Complicated TB Cases

Gregory M. Gauthier, MD, MS
Associate Professor (CHS)
Department of Medicine
Division of Infectious Diseases
University of Wisconsin - Madison
Objectives

• Importance of silicosis in patients with LTBI
• Clinical features & approach to prosthetic joint infection with tuberculosis
• Management of TB in patients with cirrhosis
• Clinical features & course of TB lymphadenitis
• Approach and management to drug toxicity
Case #1

71 y.o. male with a left prosthetic knee and pulmonary silicosis related to sand-blasting developed a boil on the posterior left knee in early January 2014. The boil began draining and was associated with progressive pain, swelling, and erythema of the left knee. His infection failed to respond to anti-staphylococcal therapy. CT of the left knee demonstrated a large popliteal abscess, moderate effusion, and synovial inflammation.
Case #1
Case #1

Patient underwent operative debridement

Stains:
1) Gram stain: GPC, GNR
2) Fungal smear: negative
3) AFB of tibial pseudomembrane: 1-9 AFB / 10 OI fields

Cultures:
1) Anaerobes
2) Actinomyces spp.
3) Prevotella/porphyromonas
4) Peptostreptococcus
5) Mycobacterium tuberculosis
Case #1

Sputum
AFB smear: 1 – 9 AFB / 100 OL fields
PCR: MTB complex
Culture: M. tuberculosis
Silicosis

• United States
  – 2 million U.S. workers at risk for silicosis
    • Mining, Quarry, ceramics, masonry
    • Sandblasting

• Silicosis outside the United States.
  – China
  – Brazil
  – South Africa

Silica exposure & silicosis increases risk for developing active TB

<table>
<thead>
<tr>
<th>Country</th>
<th>Occupation</th>
<th>Silicotuberculosis</th>
<th>General Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany¹</td>
<td>Coal mining</td>
<td>33.9 / 100,000 (4x)</td>
<td>8.2 / 100,000</td>
</tr>
<tr>
<td>South Africa²</td>
<td>Gold Mining</td>
<td>3,085 / 100,000 (9x)</td>
<td>344 / 100,000</td>
</tr>
<tr>
<td>South Africa³</td>
<td>Gold Mining</td>
<td>2,707 / 100,000 (9x)</td>
<td>300 / 100,000</td>
</tr>
<tr>
<td>China⁴</td>
<td>Variable</td>
<td>3019 / 100,000 (8.6x)</td>
<td>349 / 100,000</td>
</tr>
<tr>
<td>Sweden⁵</td>
<td>Mining</td>
<td>29 silicoTB / 712 silicosis (30x)</td>
<td>1 MTB / 810</td>
</tr>
</tbody>
</table>

- Amount of silica exposure influences risk for active pulmonary tuberculosis.⁴,⁶
- Patients with silica exposure but no radiographic findings of silicosis remain risk for active MTB.⁴,⁶
- Patients remain at risk for active pulmonary MTB even after silica exposure ends.⁴,⁶

References
3. Cowie RL AJRCCM 1994
4. Chang IJTLD 2001
Case #1

Approximately 22-23 years ago, the patient was exposed to *M. tuberculosis* through a co-worker with active pulmonary tuberculosis. The patient tested positive by PPD and received prophylaxis for 12 months with a single agent. He cannot remember the name of the medication.
Silicosis and LTBI

How effective is therapy for LTBI in silicosis?

• Hong Kong (1981 – 1987)
  
  R3 = HR6 = R3
  50% reduction in active TB
  No increase in drug resistance

Case #1

The abscess tracked down the left knee prosthesis. What is the best course of action (select all that apply)?

A) Salvage of the prosthesis
B) Removal of the prosthesis
C) Anti-tuberculosis therapy for at least 6 months
D) Lifelong suppression of infection
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B) Removal of the prosthesis
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MTB & Prosthetic Joint Infection (PJI)

• Incidence: rare – limited to case reports
  Risk factors: Older age, history of prior TB, Immunosuppression.

• Pathogenesis
  1) Local reactivation of MTB following joint replacement
  2) Hematogenous spread of MTB from a distant focus
     • 33% (5/15) in 1 pooled analysis for TKA

• Clinical presentation: mimics bacterial infection
  Pain, swelling, abscess, sinus tract formation
  ± bone erosions, ± loosening of the prosthesis
  CXR can be normal, show active TB, or healed TB.

