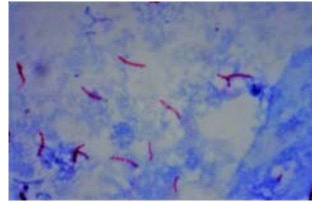

Updates in Pediatric Tuberculosis

Arsala Bakhtyar, MD

Beaumont Health

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Disclosure

- I have no relevant disclosures.

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Childhood TB

- A disease with substantial global burden
- In the last decades some advances have been made
- Only recently, scientific community has arrived at a consensus regarding a standard case definition and have developed guidelines to support a standardized approach for evaluation of new TB diagnosis in children Worldwide burden of the disease is huge.
  - Approx 9 million new cases
  - 12 million prevalent cases
  - 1.5 million deaths due to TB occur annually.
  - Of the 8.8 million new TB cases in 2010, approximately 500,000 were diagnosed in children less than 15 years of age.

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Childhood TB

- Source case→ exposure →LTBI→or TB disease.
- Infant with untreated LTBI 30-40%life time risk
- HIV infected patient s have a 5-10% risk of developing TB disease.
- Immunocompetent children also have a 5-10% risk.

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Wayne county outbreak 2018-19

10 year old girl from Vietnam, presented with 2 weeks of worsening fevers and cough to an urgent care.

- Fever, cough, fatigue and weightloss
- Migrated 6 months ago to the US
- CXR abnormal at urgent care
- Admitted to inpatient unit at Beaumont Health Dearborn
- Work up for Community acquired pneumonia initiated.

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Immigrant workup

- TST on immigration 7mm induration
- No CXR was performed
- Child was healthy at the time of immigration.

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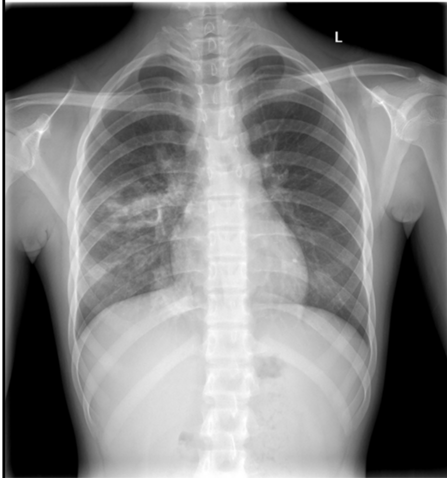
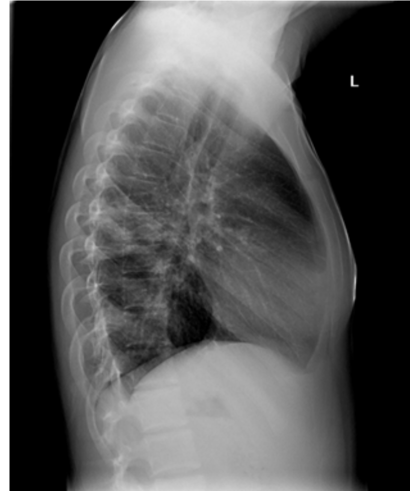
Chest X-ray





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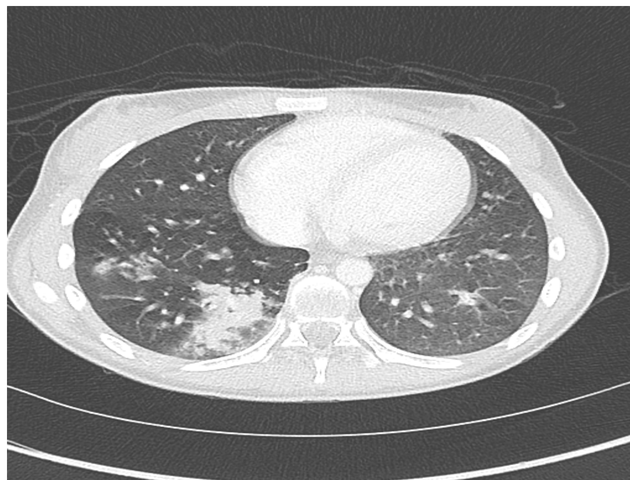
CT SCAN



