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Advanced Concepts in Pediatric TB: Treatment of Tuberculosis Disease

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Objectives

At the end of this session, participants will be able to:

- Understand the mechanisms and patterns of antimicrobial resistance in TB
- Understand the rationale for various treatment regimens of drug-susceptible and MDR-TB
- Plan the treatment for pulmonary and extra-pulmonary TB in children
- Plan follow-up evaluation for a patient undergoing treatment for TB disease: repeat cultures, radiographs, assessment and management of common adverse reactions to anti-TB drugs in children

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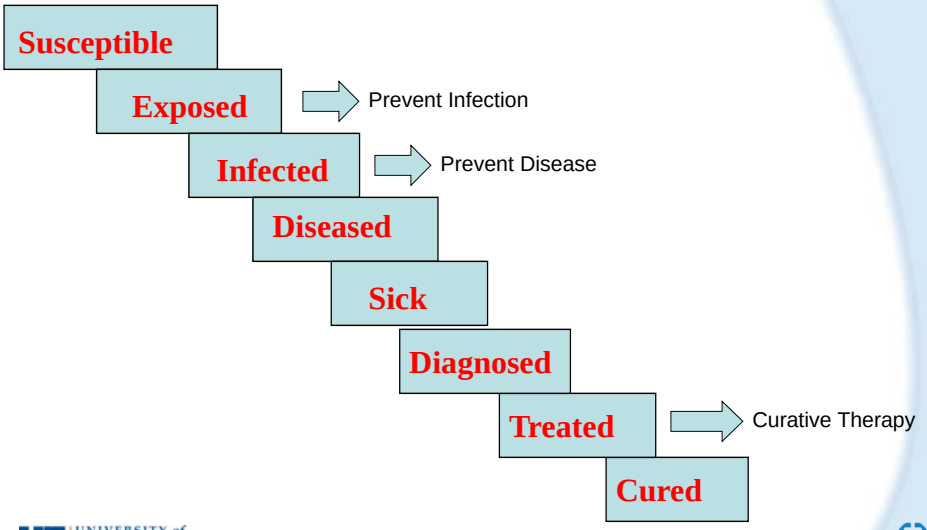
Transitions in Tuberculosis



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Drug Resistance in Tuberculosis

The development of drug resistance in *M. tuberculosis* is the result of a conspiracy among the organism, the patient, the doctor and the healthcare system!

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Drug Resistance in *Mycobacterium Tuberculosis*

- Genetic loci for resistance on chromosome, unlinked
- Resistance of drugs independent
- Frequency of mutations at loci is known
- More likely to have mutations when mycobacterial population is larger: infection vs. disease
- Primary - resistance present when infection acquired
- Secondary - resistance develops while on therapy

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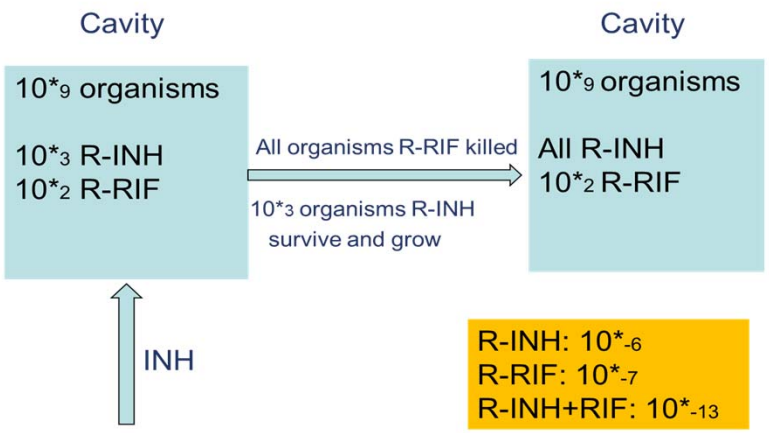
Preventing Drug Resistance in TB