• Microbiology
  Not uncommon for co-pathogens to be present

MTB & Prosthetic Joint Infection (PJI)

• Diagnosis
  – AFB stain & Mycobacteria culture
    • Synovial fluid
    • Periprosthetic tissue
    • Bone
  – Evaluation for extra-articular infection
    • Comprehensive physical examination
    • CXR (PA & Lateral) along with sputum culture

MTB & Prosthetic Joint Infection (PJI)

• Management
  – PJI not addressed in MTB guidelines due to its rarity
  – Management is based on:
    • Early onset (≤ 6-8 wks) versus late onset (> 6-8 wks)
    • Presence or absence of prosthesis loosening
    • Presence or absence of underlying osteomyelitis
  – Washout with retention of the joint
    • Early onset, no prosthesis loosening, no bone destruction
  – 2-stage prosthetic joint replacement
    • Late onset, loosening of the prosthesis, bone destruction
    • Timing of the 2nd stage is not well defined
  – Anti-tuberculosis therapy
    • Duration not well defined, 6 - 18 months

Case #1

The patient’s left prosthetic knee was not salvageable. Unfortunately, placement of another prosthesis was not feasible. Intra-operatively, there was purulence in the bone marrow. He underwent above-the-knee amputation.
Case #1

What is the best option for treating disseminated tuberculosis in this patient with underlying silicosis?

A) INH, Rif PZA ETH x 2 mo → INH, RIF x 4 mo
B) INH, Rif PZA ETH x 2 mo → INH, RIF x 7 mo
C) An injectable agent needs to be added.
D) Lifelong suppressive therapy is needed.
Case #1

What is the best option for treating disseminated tuberculosis in this patient with underlying silicosis?

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D) Lifelong suppressive therapy is needed.
Case #1

The patient was started on 4-drug regimen consisting of daily INH 300 mg, rifampin 600 mg, ethambutol 1600 mg, and pyrazinamide 2,000 mg, and vitamin B6 50 mg. Piperacillin-tazobactam was started to treat anaerobes, actinomyces, and peptostreptococcus.
# Management

## Bone & Joint infection (Guidelines: 6 – 9 mo)

<table>
<thead>
<tr>
<th>Study (Spinal TB)</th>
<th>Regimen</th>
<th>N</th>
<th>Favorable Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRC 1999</td>
<td>Rad 6 HRS</td>
<td>24</td>
<td>96% (23/24)</td>
</tr>
<tr>
<td></td>
<td>Rad 9 HRS</td>
<td>26</td>
<td>96% (25/26)</td>
</tr>
<tr>
<td></td>
<td>Rad 6 HR</td>
<td>82</td>
<td>88% (72/82)</td>
</tr>
<tr>
<td></td>
<td>Amb 6 HR</td>
<td>82</td>
<td>91% (75/82)</td>
</tr>
<tr>
<td></td>
<td>Amb 9 HR</td>
<td>86</td>
<td>97% (84/86)</td>
</tr>
<tr>
<td>Wang et al., 2013</td>
<td>Rad 2 SHRZ → 2- 4 HRZ</td>
<td>96</td>
<td>94% (90/96)</td>
</tr>
<tr>
<td></td>
<td>Rad 2 SHRZ → 7 HRZ</td>
<td>89</td>
<td>96% (85/89)</td>
</tr>
</tbody>
</table>

## Silicosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>N</th>
<th>Relapse at 3 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRC 1991</td>
<td>HRZS 3x/wk x 6 mo</td>
<td>41</td>
<td>22% (9/41)</td>
</tr>
<tr>
<td></td>
<td>HRZS 3x/wk x 8 mo</td>
<td>30</td>
<td>2% (2/30)</td>
</tr>
</tbody>
</table>
Case #1

- 12 days into 4-drug therapy:
  - Tbili 0.9 → 2.0 (normal 0 – 1.4 mg/dL)
  - AST 34 → 269 (normal 0-50 U/L)
  - ALT 24 → 142 (normal 12 – 78 U/L)
  - AP 67 → 106 (normal 45-117 U/L)
  - Ammonia 37 (normal 0-40 umol/L)
Case #1

The patient's anti-tuberculosis regimen was stopped due to the rise in his AST and ALT. Once his liver function tests improve, how should 1st-line therapy be restarted?

