



Challenging Cases of Pan- susceptible Tuberculosis

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Objectives

At the completion of this session, the participant will be able to;

- Identify diagnostic delays in tuberculosis (TB) and its effect on treatment decisions to enhance clinical outcomes for patients with TB disease
- Know how to manage patients with underlying medical conditions that impact treatment and clinical outcomes of TB disease
- Recognize and manage adverse effects of first-line TB drugs that challenge treatment completion within the expected time frame to ensure optimum outcomes in patients with TB disease

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Indian male with cirrhosis (1)

- 41yo Indian male with cirrhosis due to alcohol abuse
- HIV-negative; both Hepatitis B and C-negative
- 2/11/2016 admitted for presumed peritonitis; Denied fever, chills, night sweats or chronic cough
 - Platelets 35K; WBC 17K, HGB ~10
 - AST 64, ALT 102, T. Bili 3.3.
 - Creatinine, electrolytes, ammonia levels normal
 - Paracentesis: 22,000 WBC, >50% polys, 43% lymphs, normal ADH
- Recent travel to India 11/2015, where he had a brief respiratory illness that later resolved

Indian male with cirrhosis (2)

- After admission, his counts decreased: WBC 2.7, Plts 17k, Hgb 8.5.; providers felt he had heparin-induced thrombocytopenia
- Wife noted an episode of “staring” for what she thought lasted 15 minutes
- Head CT 2/10 showed ring enhancing lesions with edema, no shift or hydrocephalus
- Repeat head CT 2/12 showed hemorrhage into some of the lesions, concern for metastatic disease

Indian male with cirrhosis (3)

- LP not done given cerebral edema, low platelets
- Full body CT: Pleural effusion, consolidation in the RUL and RML, several cavitory pulmonary lesions, cirrhotic liver w/ ascites; No other evidence of malignancy
- 2/14 follow up head CT showed increased edema, no new hemorrhage
- 2/15 antibiotics started for “brain access”; with vancomycin/rocephin/flagyl; No quinolone
- 2/17 head MRI: new R. MCA ischemic stroke

Indian male with cirrhosis (4)

- Given CNS lesions, cavitory lung lesions, cirrhosis/ascites and foreign-birth/travel to India, providers consulted SNTC to ask how to proceed with evaluation and treatment of possible TB.
- How should you make the diagnosis of possible TB?

How should you make the diagnosis of possible TB?

1. AFB smear, culture and susceptibility testing on sputum
2. AFB smear, C&S, nucleic acid amplification (NAAT) on sputum
3. AFB smear, C&S, NAAT on sputum and urine
4. AFB smear, C&S, NAAT on sputum, urine LAM
5. AFB smear, C&S, NAAT on sputum, give platelets and FFP then do LP and/or paracentesis and test ascites fluid by AFB smear, C&S and NAAT.

Diagnosis of Active TB Disease

- Evaluate anatomic site(s) of signs or symptoms (sputum, ascites, CNS, urine, bone marrow, etc):
 - AFB C&S: smear within 24h, culture 2-6wks
 - Cultures suspected of being MTBC can be ‘probed’ with a molecular probe test which can detect MTBC, MAC (*Mycobacterium avium* complex), *M. gordonae* and *M. kansasii*.



Diagnosis of Active TB Disease

- Molecular methods more sensitive and specific than culture (gold standard), same day results (<2h)
- Nucleic Acid Amplification Test performed directly on specimen
 - Referred to as NAAT, NAT, or PCR
 - Diagnosis of MTBC and susceptibility testing (genes)
 - GeneXPERT: M. TB and *rpoB* detection (90 min)
 - Hain GenoType MTBDR*plus* assay- *rpoB*, *inhA*, *katG*
 - If not available in the lab you send specimens to, that lab should refer out (State HD, UFL, CDC)

CDC GeneXpert Recommendations, 2013: <http://www.cdc.gov/mmwr/pdf/wk/mm6241.pdf>

Boehme CC, et al.. N Engl J Med. 2010;363:1005-1015. Epub 2010 Sep 1.

Boehme CC, et al. Semin Respir Crit Care Med 2013;34:17–31.



Future of TB Diagnostics

- Globally, there is a critical need for highly sensitive and specific TB diagnostic ‘point-of-care’ tests that can replace smear microscopy at any clinical site, or even better, by community health workers conducting home visits.
- New tests are being developed, including urine, serology and breath based tests.
 - Matthew Bates & Alimuddin Zumla (2016) *The development, evaluation and performance of molecular diagnostics for detection of Mycobacterium tuberculosis*, *Expert Review of Molecular Diagnostics*, 16:3, 307-322,

Urine LAM

- Can detect mycobacterial cell wall lipopolysaccharide lipoarabinomannan (LAM) in urine
 - Particularly useful in patients with HIV-TB, incrementally greater sensitivity with progression of immunodeficiency
 - WHO has conditionally recommended its use to assist in TB diagnosis in hospitalized patients with low (<+100cells/ul) CD4 cell counts or patients who are seriously ill.
 - May be prognostic marker for identifying HIV+ patients with highest mortality risk who may potentially benefit from closer follow-up or adjunctive interventions used in combination with TB treatment and ART

Urine LAM

- **Peter et al. *Effect on mortality of point-of-care, urine-based lipoarabinomannan testing to guide tuberculosis treatment initiation in HIV-positive hospital inpatients: a pragmatic, parallel-group, multicountry, open-label, randomised controlled trial.***
 - Missed and delayed diagnoses of TB is a major challenge in individuals with HIV co-infection.
 - Challenges obtaining sputum samples, limited yield in extrapulmonary TB, urine is favorable alternative sample
 - RCT suggests that a LAM-guided, prompt anti-tuberculosis treatment initiation strategy can reduce 8-week mortality in HIV-positive hospital inpatients.

Indian male with cirrhosis (5)

- Given his declining mental status with significant underlying illness, new CVA on CT/MRI, the patient may need to be intubated (unless he has DNR order)
- Obtain a sample for AFB C&S by deep tracheal wash
- Obtain rapid molecular test for M. TB (geneXPERT, HAIN)
- Start TB treatment after sample obtained
- Consider transfusion of platelets/FFP and obtain samples for C&S, PCR, histopath as able.

- What regimen should you use given his cirrhosis?

What TB regimen should you use in this patient with cirrhosis?

1. Standard RIPE, careful monitoring of liver function
2. INH/RIF/EMB with no PZA, careful monitoring of liver function
3. INH/RIF+ levaquin, careful monitoring of liver function
4. Rifabutin, levaquin, EMB, careful monitoring of liver function
5. Some other liver-sparing regimen

Hepatotoxicity of Antituberculosis Therapy

- Hepatotoxicity risk: INH, Rifampin/rifapentine, PZA, ETA, PAS
- Ethambutol: One report of EMB-related liver cholestatic jaundice, with unclear circumstances; Safe in liver disease
- Fluoroquinolones: Ciprofloxacin and moxifloxacin metabolized in part by the liver, whereas gatifloxacin, levofloxacin, ofloxacin largely excreted unchanged by kidneys.
 - Reversible transaminase elevation among FQ in up to 2- 3% of cases.
 - Severe hepatocellular injury and cholestasis reported to occur <1% of all FQ recipients, excluding trovafloxacin (withdrawn from market)
- Rifabutin: At 150–300 mg/day, hepatotoxicity uncommon per 2006 ATS gls; 2016 Curry guide says risk same as rifampin

Ref: 1. Saukkonen JJ et al. Am J Respir Crit Care Med Vol 174. pp 935–952, 2006.