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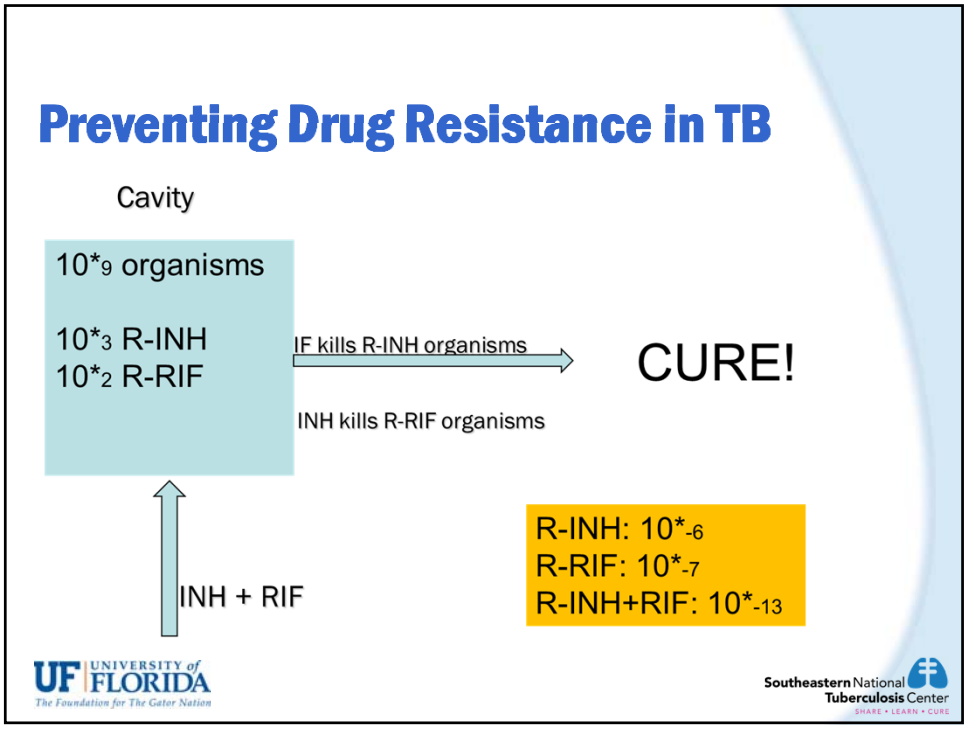
Preventing Drug Resistance in TB
Cavity
10*9 organisms
10*3 R-INH
10*2 R-RIF
IF kills R-INH organisms
INH kills R-RIF organisms
CURE!
INH + RIF
R-INH: 10*-6
R-RIF: 10*-7
R-INH+RIF: 10*-13
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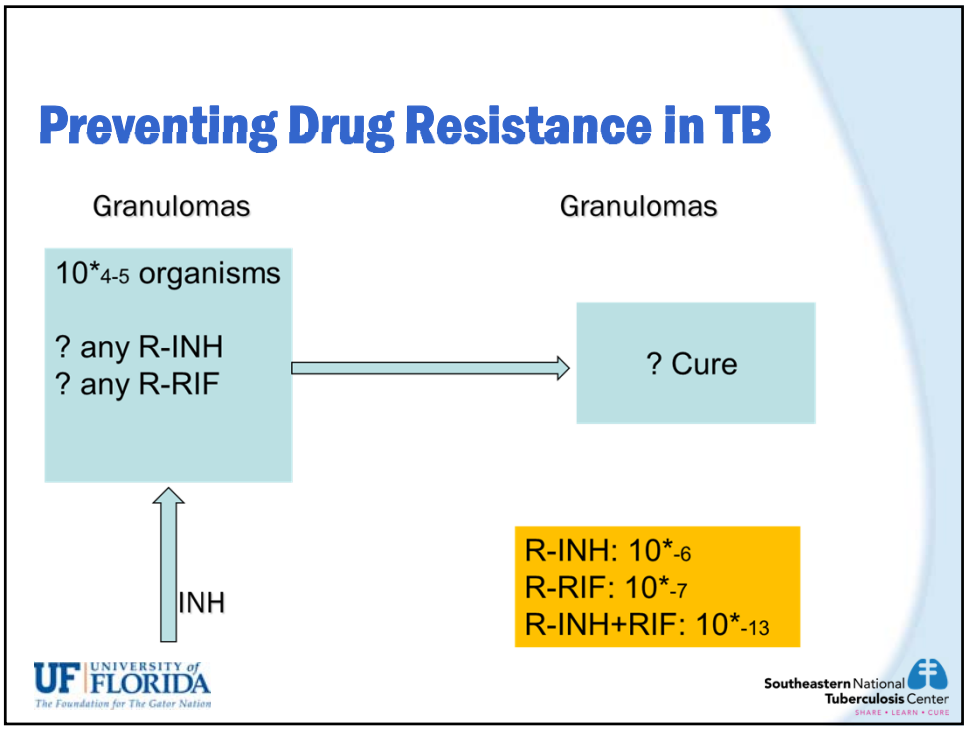
Preventing Drug Resistance in TB
Granulomas
Granulomas
10*4-5 organisms
? any R-INH
? any R-RIF
? Cure
INH
R-INH: 10*-6
R-RIF: 10*-7
R-INH+RIF: 10*-13
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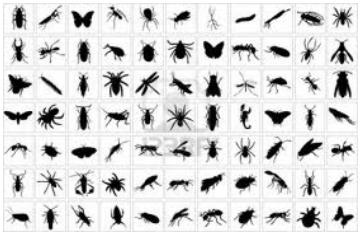
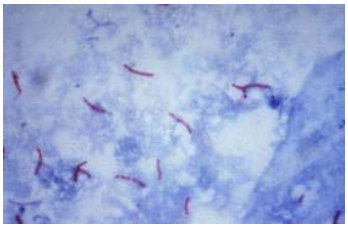
Treatment of Tuberculosis