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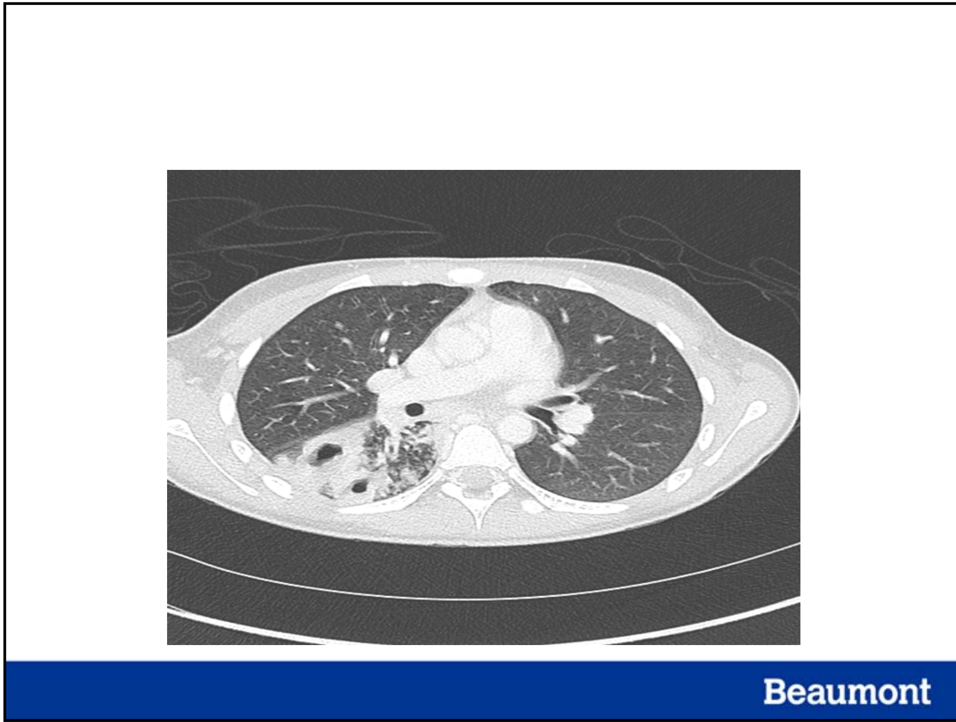

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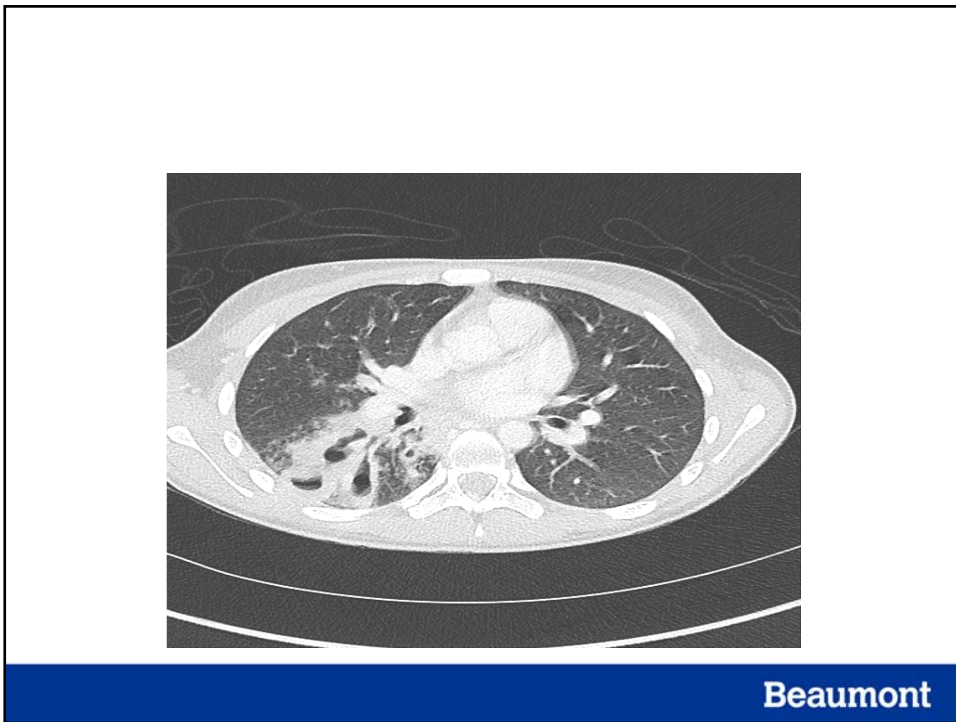

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Diagnosis and Treatment

- AFB smear 4++
- M. tuberculosis DNA DETECTED by PCR, Rifampin resistance mutation not detected by PCR.
- IGRA positive; HIV negative.
- Child was started on INH, rifampin, PZA, ethambutol and Vitamin B6

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Press release

- https://www.clickondetroit.com/news/public-health-department-confirms-tuberculosis-case-at-taylor-school

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Contact Investigation

- Mother, 2 sisters: IGRA positive; CXR normal
- Aunt: IGRA negative
- School investigation:
- Tested over 300 children
  - ~20 children **PPD+,** CXR normal
  - 3 children <5 years placed on "window" prophylaxis.
- 2 additional active TB cases.-currently on treatment
  - 1) rode the same school bus daily
  - 2) classmate; sat right across on the same table as the index patient.