2. Drug Resistant TB: A Survival Guide for Clinicians, 3rd edition. <http://www.currytbcenter.ucsf.edu>

3. Devarbhavi and Andrade. Semin Liver Dis 2014; 34(02): 145-161.



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Hepatotoxicity of Antituberculosis Therapy

- Aminoglycosides: Presumed safe in severe liver disease; however, use with caution—some patients with severe liver disease may progress rapidly to hepato-renal syndrome.
- Capreomycin: Presumed safe in severe liver disease; however, use with caution—some patients with severe liver disease may progress rapidly to hepato-renal syndrome.
- Cycloserine: Not associated with hepatotoxicity
- Linezolid: Rarely associated with increased transaminases.
- Imipenem/cilastin: Elevated LFTs noted in up to 6% of patients, but no definite liver damage has been documented.

Ref: 1. Saukkonen JJ et al. Am J Respir Crit Care Med Vol 174. pp 935–952, 2006.

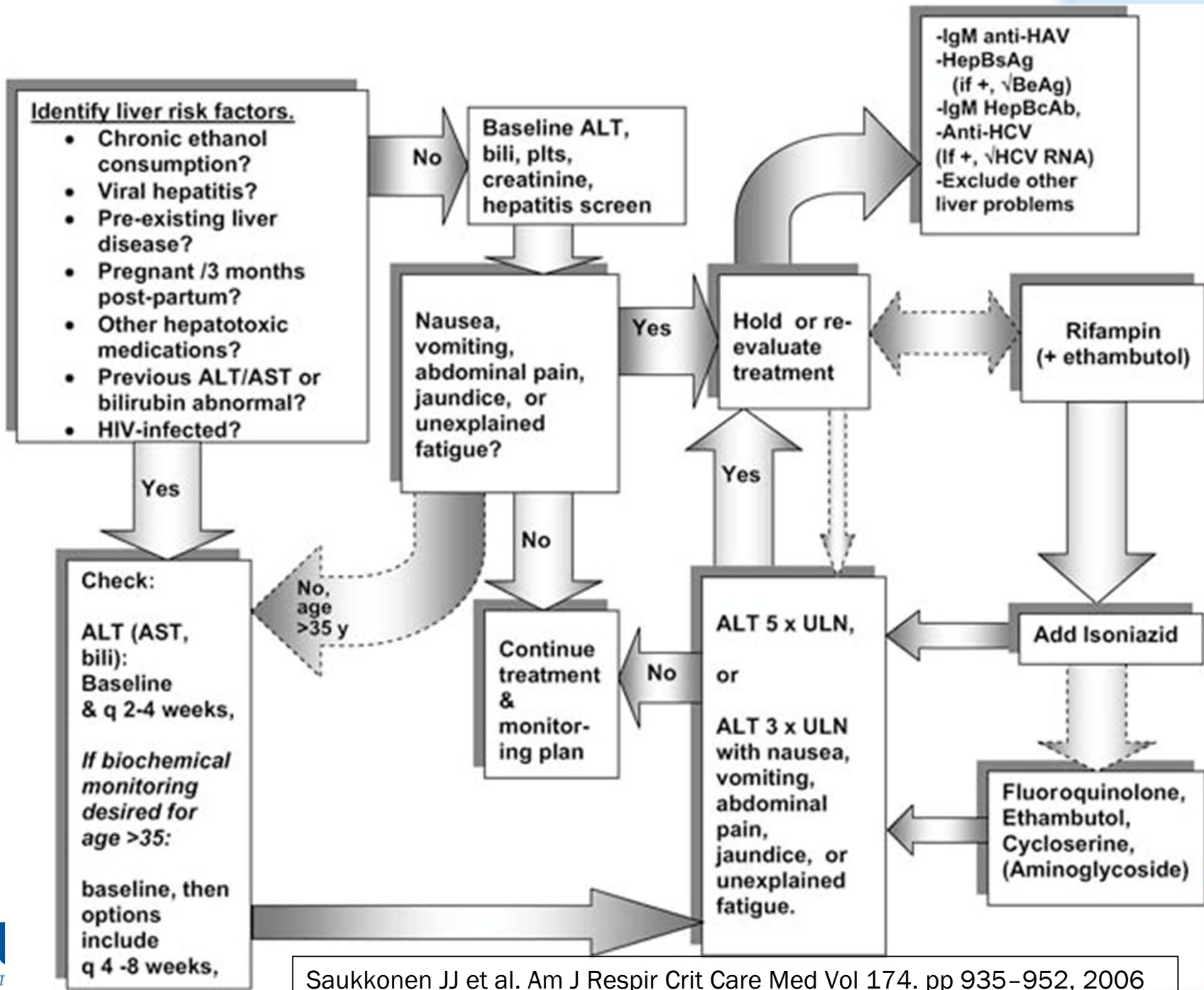
2. Drug Resistant TB: A Survival Guide for Clinicians, 3rd edition. <http://www.currytbcenter.ucsf.edu>

3. Devarbhavi and Andrade. Semin Liver Dis 2014; 34(02): 145-161.

An Official ATS Statement: Hepatotoxicity of Antituberculosis Therapy

(Saukkonen JJ et al. Am J Respir Crit Care Med Vol 174. pp 935-952, 2006)

- In patients with cirrhosis, RIF and EMB, with FQ or cycloserine, for 12 to 18 months may be considered.
- For patients with encephalopathic liver disease, consider EMB with a FQ, cycloserine, and capreomycin or AG for 18-24 mos.
- Some providers avoid AG in severe, unstable liver disease due to concerns about renal insufficiency, or bleeding from injected meds in patients with thrombocytopenia and/or coagulopathy.
- Curry Guidelines for Drug Resistant TB (2016):
 - If ESLD and further worsening could be life-threatening, consider LFX, EMB, an AG, and CS if appropriate. LZD, BDQ, and CFZ are alternatives
 - If the liver disease not imminently life-threatening, the use of a rifamycin in the regimen is advised if the isolate is susceptible.



Saukkonen JJ et al. Am J Respir Crit Care Med Vol 174. pp 935-952, 2006

TB medications and CNS penetration

- INH: Cidal; Readily diffuses into CSF independent of meningeal inflammation (small size, lipophilic); levels approach serum.
- PZA: Cidal (semi-dormant); Crosses freely into CSF.
- Ethambutol: Static, only cidal at high concentrations; penetrates meninges poorly
- Rifampin: Cidal; CSF penetration variable, typically achieves only 10–20% of serum concentrations in CSF (may be better in inflamed meninges), still important contribution to regimen. Some recommend high-dose RIF in TB meningitis-900mgIV QD
- Rifabutin: Cidal; penetrates inflamed meninges
- Levaquin and moxi: Cidal; moderate CNS penetration, even with uninflamed meninges (Concentrations are 65% of serum)

TB medications and CNS penetration

- Aminoglycosides: Cidal; Variable penetration; better in inflamed meninges
- Capreomycin: Cidal; little data for penetration of meninges
- Cycloserine: Static; CSF concentrations approach serum; but CNS toxicity so contraindicated in significant CNS disease (seizure disorder, psychotic disease, or alcohol abuse)
- Linezolid: Cidal *in vitro*; Good CNS penetration, used to treat bacterial meningitis
- Ethionamide: Weakly cidal; Concentrations approach serum; dosed on high end of range for patients with meningitis
- PAS: Static; Poorly penetrates CSF, better if inflamed
- Meropenem: limited clinical experience, Adequate CSF penetration, less seizure risk than imipenem (**contraindicated**)