"More bugs More drugs!"





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Roles of Specific TB Drugs in Regimens

Isoniazid
- Bactericidal
- Prevents emergence of resistance to other drugs

Rifampin
- Bactericidal
- Prevents emergence of resistance to other drugs

Ethambutol
- Bacteriostatic at lower doses
- Prevents emergence of resistance to other drugs

Pyrazinamide
- Allows for shorter durations of therapy

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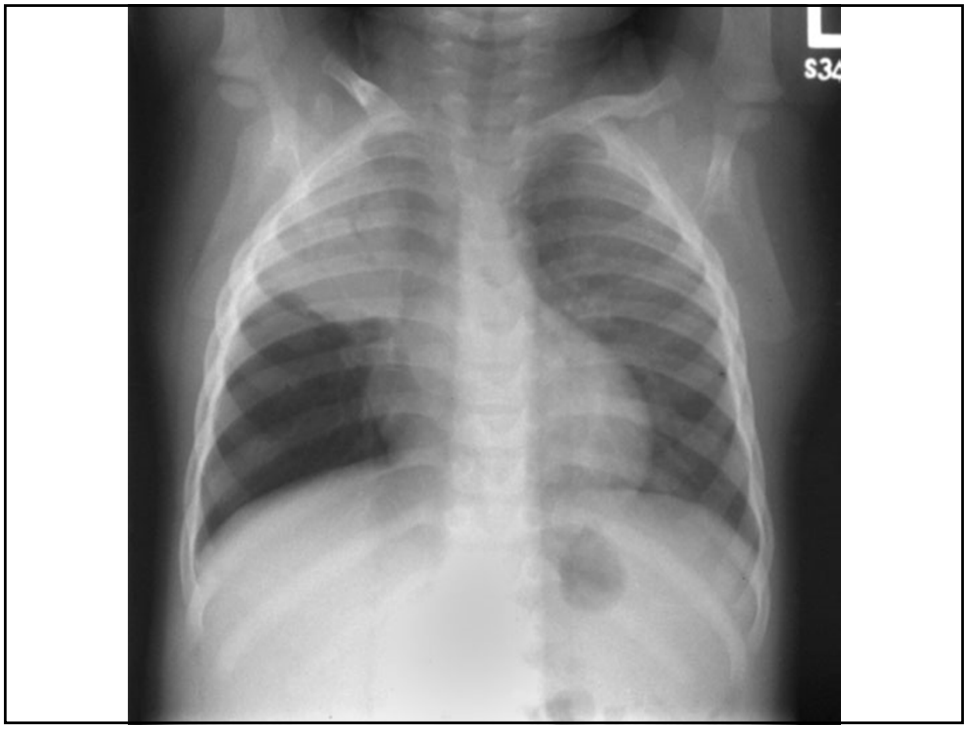
Case 1

A 3 year old girl, who has been in contact with her uncle who was recently diagnosed as a TB suspect, has been well. Her physical examination is normal. A TST yields 18 mm of induration. Her chest radiograph is normal. She is started on isoniazid.