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Twist in the case

- Isoniazid **resistance** confirmed by MDHHS laboratory
- Child placed on Rifampin, Moxifloxaxin, Ethambutol and pyrazinamide
- 7x/week DOT for 9 months
- Doing well.

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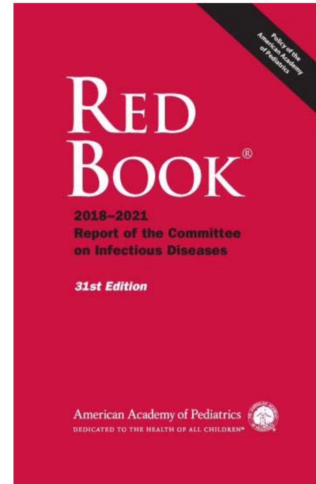
Updates in the 2018 Redbook

- Tests of infection
- Treatment options
- Administration Routes
- Monitoring/followup



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Comparison of TST and IGRA

charateristic	TST	IGRA
Antigen studied	Many	ESAT-6, CFP-10, (TB-7.7)
Cross reactivity with BCG	yes	unlikely
Cross reactivity with NTM	yes	Less likely
Estimated sensitivity , TB in Immunocompetent adults	75-90%	75-95%
Estimated specificity ,TB in immunocompetent adults	70-95%	90-100%
Distinguish Tb infection vs disease	No	No
Boosting	Yes	No
Patient visits required	Two	one

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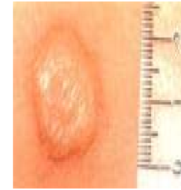
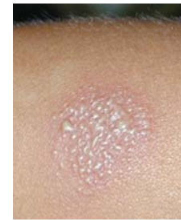
What is a positive TST

≥5mm	≥ 10mm	≥15mm
HIV infected	Children <4 years	Anyone , even without risk factors.
Contact with TB case	Children exposed to high risk adults	
Child in whom you suspect TB	Immigrants from high prevalence regions	
	Immunocompromised children or diabetic	





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TST advantages

- Cost
- Easily available
- Can be done anywhere
- No need for blood draw
- No borderline or indeterminate results.

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TST disadvantages

- Up to 20% of children don't return for TST interpretation
  - But > 20% of parents are upset when a blood draw fails
- • Sliding scale is confusing Redbook table 3.82 is not
- There are issues
- with variation in
- TST induration
- measurement -
- Come on - how hard is it to measure a bump on an arm?

Table 3.82. Definitions of Positive Tuberculin Skin Test (TST) Results in Infants, Children, and Adolescents[a]

Induration 5 mm or greater
Children in close contact with known or suspected contagious people with tuberculosis disease
Children suspected to have tuberculosis disease:
- Findings on chest radiograph consistent with active or previous tuberculosis disease
- Clinical evidence of tuberculosis disease[b]

Children receiving immunosuppressive therapy[c] or with immunosuppressive conditions, including human immunodeficiency (HIV) infection

Induration 10 mm or greater
Children at increased risk of disseminated tuberculosis disease:
- Children younger than 4 y
- Children with other medical conditions, including Hodgkin disease, lymphoma, diabetes mellitus, chronic renal failure, or malnutrition (see Table 3.83)

Children with likelihood of increased exposure to tuberculosis disease:
- Children born in high-prevalence regions of the world
- Children who travel to high-prevalence regions of the world
- Children frequently exposed to adults who are HIV infected, homeless, or incarcerated; users of illicit drugs; or residents of nursing homes

Induration 15 mm or greater
Children 4 y or older without any risk factors

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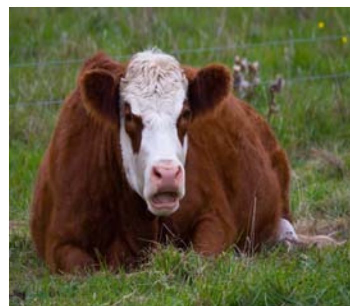
I MEAN WE SKIN TEST COWS!!!