Indian male with cirrhosis (6)

- Liver-sparing regimen

- Linezolid 600mg IV qd
- Levaquin 750mg IV qd (cleared renally)
- Amikacin 15mg/kg/d IV qd
- EMB safe in liver disease, concern he can't take/absorb oral meds if peritonitis or other abdominal disease (even if per tube).
- Given elevated Bili, avoid RIF for now, add later if he improves
- Avoid PZA, potential to worsen underlying liver disease
- Cycloserine may not be best given likely seizure, alcohol abuse
- Given his CNS disease, try to include INH with good CNS penetration, with low threshold to stop if any change in LFTs.
- Pyridoxine (B6) 50mg-100mg

Indian male with cirrhosis (7)

- LP and/or brain bx if patient and plt count improve (consider transfusion just before LP).
- Bone marrow biopsy to assess his pancytopenia, culture for various organisms including M. TB
- Repeat paracentesis to test ascitic fluid if possible
- Can stop Vanco if linezolid started (staph coverage), consider if rocephin still needed with Levaquin added, Continue Flagyl if concerned for brain access.
- Given poor prognosis, if he succumbs, autopsy with AFB C&S, PCR, histopath of brain and lung lesions
 - public health risk if pulm TB; treatment of contacts

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"I think we should cut back on my antidepressant.
I watched 'Old Yeller' and it was hysterical."

Pregnant Female with Cavitory TB (1)

- 30y.o. female born in Mexico
- 8 months pregnant, has gained no weight
- 15mm TST, no BCG vaccination
- Cough x 12 months, mild-to-moderate chest pain superior to L. breast upon deep breathing, end-inspiratory musical wheeze L. upper lobe
- CXR: L. apical cyst and L. cavitory lesion consistent with TB.
- What do you want to do next?

How should you evaluate pregnant woman with cavitary lung disease?

1. Chest CT to further evaluate her lung involvement, other possible sites of disease
2. Sputum C&S, empirically treat for TB if smear positive
3. Sputum C&S, wait for rapid molecular testing for resistance before starting TB therapy
4. Induced delivery ASAP, treat mom aggressively for TB after delivery of baby

Pregnant Female with Cavitory TB (2)

- Suspected of TB; mask & isolation, CI began.
- GeneXPERT (+)MTB, (-) Rif resistance; Smears positive, cultures pending
- Ordered HAIN test for rapid INH resistance testing since FB, not using PZA, cavitory disease, unclear fetal involvement
- **Recommended ultrasound to assess baby ASAP**
- **Would you consider expanded regimen? (foreign born, significant disease in advanced pregnancy).**

Would you consider expanded treatment regimen in a woman who is 8 months pregnant with Cavitory TB?

1. No-start RIF/INH/EMB
2. Yes-Start RIF/INH/PZA/EMB
3. Yes-Start RIF/INH/EMB +FQ

Treatment of TB in pregnant women

- **Aminoglycosides** are the only TB drugs that have well-documented teratogenicity.
- **INH, RIF, EMB** not associated with teratogenic effects.
- For pan-susceptible TB during pregnancy, use of **pyrazinamide (PZA)** is generally avoided in the United States due to lack of safety data.
 - Recommended during pregnancy by WHO and IUATLD as toxicity to the fetus has not been documented
 - Recommended in drug-resistant TB if isolate susceptible
- **Rifabutin (RFB), CS, and PAS** not extensively studied, but animal models and anecdotal human reports have not shown toxicity.

Treatment of TB in pregnant women

- Little evidence supporting significant risk to the fetus in patients who have received FQ for bacterial infections (shorter exposure than with TB).
 - Curry Guide indicates that FQ may be safe to use for DR TB in pregnancy if needed, especially after 1st trimester
- Available data does not demonstrate any serious arthropathy or other severe toxicity in children given FQ.
- Poorly treated TB in pregnant women associated with poor fetal outcomes. Benefits of treating TB in pregnancy generally outweighs risk of specific drugs for fetus.

S. Thee et al. Tuberculosis 95 (2015) 229-245.

Padberg, S et al. Antimicrob. Agents Chemother. August 2014 vol. 58 no. 8 4392-4398.

Starke JR and Donald PR, eds. Handbook of Child and Adolescent Tuberculosis, 2016. Oxford University Press, New York.

Pregnant Female with Cavitory TB (3)

- Communicate with OB-GYN before delivery
- Until the HAIN results available:
 - If she is very sick, consider starting treatment with INH, RIF and EMB plus levaquin 750mg (moxi has hepatic metabol)
 - If stable can wait for HAIN results to guide treatment
 - At least 9 months without use of PZA, cavitory disease
- Culture placenta at delivery, PCR for rapid testing, pathologic exam for evidence of TB
 - No formalin or other fixative-inhibits mycobacterial culture

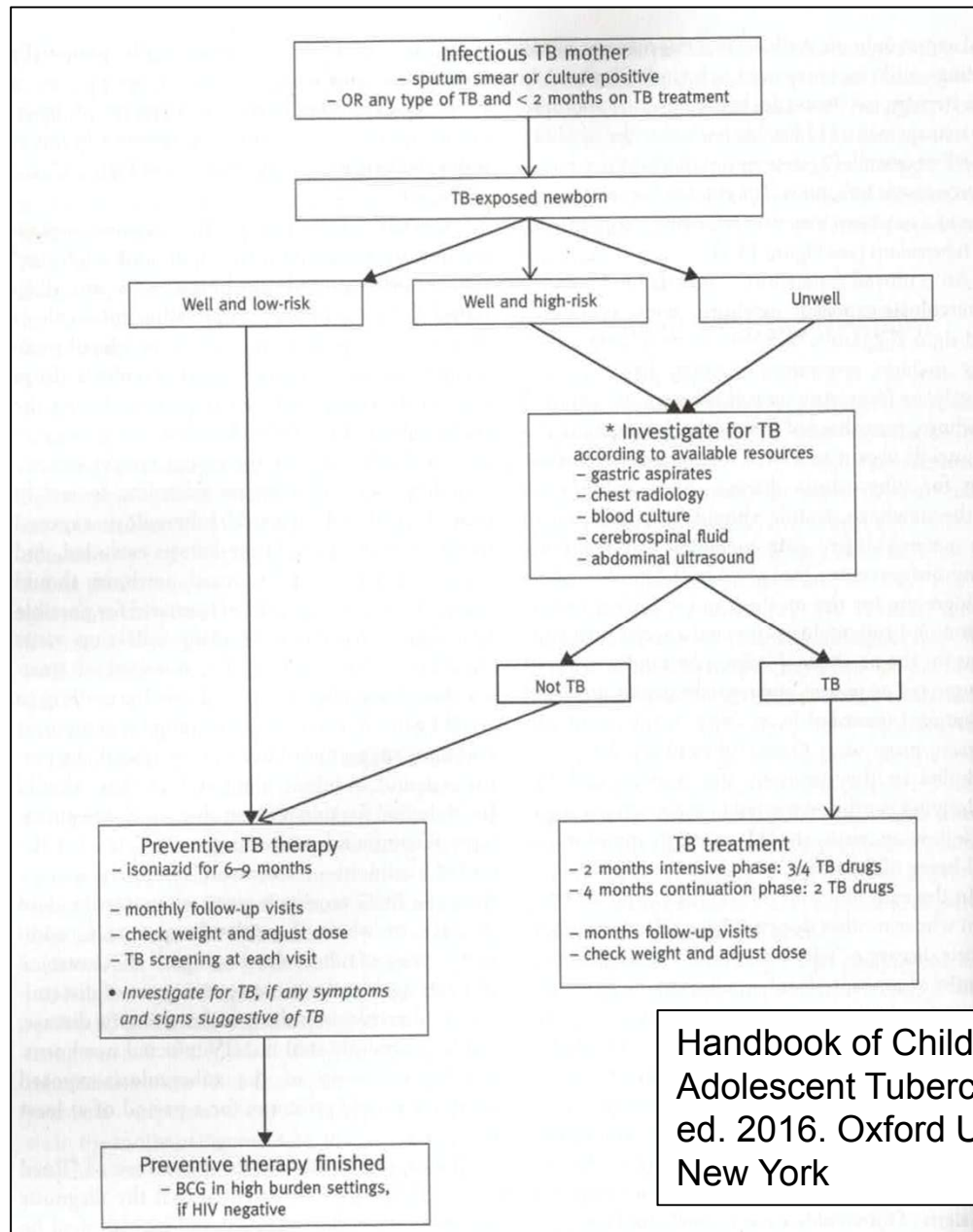
How should you manage the newborn?