Case 1 (cont.)

Two months later, she develops a low-grade fever, mild cough and a stuffy nose. She is seen in an emergency department where diminished right upper lobe breath sounds are noted. Her chest x-ray shows…



Case 1 (cont.)

A CT scan of the chest revealed enlarged right hilar lymph nodes with external compression of the right upper lobe bronchus. A bronchoscopy revealed some caseous material in the right upper lobe. Mycobacterial cultures were negative.

What would you do?

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Choices

1. Keep treating her with isoniazid alone
2. Start her on RIPE therapy
3. Start her on RPE therapy
4. Start her on RIP therapy
5. Start some other regimen

Points To Ponder

What is the real difference between TB infection and TB disease in children?

- The organism is present in both cases
- We can sometimes culture the organism from children with recent infection but no clinical disease
- We treat infection with 1 or two drugs, disease with 3-4 drugs
- The functional difference is the burden of organisms
- Infection and disease are on a continuum – when does "infection" turn into "disease"?
- The convention is that it is disease when "we can see it with our eyes or feel it with our fingers"

Considerations for Pediatric TB Treatment Regimens

- Very few true RCTs have been performed for intrathoracic TB, almost none for extrapulmonary TB
- Regimens that work in adults tend to work in children; may define the *maximum* treatment children require
- However, adult data do not necessarily define the *minimum* treatment required by children
- Children generally tolerate existing drugs and drug regimens better than adults
- New drugs and shorter regimens will need to be tested in children of various ages

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Therapy: TB Disease in Children

- Start 3- or 4-drug therapy – RIP or RIPE
  - INH, rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB); INH/RIF are the backbone of therapy
  - May start with RIP if risk of drug resistance is low
- Use PZA only during 1st 2 months for susceptible TB
  - This is the 'shortening agent' from 9 to 6 months of therapy
- Stop EMB once culture results known, if pan-susceptible TB
  - This is insurance in case there is drug-resistant TB
- Anticipate minimum 6 month therapy, and we often extend it to longer periods, especially for extrapulmonary disease
- ***Always*** administered by directly observed therapy (DOT)

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Ethambutol

- Metabolized faster by children than adults
  - Same mg/kg dose results in lower serum levels in children
- Consequently, risk of optic neuritis is very low
- You can feel very comfortable using ethambutol even in the pre-verbal child in whom visual acuity screening is challenging!
- Remember, however, that it crosses the blood-brain barrier poorly and should not be used for meningitis [although WHO recommends it]

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Regimen 1 for Treatment of Pulmonary Drug-Susceptible TB

6 month standard regimen

Initial phase

INH, RIF, PZA, EMB daily (7 or 5 days/week) for 8 weeks

Continuation phase options

1) INH, RIF daily (7 or 5 days/week) for 18 weeks

2) INH, RIF intermittently (2 or 3 days/week) for 18 weeks

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Regimen 2 for Treatment of Pulmonary Drug-Susceptible TB

6 month daily +intermittent options

Initial phase

INH, RIF, PZA, EMB daily (7 or 5 days/week) for 2 weeks, then 2 or 3 days/week for 6 weeks

Continuation phase

INH, RIF intermittently (2 or 3 days/week) for 18 weeks

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Regimen 3 for Treatment of Pulmonary Drug- Susceptible TB

6 month intermittent dosing options

Initial phase

INH, RIF, PZA, EMB intermittently (3 days/week) for 8 weeks

Continuation phase

INH, RIF intermittently (3 days/week) for 18 weeks

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Regimen 4 for Treatment of Pulmonary Drug-Susceptible TB

