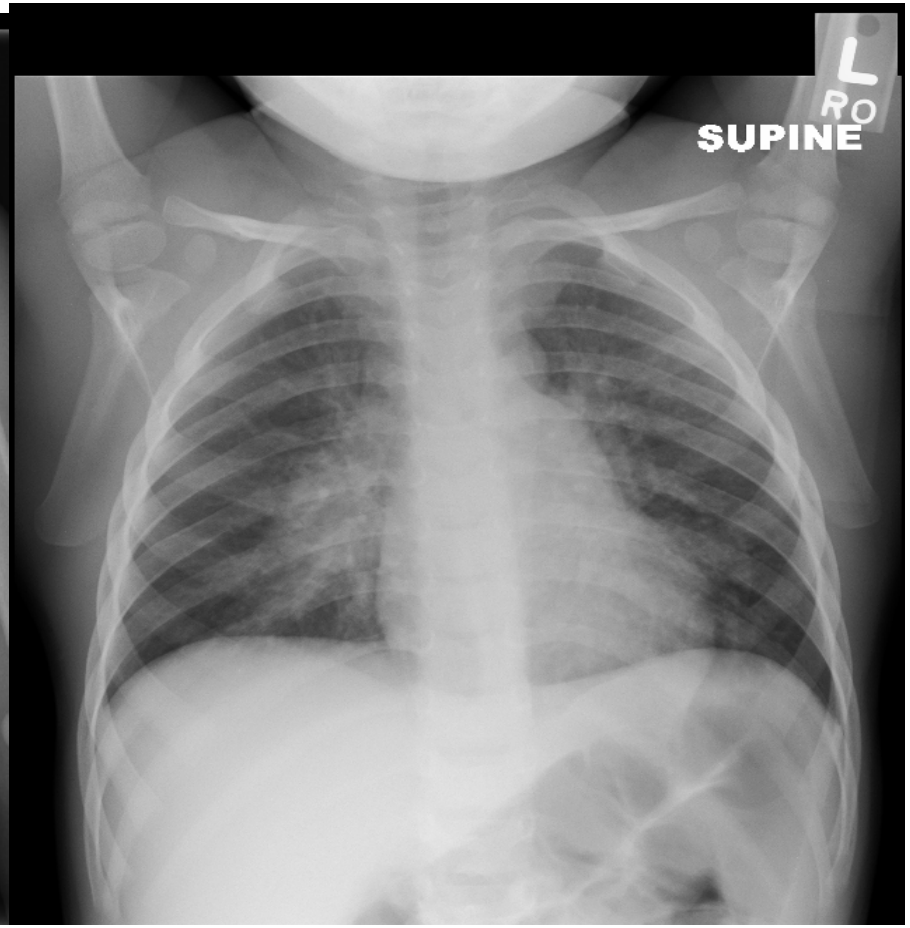
- Wife IGRA positive, abdomen shielded and CXR done (negative)
- 14 year old IGRA negative
- 3 year old IGRA negative
- 10 month old IGRA positive

CXRs

3 year old



10 month old



Do you want to treat? For what?

- Pregnant wife
- 14 year old
- 3 year old
- 10 month old

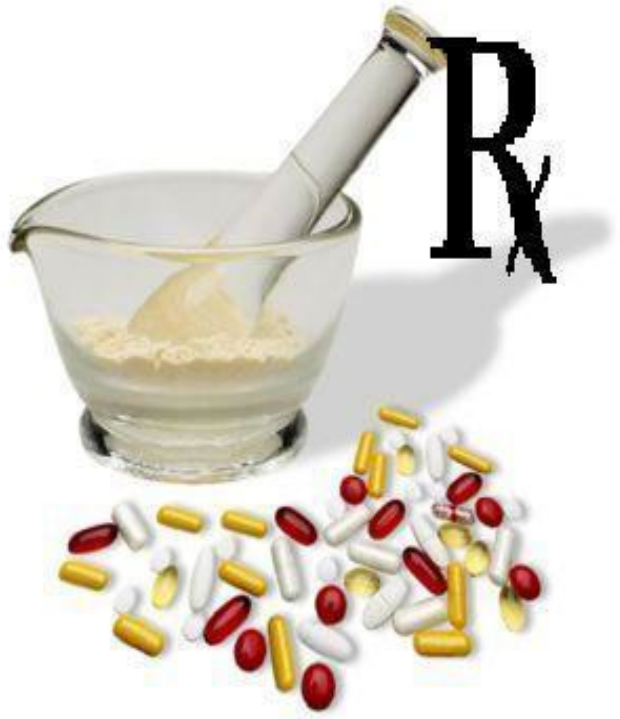
TB Prevention After Exposure

- Household contact with contagious person
  - Teen or adult with pulmonary TB disease
  - Usually ≥ 4 hours of contact
- Initial TB test negative
  - Window period for TST conversion (8-10 weeks)
- CXR and physical exam normal

❖LTBI treatment recommended:

- For children <4 yrs of age
- Immunosuppressed patients
- Patients on tumor necrosis factor-alpha blockers
- May prevent progression to disease during window period

- Repeat TST 8-10 wks after exposure
- May stop INH if 2nd TB test is negative in immunocompetent patients



Slide shamelessly stolen from Dr. Kim Smith

Before Treatment of LTBI: Exclude Active Tuberculosis!

- Absence of symptoms
- Negative CXR
- Negative medical evaluation
- Order and wait for sputum culture if any question

Do you want to treat? For what?