1. Obtain TST, IGRA on infant, if negative and clinical exam appears normal start INH
2. Gastric aspirate for AFB C&S (x3), if negative and clinical exam is normal start INH
3. TST, IGRA, CXR, gastric aspirate for AFB C&S (x3) and clinical exam is normal, start INH
4. CXR, gastric aspirate for AFB C&S (x3) and lumbar puncture, if normal start INH

Congenital TB

- Women who have only pulmonary TB are not likely to infect the fetus, but can infect the infant after delivery
- Rare, but utero infections can occur with maternal bacillemia, reported in women from endemic countries who had IVF for infertility was likely sub-clinical GU TB
- If congenital TB suspected, perform TST, IGRA, CXR, LP, and appropriate cultures (e.g. gastric aspirate), radiology
- TST usually negative, so if TB suspected, treat with IRZ plus aminoglycoside
- Examine placenta for granulomata, AFB and culture
- Steroids if CNS TB suspected

Figure 13.4. Approach to TB-exposed Newborn from a Potentially Infectious Mother



Handbook of Children and Adolescent Tuberculosis. J. Starke, ed. 2016. Oxford University Press, New York

Congenital TB

- INH/B6 for baby if congenital TB is ruled out
 - INH 10mg/kg (range 7-15mg/kg) until infant is 3-4 months of age and TST is performed
 - If TST positive, re-assess for TB disease
 - If TB ruled out and TST (+), complete 9 mo. INH, evaluate monthly for signs of illness or poor growth
 - If TST (-), mom has good response and compliance to treatment, stop INH
 - INH should be supplemented with B6 (pyridoxine) 6.25 mg/day, amount should be in a liquid infant multi-vitamin

Pregnant Female with Cavitory TB (4)

- Baby appeared healthy & normal size by US at 8 mos
- Hospital provider felt potential risk of quinolone in pregnant women higher than risk of INH resistance
- Miscommunication among hospital providers, PZA never dc'd before delivery, meds only started 2/12?
- Delivered 2/17/16 in OR w/ AI Controls
 - Baby apgar scores 9/9, healthy appearing, no distress
 - NI CXR, exam, AFB smear (-) on gastric aspirate, nl LP
 - Baby was feeding well after birth
 - Placenta neg for M. TB by PCR, C&S pending, grossly nl

Should you separate mother and baby after delivery?

1. Yes
2. No

Separation of Mother and Infant

- 2015 Red Book® Committee on Infectious Diseases; American Academy of Pediatrics; David W. Kimberlin et al:
 - Mother (or household contact) has clinical signs and symptoms or abnormal findings on CXR consistent with TB disease: baby should be evaluated for congenital TB, mother should be tested for HIV, separate until mother has been evaluated, and if TB is suspected, until mother and infant are receiving appropriate antituberculosis therapy, the mother wears a mask, and the mother understands and is willing to adhere to infection control measures.
 - Once the infant is receiving INH, separation is not necessary unless the mom has suspected MDR TB or has poor adherence to treatment and DOT is not possible.

Pregnant Female with Cavitory TB (5)

- Mom still smear (+) at delivery, clinically improving
- Confusion if she had actually received 2 weeks of therapy with RI(P)E
- Mom and baby separated at birth, minimal exposure
- Mom has had prolonged positive smears, allowed to hold baby with mask for short periods
- No breastfeeding, but pumps and gives bottled breastmilk
- Baby continues to develop normally, treated with INH and B6 (6.25mg/d) after TB ruled out

Breastfed babies of mom's on INH should also have B6

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“I’d like you to eat more fruit and vegetables, but they’re not covered by your health insurance plan.”

Honduran Male with Chronic Diarrhea

- 27 y.o. Honduran Male
- Came to the U.S. July 2004
- 06/07/2012 he presented to a S. Florida Hospital
- Complained of chronic diffuse abdominal pain and intermittent episodes of diarrhea
- 3 year history of symptoms
- Reported 40 pound weight loss
- Unable to work in previous months due to illness



Honduran Male with Chronic Diarrhea (2)

- Denied traveling outside of U.S. for the past 9 y
- 6 years prior, crack and heavy alcohol use x 1y
 - Since that time, he drank one 12 pack on the weekends, smoked marijuana and cigarettes
 - 9 mo. ago, he stopped drinking alcohol, smoking marijuana and cigarettes
- Denied IVDA, incarceration, homeless shelters
- Worked in landscaping
- Living with his cousin's family but denied anyone in the family having TB

Honduran Male with Chronic Diarrhea (3)

- Abdominal CT: colitis ascending, transverse colon
- Colonoscopy with biopsy demonstrated Crohn's ds
- Patient discharged home, followed as outpatient
- Treated initially with steroids and methotrexate without resolution of symptoms
- Eventually started on Humira 40mg SQ in April 2013, receiving 3 doses each 2 weeks apart
- Reported 1 wk improvement after 1st dose Humira
- Diarrhea worsened after initial improvement



Significant mural thickening of the proximal transverse colon with pericolic fat stranding (white arrow).

From: Kiley W.J. Loh. J Travel Med. 2011 May-Jun;18(3):221-3.



CT scan of the abdomen demonstrates thickening of the wall of the small intestine (arrows) of up to 8mm

From: Koschny R et al. Z Gastroenterol. 2013 Oct;51(10):1177-83.

Honduran Male with Chronic Diarrhea (4)

- Patient presented to Hospital again complaining of several episodes of watery stools daily, low grade fever, anorexia, generalized weakness, and continued weight loss.
- What do you think is going on?
- What should you do next?