9 month without pyrazinamide options

Initial phase

INH, RIF, EMB daily (7 or 5 days/week) for 8 weeks

Continuation phase options

1) INH, RIF daily (7 or 5 days/week) for 31 weeks
2) INH, RIF intermittently (2 or 3 days/week) for 31 weeks

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WHO Rapid Advice – 2010 Pulmonary and Lymph Node TB in Children

- Standard therapy is 2HRZE + 4HR
- Where prevalence of HIV and INH resistance are low, therapy can be 2HRZ+4HR
- In HIV uninfected children with fully drug-susceptible TB, thrice weekly regimens can be used in the continuation phase with well established DOT [*Weak recommendation, very low-quality evidence*]
- Children with HIV infection should not receive intermittent regimens [*Strong recommendation, low-to-moderate quality evidence*]

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WHO Rapid Advice – 2010 Meningeal and Osteoarticular TB

- Children with suspected or confirmed tuberculous meningitis should be treated with HRZE for 2 months, followed by HR for 10 months, the total duration of therapy being 12 months. Standard doses should be used. [Strong recommendation, low-quality evidence]

- Children with suspected or confirmed osteoarticular tuberculosis should be treated with HRZE for 2 months followed by HR for 10 months, the total duration of therapy being 12 months. Standard doses should be used. [Strong recommendation, low-quality evidence]

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Notes on TB Drugs

Drug	Side Effects	Other notes
INH	Peripheral neuropathy; seizures in overdose; hepatotoxicity	B6 helps prevent neuropathy and is only treatment for INH seizures, but doesn't prevent hepatotoxicity
RIF	Orange discoloration of secretions; inactivates oral contraceptives; many drug interactions; hepatotoxicity	Please warn of **orange** urine!
PZA	Can increase uric acid → gout symptoms; rash; pruritis; hepatotoxicity	Of 1st-line drugs, greatest association with hepatotoxicity
EMB	Optic neuritis, red-green color blindness	Despite side effects, has very poor CNS penetrance and not used for meningitis

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Medication Tolerance

- Children
  - 5% risk of adverse effects in children
    - Most are minor – abdominal pain without elevation in LFTs
    - 3.3% incidence of elevated LFTs with INH and Rifampin (usually asymptomatic)
    - Hepatotoxicity most often caused by pyrazinamide
  - Peripheral neuropathy quite rare before adolescence
- Adults
  - Hepatotoxicity:
    - 3-4% with INH alone
    - Up to 5% with INH and Rifampin
  - Peripheral neuropathy: 4%

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Case 2

A 17 year old boy with Crohn's disease does poorly with conventional therapy. Before starting Remicaid (infliximab), 2 TSTs yield no induration. About 6 weeks after starting Remicaid, he develops fever, a 5 lb. weight loss, cough and some respiratory distress. His chest x-ray shows…

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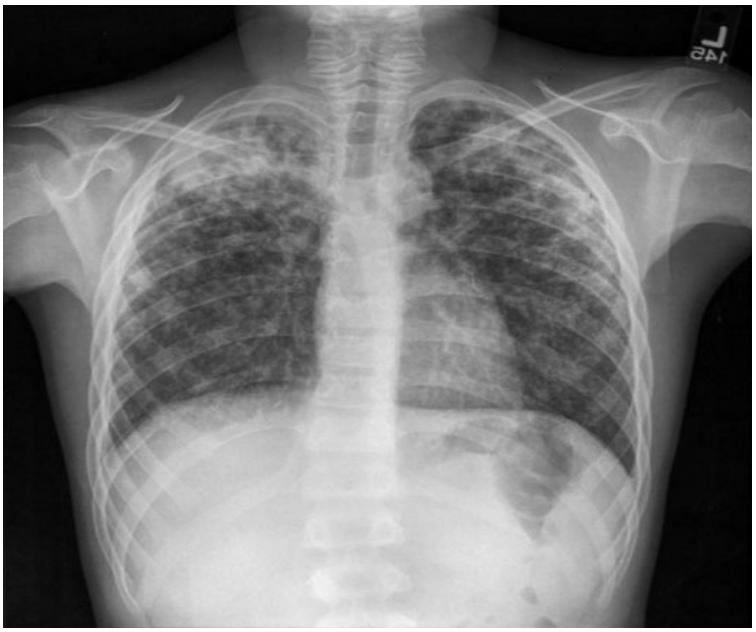

Case 2 (cont.)