- Pregnant wife
- 14 year old
- 3 year old
- 10 month old

- LTBI
- Rescreen in 8-10 weeks
- Window prophylaxis and rescreen in 8-10 weeks
- Treatment for TB disease

TREATMENT OF TUBERCULOSIS IN CHILDREN

STAGE OF TB	SKIN TEST or IGRA	CXR	SYMPTOMS	TREATMENT
Exposure Child <4 years of age Household contact with adult with active pulmonary disease	Negative	Normal	None	Meds: INH window prophylaxis Duration: 8-10 weeks Repeat skin test: 8-10 wks after last exposure, if positive ≥ 5mm, see LTBI
Latent TB infection (LTBI)	Positive	Normal	None	Meds: INH Duration: INH 9 mo or INH resistant LTBI: Rifampin 6 mo
Disease Pulmonary and extrapulmonary (except disseminated disease and meningitis, see below)	90% positive	Abnormal	+/-	Meds: INH, RIF, PZA (consider EMB or aminoglycoside) # Duration: 6 mo total Stop PZA after 2 mo, continue INH & RIF for drug susceptible disease DOT standard
Disease Disseminated including miliary, bone/joint and multi-site disease	TST may be negative early in disseminated TB. 90% positive if tested later	+/-	Yes	Meds: INH, RIF, PZA and EMB or aminoglycoside Duration: 9-12 mo total Stop PZA and EMB or aminoglycoside after 2 mo for drug susceptible disease. DOT standard
Disease Meningitis	50% negative early in meningitis and miliary disease. 90% positive if tested later	+/-	Yes	Meds: INH, RIF, PZA and aminoglycoside or EMB or ethionamide daily for 2 mo, followed by 7-10 mo INH and RIF daily or twice weekly Duration: 9-12 mo total for drug susceptible disease DOT standard Steroids recommended for first 1-2 mo for meningitis

Pediatric Dosing

Dosing range for daily, twice weekly, and maximum doses, as well as forms available for the first line anti-tuberculosis medications. Note: #Rifampin dose varies by age of child.

	DAILY DOSE RANGE				
	Isoniazid (INH)*	**Rifampin (RIF)# Age > 2 yrs**	**Rifampin (RIF)# Age: Birth- 2 yrs**	**Pyrazinamide (PZA)**	**Ethambutol (EMB)**
	10-15 mg/kg/day	15-20 mg/kg/day	20-30 mg /kg/day	30-40 mg/kg/day	15-25 mg/kg/day
Weight (kg)	Dose, mg	Dose, mg	Dose, mg	Dose, mg	Dose, mg
3-5	50	50-75	75-100	125	50-100
6-9	100	100-150	150-200	250	150
10-15	150	150-300	200-300	375-500	250
16-20	200	300	450	500-750	300
21-25	300	300-450	450-600	750	400
26-30	300	450-600	600	1000	600-700
31-45	300	600	600	1250-1500	800
46-50	300	600	600	1500-2000	1000
50+	300	600	600	2000	1000
TWICE A WK DOSE: Maximum Doses:	20-30 mg/kg/dose Daily: 300 mg Twice wkly: 900 mg	15-20 mg/kg/dose Daily: 600 mg Twice wkly 600 mg	20-30 mg/kg/dose Daily: 600 mg Twice wkly 600 mg	50 mg/kg/dose Daily: 2000 mg Twice wkly: 2000 mg	50 mg/kg/dose Daily: 1000 mg Twice wkly: 2500 mg
Forms Available:	Scored tablets: 100 mg 300 mg Syrup: 10 mg/ml*	Capsules: 150 mg 300 mg Syrup: compounded	Capsules: 150 mg 300 mg Syrup: compounded	Scored tablets: 500 mg	Tablets: 100mg 400 mg

Repeat testing after 8-12 weeks

- 14 year old Quantiferon still negative
  - What do you want to do with him?

- 3 year old's TST is still negative
  - What do you want to do with him?

The patient is doing great taking the medications but…..his LFTs are rising….

Evaluation for Hepatoxtocity

- He denies alcohol or over the counter drug use
- He is feeling much better since starting TB treatment and all symptoms have resolved but he has been feeling nauseated for the past 3 days.
- You collect a CMP and his AST is 137 (ULN 40) and ALT 187 (ULN 40)
- Next steps?

Next steps

- Stop the medications. Cool the patient off.
- When LFTs have returned to < 2 times the ULN, you are ready to challenge
- Start with rifampin and ethambutol, then INH, then strongly consider whether you need PZA
  - Wait 3-7 days between additions
  - Check LFTs before starting the next drug (and wait for the results, please)
  - If LFTs rise stop the last drug added and go to the next
- Have a plan if he does not tolerate all 4 drugs

What if the Patient Doesn't Tolerate……?

- Isoniazid
  - Can be replaced with a fluoroquinolone
  - INH resistant or intolerant disease should be treated with RZE + a fluoroquinolone
- Rifampin
  - Try replacing with rifabutin
  - If patient is intolerant to rifampin and rifabutin, consider a BPaL(M)
- Ethambutol
  - Do you need it? If the patient is pansusceptible, no, you do not
- Pyrazinamide
  - Not necessary to replace
  - Without PZA you need to treat for at least 9 months

How is it cleared?

• INH	• Liver
• Rifampin	• Liver
• Rifabutin	• Liver/kidney
• Ethambutol (EMB)	• Kidney
• Pyrazinamide (PZA)	• Kidney (liver metabolites)
• Moxifloxacin	• Liver
• Levofloxacin	• Kidney
• Amikacin	• Kidney
• Linezolid	• Neither liver or kidney

Thank you for your attention

Questions?