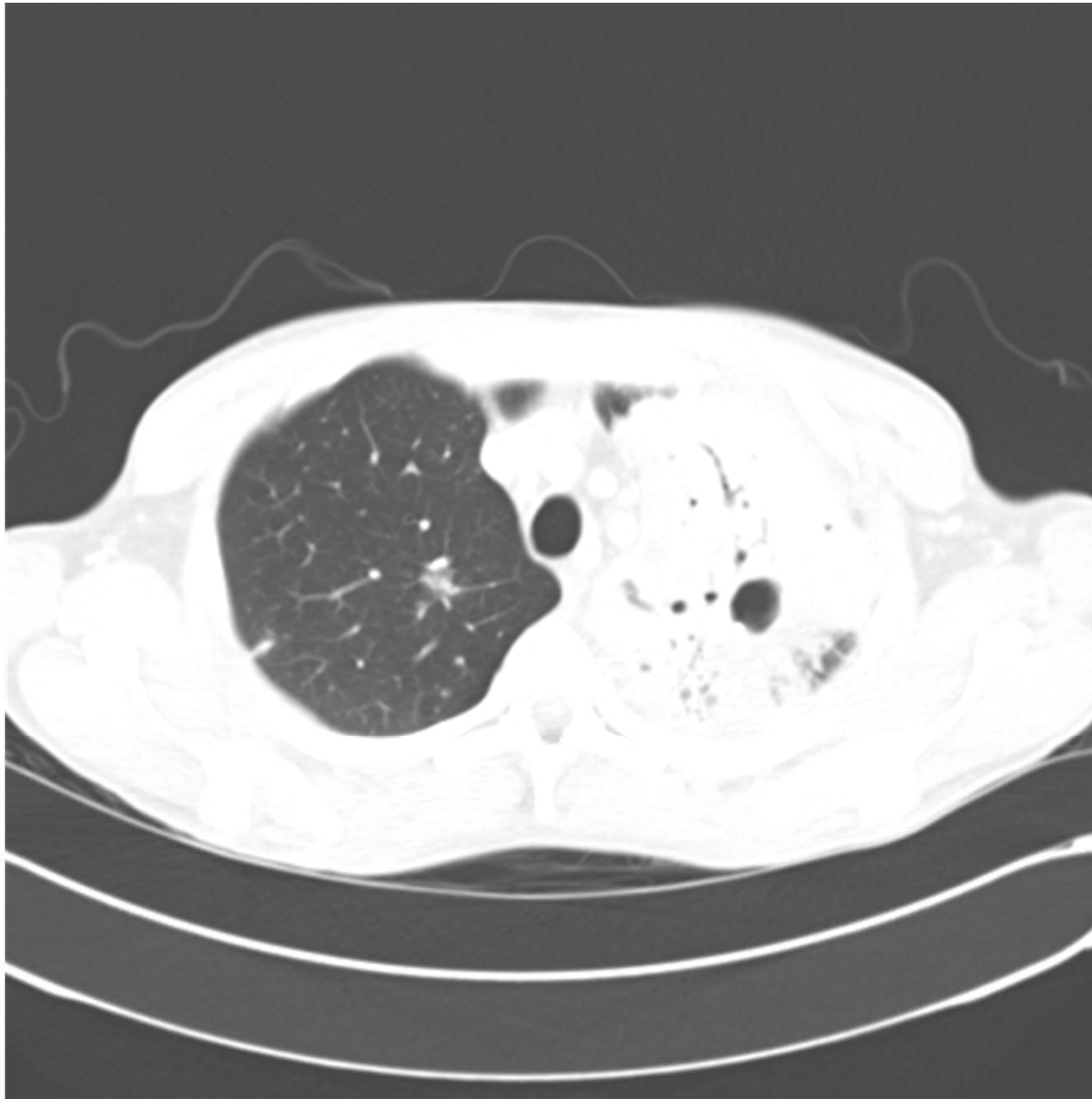
Honduran Male with Chronic Diarrhea (5)

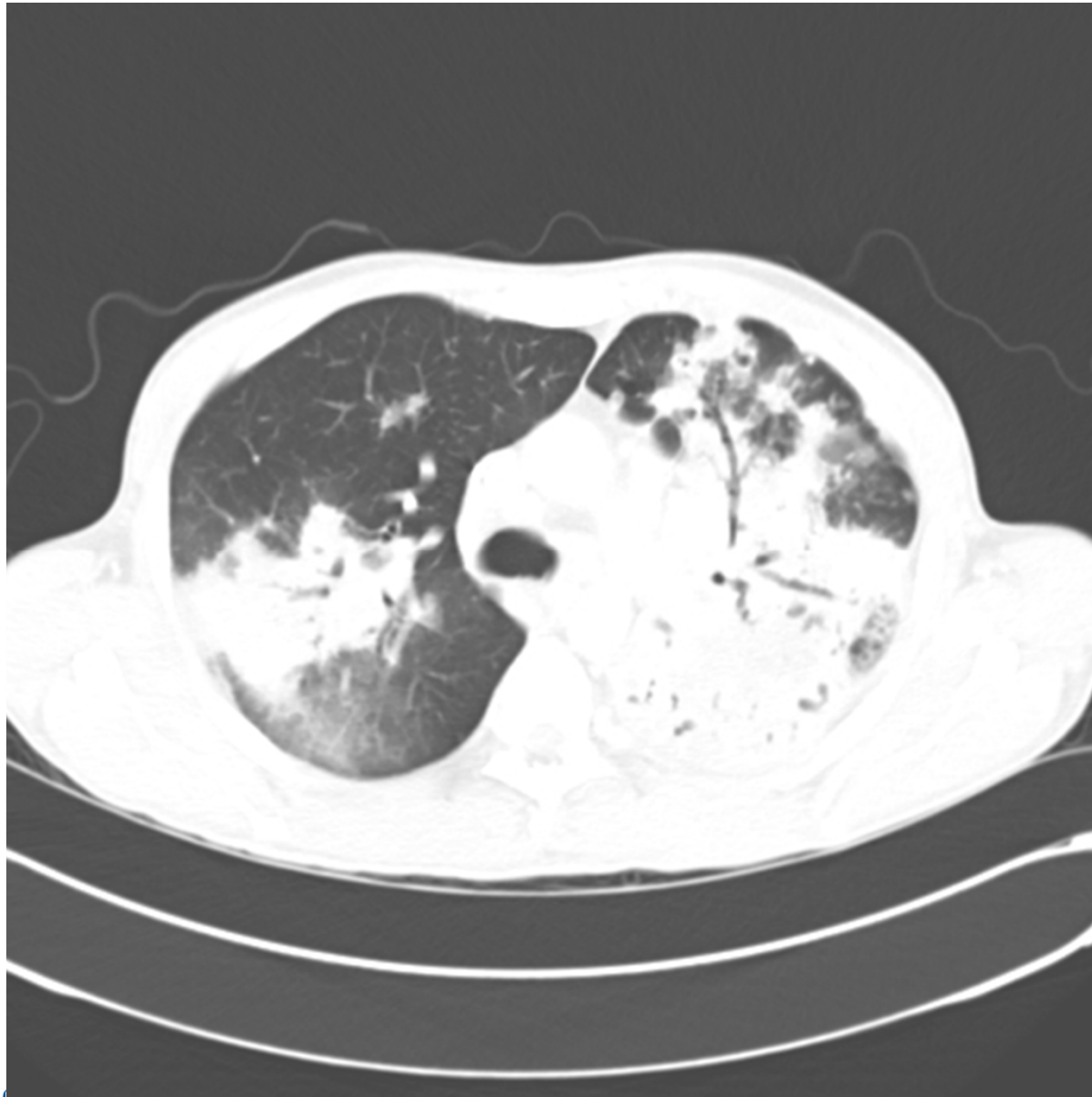
- Quantiferon was negative on 05/24/2013
- Treated with Flagyl and Levofloxacin for presumed GI bacterial infection
- CXR was obtained