He is started on 4-drug therapy for tuberculosis and he responds well clinically. Sputum culture is positive for pan-susceptible *M. tuberculosis*, and ethambutol is stopped. After 5 weeks of treatment, he develops abdominal pain and decreased appetite, losing 6 pounds. Physical exam reveals abdominal tenderness, worse in the RUQ. An AST is 1,750; an ALT is 1330.

What would you do?

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Choices

1. Stop all TB drugs
2. Stop current drugs and start amikacin and a fluoroquinolone
3. Stop current TB drugs and start ethambutol and amikacin
4. Stop current TB drugs and start ethambutol, amikacin and a fluoroquinolone
5. Something else

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Case 2 (cont.)

All anti-TB drugs are stopped, and he is started on amikacin (IV) and ethambutol (oral). After 2 difficult weeks, his AST and ALT are below 100. Reintroduction of isoniazid leads to abdominal pain and AST of 337.

What would you do?

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Choices

1. Stop INH until the liver cools down, then start RPE
2. Stop INH and start RPE right away
3. Stop INH until the liver cools down, then start RPE and a fluoroquinolone
4. Something else

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Medication Administration

- INH suspension only to child not taking any solid/pureed foods (< 5 kg)
- Warn parents about rifampin and urine color
- Warn adolescents about oral contraceptives
- Make sure child can tolerate all medication doses prior to discharge (for some young babies, doses may need to be divided in the course of the day)
- Intermittent therapy difficult for infants and toddlers because of the volume of medications

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Follow-up evaluations children with tuberculosis

- Skin test stays positive “forever”; unclear about the IGRAs
- Frequent chest x-rays unnecessary - at diagnosis, 1-2 months, end of therapy
- Follow growth & development closely
- Adequate nutrition
- Routine liver enzyme monitoring not necessary
- Routine vitamin B6 not necessary except breast-feeding, pregnant adolescents, poor diet

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Corticosteroids in Pediatric Tuberculosis

- Useful when host inflammatory response is contributing to tissue damage or dysfunction
  - meningitis
  - endobronchial
  - miliary with alveolar block
  - pericardial with constriction
  - vertebral with spinal root irritation

- Can use prednisone or dexamethasone

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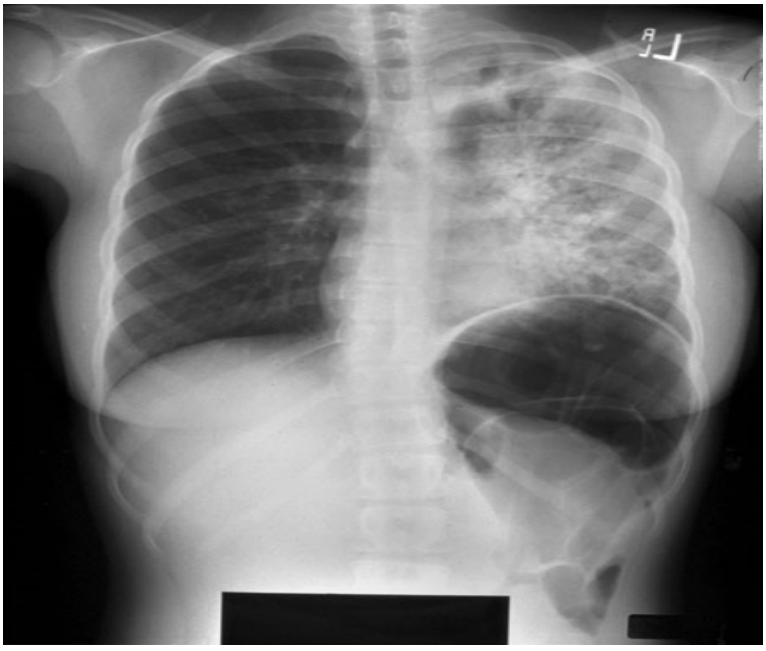
Case 3

A 15 year old girl from Nigeria arrives in Houston for her sister's high school graduation. On her way to the ceremony, she stops off at the emergency department to get some medicine for a "mild cough." You hear diminished breath sounds on the left, and get a chest radiograph…



Case 3

You start her on 4 antituberculosis medications [RIPE]. The AFB smear of her sputum is positive. Culture subsequently grows *M. tuberculosis* resistant to isoniazid, rifampin, pyrazinamide and ethambutol.