- How hard can it be?
- Toddler vs cow!!



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TST DISADVANTAGES- FALSE +

- TST Disadvantages: False positives

BCG vaccine

- But vaccine used in those countries because they have a
- lot more TB, so threshold for treating kids from these
- countries is low

CDC doesn't alter threshold for interpretation based on

- BCG status
- Nontuberculous species
- I know *other* people's children (and patients) eat

Soil☺ NOT MY KIDS.

- But kids do well with TB meds; it's ok to

over treat some

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TST COST

- Some argue that TST costs are > IGRA costs when include

indirect costs of testing

- IGRA costs often reimbursed by insurance companies
- In MI, costs about $90/test for QuantiFERONs
- But…. many of my kids and their families are uninsured
- So is the same cost model applicable for all families?
- WHO: IGRAs not recommended in low- and middle-income countries

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IGRA COST

TST IS DEFINITELY CHEAPER

https://www.findlabtest.com/lab-test/infectious-disease-testing/tb-blood-test-cost-quest-19453

TB Blood Test Cost will be between $149.00 and $206.00

TB Blood Test Cost minimal is in Accesa Labs (QuantiFERON Gold TB, Blood) with price $149.00. TB Blood Test Cost max is in Personalabs (Tuberculosis-QuantiFERON-TB Blood Test) with price $206.00. This laboratory test is available in 4 online lab test stores.

$149.00 Order | Accesa Labs | **QuantiFERON Gold TB, Blood** $149.00
Covered tests: QuantiFERON®-TB Gold (Quest)
Covered components: Mitogen-Nil, Tb-Nil, Nil, Quantiferon(R)-Tb Gold
Blacklisted States: NY, NJ, MA, MD, RI

$189.00 Order | DirectLabs | **QuantiFERON®-TB Gold (Tuberculosis)** $189.00
Covered tests: QuantiFERON®-TB Gold (Quest)
Covered components: Mitogen-Nil, Tb-Nil, Nil, Quantiferon(R)-Tb Gold
Blacklisted States: MD, NJ, NY, RI

$199.00 Order | RequestATest | **QuantiFERON-TB Blood Test** $199.00
Covered tests: QuantiFERON®-TB Gold (Quest)
Covered components: Mitogen-Nil, Tb-Nil, Nil, Quantiferon(R)-Tb Gold
Blacklisted States: NY, NJ, RI

$206.00 Order | Personalabs | **Tuberculosis-QuantiFERON-TB Blood Test** $206.00
Covered tests: QuantiFERON®-TB Gold (Quest)
Covered components: Mitogen-Nil, Tb-Nil, Nil, Quantiferon(R)-Tb Gold
Blacklisted States: NJ, RI, NY

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2015-2018 Redbook- IGRA

Recommendation	2015	2018
Age*	≥ 5 years	≥ 2 years
Preferred test for BCG recipient	Yes	Unchanged
Use in immunocompromised children	Cautiously	Unchanged

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THERE ARE ROLES FOR BOTH

- IGRAs when TSTs:
  - -TSTs are ambiguously read
  - -You suspect TB disease and the TST is 0mm
  - -Immunocompromised kids
  - -Families need more convincing prior to treatment

- TSTs when IGRAs:
  - -IGRAs are borderline or indeterminate
  - -You suspect TB disease and the IGRA is negative or uninterpretable
  - -Immunocompromised kids

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Sputum Culture

- Ask a child to give you sputum and you will know what I am talking about!!

- Culture is still gold standard if we get sputum- not spit.

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GenXpert

- Again depends on sample
- Children have paucibacillary disease that limits their diagnosis
- If negative; does not help much
- If positive; of course believe it!