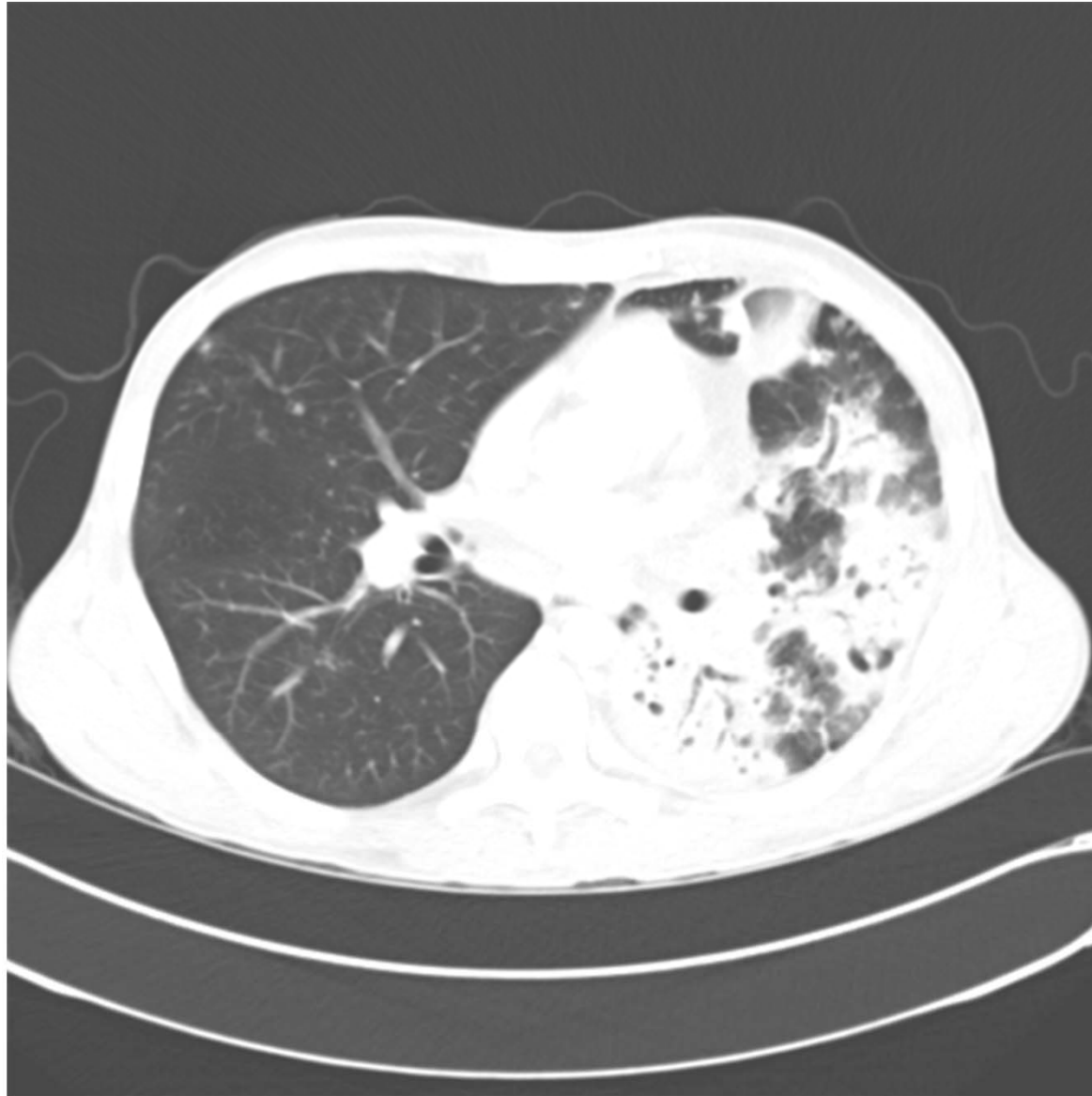


Honduran Male with Chronic Diarrhea (6)

- CXR 05/28/2013: severe airspace disease bilaterally suggestive of multifocal pneumonia
- Chest CT 05/29/2013: bilateral airspace process with consolidation L>R, consistent with multifocal pneumonia; cavitary change on the left along the upper lung measuring 2.6x2.2cm; bilateral small pleural effusions







Honduran Male with Chronic Diarrhea (7)

- 06/01: Sputum AFB 4+
- 06/05: PCR positive for M.TB complex
- 06/07: HAINS test negative for mutations (no resistance to INH and RIF)
- Conventional susceptibilities lost due to culture contamination
- How should you treat this patient's TB? What about his crohn's disease?

Honduran Male with Chronic Diarrhea (8)

- He was started on IV INH, RIF, and Levofloxacin; as well as oral EMB and PZA
- Intestinal biopsies obtained previously were re-evaluated and were consistent with granulomatous disease
- 07/11/2013 Patient transferred to TB Unit for further management of disseminated TB
- Patient had ongoing intermittent spiking fevers
- Symptoms continued with loss of appetite, ongoing productive cough, and diarrhea.

What could be causing persistent fevers?

1. TB slow to respond causing persistent fevers
2. Malabsorption of TB medications
3. Development of new drug resistance
4. New hospital acquired infection
5. Possible IRIS after stopping Humira

Honduran Male with Chronic Diarrhea (8)

- Pan-cultures were negative except for positive AFB sputum cultures for M.Tb.
- On 07/26/2013, patient became tachycardia, hypotensive.
- Patient was transferred to MICU and started on aggressive IVF hydration and vasopressors.

- What should you do at this time?

Honduran Male with Chronic Diarrhea (9)

- 07/26/2013 ID was consulted and started on Vancomycin empirically and re-cultured.
- PICC Line was removed at that time.
- Patient also found to adrenally insufficient → military TB vs steroid induced deficiency?
- Patient started on IV Solu-medrol

Immune reconstitution inflammatory syndrome

- IRIS is either 1) a paradoxical clinical deterioration or 2) an unmasking reaction to an occult infection that occurs due to an inflammatory process resulting from immune recovery that cannot be explained by drug toxicity or the opportunistic infection itself.
 - Informally defined as worsening of clinical symptoms or radiographic evidence after the initiation of antimicrobial treatment in a patient who initially improved
 - IRIS first described in patients infected with HIV who clinically deteriorated following initiation of HAART despite successful virological control and immunological recovery

Immune reconstitution inflammatory syndrome

- The pathophysiology behind IRIS incompletely understood.
- IRIS in HIV patients typically presents within weeks to months following the initiation of HAART
- Timing of development of IRIS following withdrawal of immunosuppressive therapy depends on the specific drug and the dosing interval and thus the half life of the drug.
 - May also be related to the rapidity of drug removal

Immune reconstitution inflammatory syndrome

- Diagnosis of exclusion
- No diagnostic test available
- Consider other reasons patient may not be improving, or may worsen after initial improvement:
 - Other opportunistic infections
 - Nonadherence
 - Malabsorption of medications
 - Drug Resistant TB
 - Inability of drugs to penetrate affected area

Immune reconstitution inflammatory syndrome

- Mortality associated with IRIS rare except CNS involvement
 - Neurologic involvement has been reported in ~12% of cases
- Most cases treated with supportive care (antipyretics, NSAIDs, IV fluids)
- When life threatening, corticosteroids are used
- If patient is already on ART, no need to stop it unless there is concern for toxicity
- Although current guidelines recommend holding biologic agents in setting of OIs, temporary continuation or dose reduction while TB treatment is initiated may prevent or dampen development of IRIS after discontinuation of TNF- α inhibitors

Adrenal Gland Manifestations of TB

- TB can cause adrenal insufficiency (AI) by direct glandular involvement, extra-adrenal infection or as a by-product of anti-tuberculosis therapy.
- Demonstrate depressed morning plasma cortisol levels with a diminished response to synthetic ACTH
- Lab abnormalities: Anemia, hyponatremia, hyperkalemia
- Malaise, anorexia, orthostatic hypotn, hyperpigmentation
- Increased suspicion with concurrent autoimmune ds, metastatic malignancy, sarcoidosis, amyloidosis, or treatment with potential adrenal suppressants
 - HIV increases risk of AI, but not shown in TB patients

Honduran Male with Chronic Diarrhea (10)

- 07/30/2013 Patient stabilized and was weaned off pressors; transferred out of ICU.
- Patient continued to clinically improve → afebrile, appetite improved, patient started gaining weight.
- 08/09/2013, patient was placed on PO TB meds.
- Patient changed back to oral prednisone
- Patient continued to be AFB smear positive through 09/29/2013 (RIPE started early June)
- What should you do now?