What would you do?

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Choices

1. Continue the RIPE therapy and wait for the full drug susceptibility report
2. Stop all drugs and wait for the full drug susceptibility report
3. Start Moxi, an aminoglycoside, Cycloserine and PAS
4. Start the regimen above plus linezolid
5. Something else

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RIFADIN
300 mg
Pyrazinamide
Tablets, USP
500 mg
500 TABLETS
DIXON'S
Isoniazid
Tablets, USP
300 mg

Treatment of Drug Resistant TB in Children

INH mono-resistance: well-treated with 6-9 months of rifampin, pyrazinamide and ethambutol

MDR- TB: treatment must be individualized depending on

- Exact drug susceptibility profile
- Anatomic location of disease
- Extent of disease
- Tolerance of medications
- Requires 4-6 drugs to which the organism is susceptible, at least 2 being bactericidal

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Some Issues in the Management of MDR-TB in Children

- Clinical trial data are extremely limited
- Optimal drug combinations are unknown
- Optimal durations of therapy are unknown
- Pharmacokinetic data are lacking
- Child-friendly dosing forms nonexistent
- Adverse drug effects often more difficult to assess, but children tend to tolerate drugs better
- Children have more intercurrent illnesses

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Notes on Specific Drugs for MDR-TB in Children

Amikacin: peak serum concentrations tend to be higher than in adults [20 mg/kg/day IM]

Levofloxacin: dose should be increased to 15 to 20 mg/kg/day when used for MDR-TB

Ethionamide: younger children achieve lower serum concentrations than adults; even lower if also HIV-infected

Linezolid: limited experience in children for TB; risk of optic neuritis, peripheral neuritis, bone marrow suppression [esp. thrombocytopenia]

Cycloserine: fewer neurologic effects; must give pyridoxine and should check serum levels

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Adverse Effects

Adverse Event	Likely Culprit Drugs	Identification	Management
Hepatotoxicity	INH, RIF, PZA, ethionamide, PAS, clofazimine	Tender liver, visible jaundice	Stop all drugs; Wait for liver function to return to normal; Reintroduce drugs one-by-one, every 2 days with monitoring of liver function before next drug
Visual Problems	EMB, ethionamide, PAS, linezolid	Regular testing	Stop EMB or substitute alternative drug; offer B6 with ethionamide
Hearing Problems	Amikacin, capreomycin, kanamycin	Identification through audiometry or problems in communication	Consider stopping injectable drug, substituting alternative drug, reducing dose or increasing dosing interval

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Adverse Events

Adverse Event	Likely Culprit Drugs	Identification	Management
Thyroid dysfunction	Ethionamide, PAS	Regular blood testing, clinical hypothyroidism or goiter	Consider thyroxine supplementation (0.5g daily) if clinical hypothyroidism or raised TSH and decreased fT4 If raised TSH or decreased fT4 repeat test in one month
Renal impairment	Amikacin, capreomycin, kanamycin	Regular blood testing, symptoms of high potassium	If creatinine rises or if potassium is high, stop injectable, substitute for alternative drug, dose 3 times per week or reduce dose
Severe Rash	Any drug, skin discoloration (clofazimine), cycloserine, linezolid, EMB, STM	Severe rash, peeling mucous membranes, child unwell	Stop all drugs; Wait until clinical condition improves; Reintroduce drugs one by one, every 2 days, monitor closely