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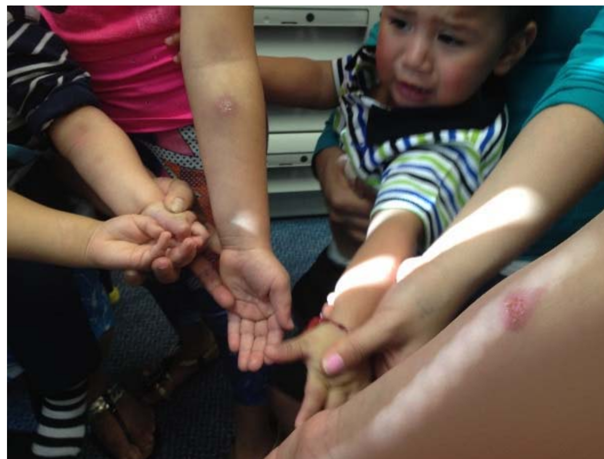
SCHOOL EPIDEMIC FUN

HIPAA RULES WERE DOWN THE DRAINS



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TB INFECTION REGIMEN

- LET'S COMPARE

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Treatment

- LTBI TREATMENT
  - Historically it has always been INH for 9 months.
  - We select regimens based on safety, tolerability, efficacy
  - We know TB therapy is effective
  - However, completion rates abysmal with the traditionally-used 9 months of INH (9H):
  - ~ 50% Completion inversely associated with duration of therapy

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Treatment for Preventing Tuberculosis in Children and Adolescents A Randomized Clinical Trial of a 3-Month, 12-Dose Regimen of a Combination of Rifapentine and Isoniazid

- 905 children (2-17-yrs-old) from US, Canada, Brazil, China, Spain
- *JAMA Pediatr 2015;169(3):247*

VARIABLE	3HP	9H	PVALUE
Progression to disease	0%	0.74%	0.11
Treatment completion	88.1%	80.9%	0.003
Discontinued due to AE	0.6%	0.25	0.63
Drug related hepatotoxicity	0%	0%	-

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Completion Rate and Safety of Tuberculosis Infection Treatment With Shorter Regimens

Andrea T. Cruz, MD, MPH, Jeffrey R. Starke, MD

- 3HP vs 4RIF vs 9H, retrospective, non-randomized, 2014-2017
- Completion not associated with race/ethnicity or test of infection
- N=667
- 3HP was given to only children over 2 years of age.
- *Pediatrics 2018;141*

Regimen	%completion
9H (given by families)	53%
9H (DOT)	89%
4RIF (families)	84%
4RIF (DOT)	97%
3HP DOT	97%

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Better Completion of Pediatric Latent Tuberculosis Treatment Using 4 Months of Rifampin in a US-based Tuberculosis Clinic

James Gaensbauer, MD, MScPH,† Kaylynn Aiona, MPH,* Michelle Haas, MD,*‡ Randall Reves, MD,*‡ Janine Young, MD,*§¶ and Robert Belknap, MD*‡*

- *Pediatr Infect Dis J* 2018;37(3):224

- 4RIF vs 9H, nonrandomized, retrospective study
- • Drug toxicity all dermatologic (1.5% in RIF, 0.7% in INH, non-signif)
- • No known treatment failures
- • Completion higher with RIF (84% vs 69%, p<0.0001)
- • Completion rates higher when:
- • IGRA used for diagnosis
  - Children identified in contact tracing
  - Shorter regimens used

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2015 VS 2018 RED BOOK

Recommendations	2015	2018
Preferred Regimen	INH	No specific preference (this is order in red book) • 3HP* • 4RIF • 9H
RIF role	Limited INH intolerance INH resistance in source case isolate	Expanded
3HP	Use in ≥ 12years	Use in ≥ 2 years

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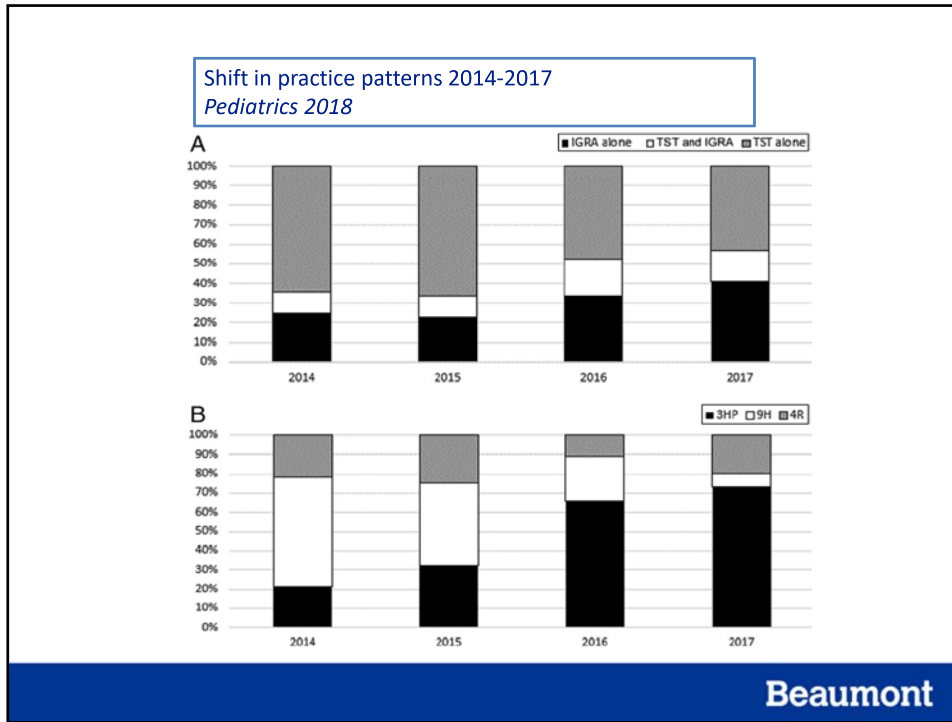