Honduran Male with Chronic Diarrhea: Therapeutic Drug Monitoring

| MEDICATION 3X WEEKLY DOSING | 2 HOUR | 6 HOUR | EXPECTED | DOSING ADJUSTMENT |
|-----------------------------------|--------|--------|----------|----------------------|
| ISONIAZID 1200MG | 14.12 | 1.83 | 9-15 | NONE |
| RIFAMPIN 900MG | 3.59 | 11.72 | 8-24 | NONE |
| ETHAMBUTOL 2GM | 3.17 | 0.75 | 4-12 | INCREASE TO 2.4GM |
| PYRAZINAMIDE 3.5GM | 83.86 | 40.48 | 60-80 | NONE |

Honduran Male with Chronic Diarrhea (11)

- 08/11/2013 M. Tb cultures finally reported as negative (conversion date-Tx started early June)
- All precautions discontinued once 3 consecutive negative M.TB cultures were obtained
- Patient gained 20.91 kg during admission.
- Tapered off prednisone w/o signs of adrenal insufficiency
- Discharged to home to be followed by CHD.
- Completed TB therapy (9 mos total, 6 mos after culture conversion).

Intestinal TB vs. Crohn's Disease

- Increasing overlap in epidemiology of these 2 diseases
- Both involve chronic process of bowel wall inflammation, intermittent luminal obstruction, fibrostenotic disease.
- Both most common in ileum
- Radiologic, clinical, pathologic pres may be identical
- On colonoscopy and ileoscopy, both can present with ulcerations, nodularity, mucosal edema, ileocecal valve and cecal deformity, fibrous bands, strictures and pseudopolyps in ileocecal area.
- Both are recognized as granulomatous colitis

Schlossberg D., ed. Tuberculosis and Non-tuberculous Mycobacterial Infections, 6th ed.. 2011. ASM Press, Washington D.C.

Signs and Symptoms of Crohn's

| Symptoms related to inflammation of the GI tract: | General symptoms with inflammatory bowel disease |
|---|--|
| Persistent Diarrhea | Fever |
| Rectal bleeding | Loss of appetite |
| Urgent need to move bowels | Weight Loss |
| Abdominal cramps and pain | Fatigue |
| Sensation of incomplete evacuation | Night sweats |
| Constipation (can lead to bowel obstruction) | Loss of normal menstrual cycle |

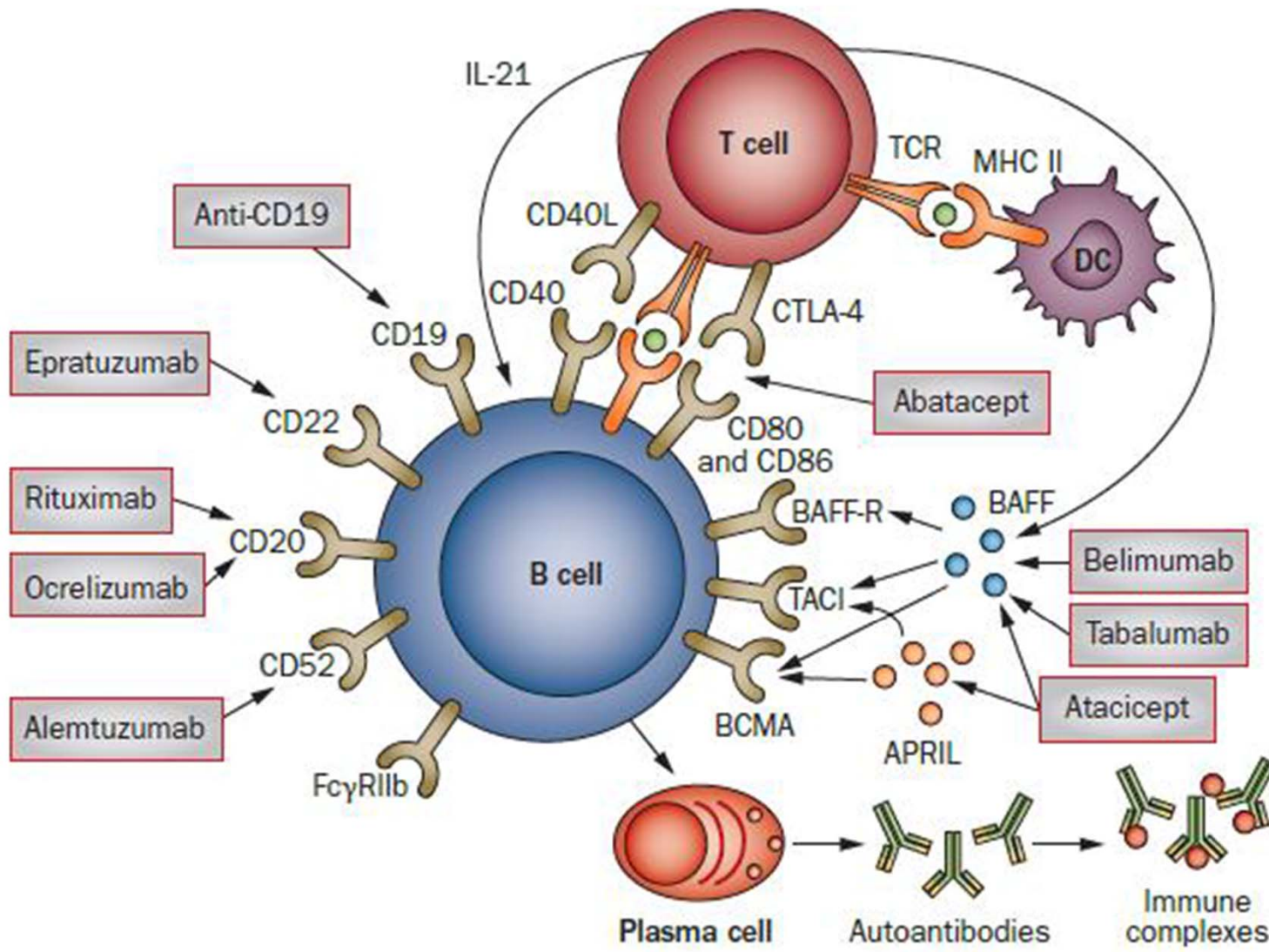
Intestinal TB vs. Crohn's Disease

- Misdiagnosis rates between CD and ITB range 50-70%
 - With expanding use of immunosuppressive agents and TNF-alpha antagonists in patients with inflammatory bowel disease, precise diagnosis is critical.
 - Treatment of CD can be toxic or exacerbate ITB
 - Misdiagnosis can delay appropriate treatment of either CD or ITB, causing increased morbidity and mortality
 - Final clinical diagnosis based on clinical hx, endoscopic studies, C&S, PCR for *MTBC*, biopsy pathology, radiology and response to therapy.
- Subset of patients req. surgery with pathological study