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Adverse Events

Adverse Event	Likely Culprit Drugs	Identification	Management
Nausea and vomiting	INH, RIF, EMB, PAS, ethionamide, PZA, clofazimine	Clinically	Considering separating the dosing of THA from the other drugs, by giving it in the evening; Consider reducing the dose of THA and building the dose back up to full dose over 2 weeks
Diarrhea	PAS	Clinically	Split dose of granules to give small doses throughout the day, Reduce dose, Consider loperamide
Peripheral neuropathy	INH, ethionamide, fluoroquinolones, linezolid, EMB, cycloserine, injectables	Clinically	Give or increase pyridoxine; If persistent or sever, stop INH

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Adverse Events

Adverse Event	Likely Culprit Drugs	Identification	Management
Neuro-psychiatric problems	INH, ethionamide, fluoroquinolones, terizidone, cycloserine	Seizures, headache, behavior changes, sleep disturbances	Verify correct dosing; Stop likely culprit drug; If symptoms persist, reintroduce and stop next most likely dose Less with terizidone than cycloserine
Joint problems	PZA, ofloxacin, levofloxacin, moxifloxacin	Clinically	Verify correct dosing; Consider reducing dose or stopping possible culprit drug; Consider trial of allopurinol
Painful injection sites	Amikacin, capreomycin, kanamycin	Clinically	Add local anesthetic to drug in equal volumes; Vary site of injection on a daily basis, If severe, consider splitting dose and giving half into two different sites Warm packs to skin

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Adverse Events

Adverse Event	Likely Culprit Drugs	Identification	Management
Bone marrow suppression	PAS, rifampin, cycloserine (anemia), linezolid	Regular blood testing, ecchymoses	PAS: B12 supplementation Cycloserine: folate supplementation Severe cases: G-CSF
Arrhythmia	Fluoroquinolones	Baseline EKG	Correct hypokalemia, hypomagnesemia; beware use of quinolones with other medications which can prolong the QTc

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Case 4

A 14 year old girl presents with a mass in her right neck and an 18 mm reaction to a TST. The mass started about 2 months ago and has grown, finally opening up and having a slightly bloody, white discharge. There is minimal pain and tenderness. She has no systemic signs or symptoms.

What would you do?

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Case 4 (cont.)

She is referred to your ENT surgeon, who performs an incision and drainage of what is a suspected lymph node. Histopathology of some tissue reveals caseating granulomas, with some AFB-positive organisms present. Culture is pending.

What would you do?

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Case 4 (cont.)

The patient is started on isoniazid, rifampin and pyrazinamide. The culture ultimately shows no growth. After 6 weeks of therapy, she develops abdominal pain and right upper quadrant tenderness.

What would you do?

Case 4 (cont.)

The AST is 572, ALT 348, Total Bilirubin is 0.6. You stop all her antituberculosis medications and let the liver enzymes drop, which they do. You restart rifampin, then pyrazinamide and she has no problems.

What would you do?

Case 4 (cont.)

Instead of re-challenging her with isoniazid, you start ciprofloxacin. She takes the medications (DOT/BIW) for a total of 9 months and does well, with only minimal scar tissue at the site. About 4 months after stopping the medications, she again develops a draining lump at the previous site of infection.

What would you do?

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Case 4 (cont.)

You are concerned about the diagnosis and the possibility of drug-resistant TB, so you refer her again to the ENT physician, who performs an excisional biopsy. Histopathology again reveals a node with caseating granulomas and rare AFB - positive organisms. You find out the entire surgical specimen was placed in formalin, and no culture was done.

What would you do?

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Case 4 (cont.)

You start the patient on rifampin, pyrazinamide and levofloxacin. Two months later, she informs you that she is pregnant (against your adamant advice).

What would you do now?

Choices

1. Quit your job
2. Transfer out of tuberculosis clinic
3. Declare her an adult and transfer her to Internal Medicine
4. Keep treating her and hope for the best
5. Take her off all TB therapy

Summary

- Children tolerate treatment for drug-susceptible TB very well. Frequent biochemical monitoring is not necessary
- A variety of regimens and schedules can be used as dictated by resources and drug tolerance
- Regimens that work in adults tend to work in children but the pK of new drugs needs to be established in children of various ages
- Children tolerate drugs used for MDR-TB fairly well
- There are no clinical trial data for specific MDR regimens in children but anecdotal experience suggests they do well with individualized therapy

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