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2015 VS 2018 RIFAMPIN DOSING

Recommendation	2015 Mg/kg	2018 Mg/kg
Standard treatment	10-20	15-20
TB meningitis	10-20	20-30
Non meningitic TB, infants and toddlers	10-20	20-30
Exceed adult maximum (600) mg	No	Yes

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Rifampin dosing

- Rifampin Dosing
- Dosing initially used for RIF was in adults who weighed far less than TB patients do today
  - Resulted in a 60-70% dose reduction
- Children metabolize many TB drugs faster than adults
  - Need higher mg/kg dose to achieve target serum concentration (8µg/mL)
- Recognition that there is substantial difference between-child variation in metabolism of certain TB drugs

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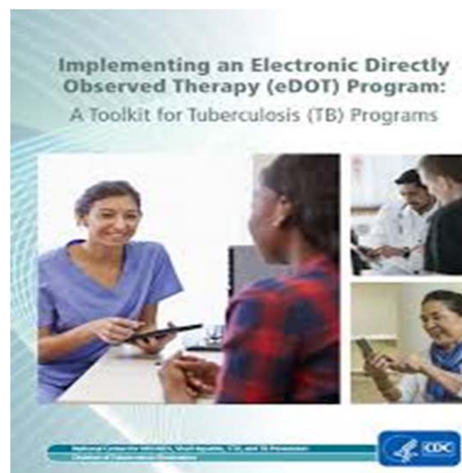
Routes of administration



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Scenario

8yo referred to see you for + IGRA performed after child didn't complete 9 INH following a positive TST

- Pediatrician restarted INH
- You delve into barriers family faces:
  - Cannot afford rifampin
  - 9 months is a LONG time
  - Family unclear on rationale for therapy
  - What do you do now?
  - Change regimen?
  - Change way we give it?

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Routes

- Self-administered therapy (SAT)

  Family fills prescription, administers medication to child
- Enhanced SAT (ESAT)

  Health department drops off meds, family administers them
- Video directly-observed therapy (vDOT)

  Health department drops off meds periodically, family uses app to securely send video of child taking meds
- Traditional (in-person) directly observed therapy (DOPT)

  Health department drops off meds, watches family administer them

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Pros and cons

Route	Pros	Cons
SAT	Low cost to system	High cost to family 50% children will complete therapy
ESAT	Removes barriers of finding pharmacy, paying for prescription, cost is between SAT and DOT	Does not address barrier of family giving medicine
vDOT	Convenient for families Low cost than DOT	Needs Internet, need to be tech savvy Secure data portal
DOT	Allows for closest monitoring of high risk children	Acceptability to some families and COST

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Monitoring while on therapy

May have to see in clinic less frequently if on DOT (or video DOT)

- Few children need baseline or serial LFTs.

Exceptions:

- Obesity
- Existing liver disease or comorbid medical conditions
- Receipt of other hepatically-metabolized medications
- Low threshold for stopping meds and checking LFTs were the child to have any GI symptoms
- Importance of anticipatory guidance

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SUMMARY
2018 AAP Redbook version 31
Release date 06/31/2018

TB TESTING:

- Endorsement of the use of IGRA for any indication in children >2 years
- Acknowledge that some experts are using IGRA in children younger than 2 years

LTBI Treatment:

inclusion of 3HP, 4R and 9H as 3 acceptable regimens. No order of preference. (in 2015 9H was preferred).

Dosage of rifampin increased to 15mg/kg/day from 10-20. For all age groups in TB meningitis dose of 20-30mg/kg/day should be considered.

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Questions???

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