TB and Biologic Agents

Biologic therapies for immune mediated inflammatory disorders (IMID)

- TNF- α inhibition: strong evidence for increased TB risk
 - Infliximab, adalimumab, golimumab, certolizumab (monoclonal antibodies)
 - Etanercept (soluble p75 receptor) (floats rather than targeted ab that hones in on TNF, associated with less risk of TB than inflix and adalim.)
- Other (*Risk compared to TNF- α inhib*)
 - CD4 co-stimulation modulator: abatacept (Less risk?)
 - B-cell (CD20+) antibody: rituximab (Less risk?)
 - Anti-IL-6 receptor antibody: tocilizumab (same risk in human data, less in animal data?)
 - Anti-IL12/IL23 antibody: ustekinumab (Less risk?)
 - JAK 1/3 inhibitor: tofacitinib (not biologic, but same risk)



TB and Biologic Agents

- **Screen prior to immunosuppression!!**
 - Prednisone, methotrexate, TNF- α inhibitors, other biologic drug
- If patient likely to be immunosuppressed for prolonged period, screen while they're relatively immunocompetent to define their TB status.
 - E.g., newly-diagnosed RA, psoriasis, Chron's, etc.
- Harder to screen these people once immunosuppressed
 - Tests don't work as well
- Currently no CDC recommendations to screen them again unless they have a risk factor potentially for being exposed
 - Contact, homeless, incarceration, high-risk travel, etc.
 - FDA labels for these drugs may say that patients should be screened at baseline and then again periodically, but CDC was not consulted

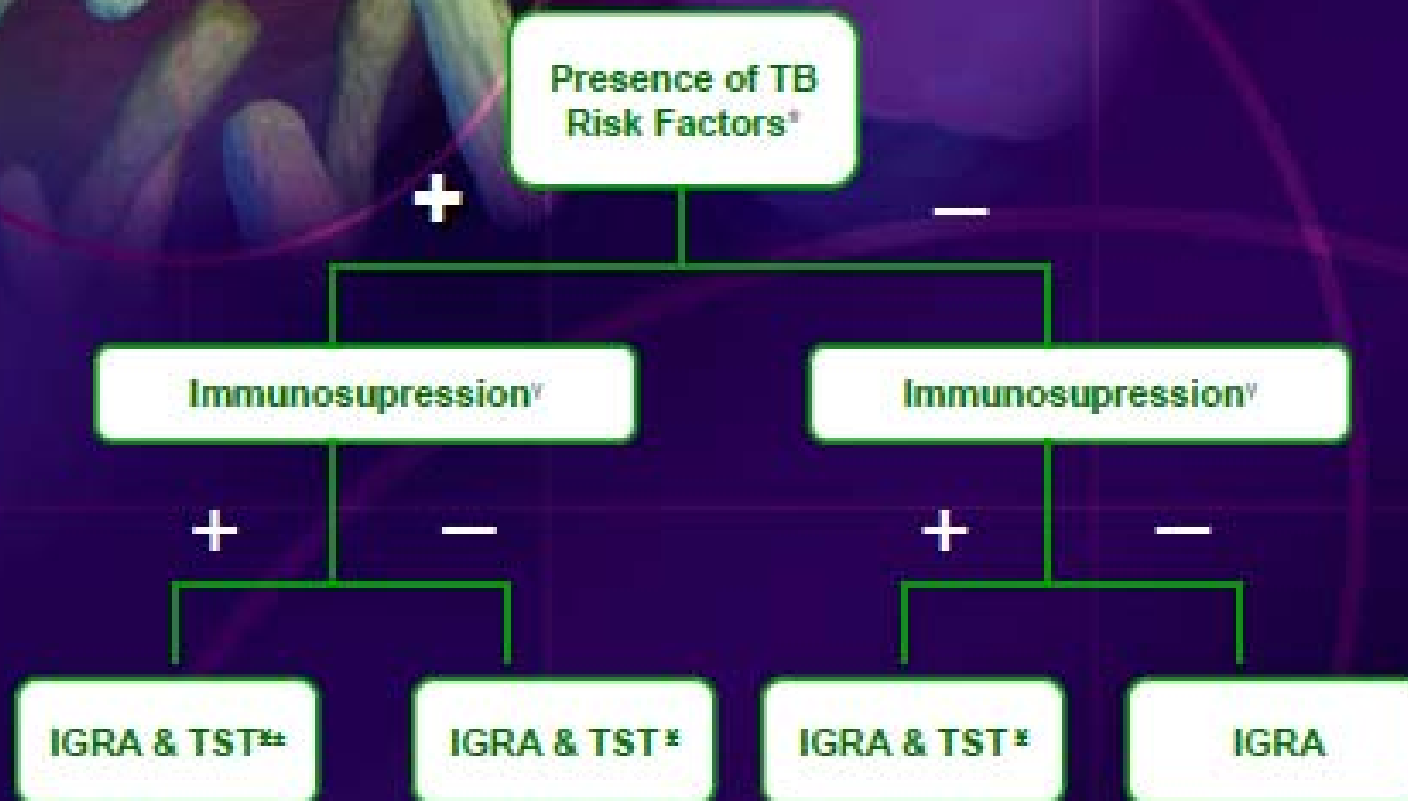


HIV+ Miner from S. Africa

- 40 y old HIV-positive male from South Africa; had worked as a miner.
 - Just immigrated 6 months ago, no prior TB screening
 - CD4 count of 12 cells/mm³, HIV viral load of >750,000 copies
-
- What TB screening test do you want to do?
 - What do you want to do if screening test is negative?
 - Does it matter if he denies contact to anyone with TB?

Managing Immunosuppressed Patients with High Risk of TB Exposure

- Incidence of false negative results increases for both TST and IGRA with advancing immunodeficiency
 - Dual testing can increase sensitivity of testing for TB infection, but both may still be false negative
 - Many experts would treat for infection if advanced immunosuppression and high risk of infection
 - Must be CERTAIN TB disease is not present before giving monotherapy for infection
 - If mod-high suspicion for active TB despite negative LTBI test, should treat as TB while awaiting further diagnostic test results



^aTB risk factors include: a history of contact to a case of active TB; birth or extended living in regions where TB is prevalent (crude incidence $\geq 20/100,000$ per year); history of working or living in jails, prisons, healthcare facilities providing care to TB patients, or homeless shelters; or history of intravenous drug use.

^bImmunosuppression includes poorly controlled rheumatoid arthritis or other inflammatory immune mediated disease, current use of biologic or non-biologic disease modifying therapies, or current use of corticosteroids, and other conditions.

^cIn regions of BCG use (or individuals with BCG history), consider a dual strategy of using both commercially available IGRAs (Quantiferon-In Tube[®] and T.Spot.TB[®]) in lieu of the TST

^dFor patients with risk factors and immunosuppressed in whom false negative results are more likely, consider repeat screening with one or both tools

TB: tuberculosis; IGRA: interferon-gamma release assay; TST: tuberculin skin test

Screening in the Biologics Setting

Words to Live By

- A priori probability reigns supreme
 - If they should be positive, then they probably are
 - If they shouldn't be positive, they probably aren't
- If risk factors, then use two screening tests
 - Maximize sensitivity
- If you don't believe your test result, **REPEAT** it!

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“Your x-ray showed a broken rib, but we fixed it with Photoshop.”

QUESTIONS???