A) Restart the same medications at the same time
B) Staggered initiation of 1st line drugs
C) Staggered initiation with titration of INH and Rifampin
Drug-Induced Hepatitis (DIH)

• Most common complication of MTB therapy
• Definition
  AST/ALT > 3x ULN with symptoms OR AST/ALT > 5x ULN asymptomatic
• Most commonly implicated drugs: INH, RIF, PZA
• ATS 2006 & CDC 2003 recommendations
  1) Stop all potential hepatotoxic drugs (INH, RIF, PZA)
  2) Assess for concomitant alcohol use & other hepatotoxic meds
  3) Testing for hepatitis viruses such as A, B, C (Also consider HEV, HIV)
  4) Consider using 3 non-hepatotoxic drugs until 1st line can be restarted
  5) When AST/ALT < 2x ULN, then start in the following order:
     RIF ± ETH -> INH -> ± PZA (if hepatitis was severe, may not want to add back PZA).
## Reintroduction of drugs

<table>
<thead>
<tr>
<th>Sharma et al. 2010</th>
<th>Arm I</th>
<th>Arm 2</th>
<th>Arm 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>58</td>
<td>59</td>
<td>58</td>
</tr>
<tr>
<td>Bili / AST / ALT / AP</td>
<td>2.31 / 318 / 344 / 294</td>
<td>2.9 / 400 / 361 / 274</td>
<td>2.1 / 275 / 288 / 255</td>
</tr>
<tr>
<td>Stop → Reintroduction</td>
<td>14 days (5-28)</td>
<td>21 days (14-28)</td>
<td>21 days (14-35)</td>
</tr>
<tr>
<td>Reintroduction</td>
<td>RHP simultaneously</td>
<td>R₁H₈Z₁₅ (ATS)</td>
<td>H₁₄R₈Z₁₅ (BTS)</td>
</tr>
<tr>
<td>Recurrence of DIH</td>
<td>13.8% (8/58)</td>
<td>10.2% (6/59)</td>
<td>8.6% (5/58)</td>
</tr>
</tbody>
</table>

Exclusion: ≤ 16 yo, ≥ 65 yo, alcoholism, HIV, any chronic liver dz including HBV and HCV, acute viral hepatitis, pregnancy

<table>
<thead>
<tr>
<th>Tahaoglu K et al. 2001</th>
<th>Group I</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>Bili / AST / ALT / AP</td>
<td>1.84 / 330 / 276</td>
<td>1.31 / 242 / 246</td>
</tr>
<tr>
<td>Stop → Reintroduction</td>
<td>18.71 (4-58 days)*</td>
<td>18.71 (4-58 days)*</td>
</tr>
<tr>
<td>Reintroduction</td>
<td>SE₁H₃₁₁R₁₂₁₈</td>
<td>Same Regimen (e.g. HRZE)</td>
</tr>
<tr>
<td>Recurrence of DIH</td>
<td>0%</td>
<td>24% (6/25)</td>
</tr>
</tbody>
</table>

*Combined data for group 1 and 2.
Case #1

The patients LFTs improved approximately 1 week of stopping therapy. Rifampin + Ethambutol + Moxifloxacin was restarted followed by reintroduction of INH after 5 days. MTB isolate with fully susceptible and moxifloxacin was stopped. He received Rifampin + INH + Ethambutol for daily 2 months followed by 10 months of 3x/week Rifampin + INH to complete a total of 12 months of therapy.
Take Home Points

• **Silicosis**
  High risk for development of active MTB
  Reactivation can occur despite treatment of LTBI
  Need to consider therapy longer than 6 months

• **Prosthetic Joint Infection (PJI)**
  Rare complication of MTB
  Late onset PJI requires removal of prosthesis

• **Drug-induced Hepatotoxicity**
  Staggered re-introduction of medications
Case #2

28 y.o. male from Mexico was transferred to UWHC in late December 2014 for fevers, nightsweats, 10 lb weight loss, right supraclavicular lymphadenopathy. On examination, he had hepatosplenomegaly with minimal ascites and a tender right supraclavicular lymph node. Liver biopsy demonstrated cirrhosis and severe steatohepatitis. Hepatology was concerned about acute alcoholic hepatitis complicating his alcoholic cirrhosis. Imaging along with lymph node biopsy.
## Case #2

<table>
<thead>
<tr>
<th>Laboratory Data</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV non-reactive</td>
<td>Total bilirubin 4.6</td>
</tr>
<tr>
<td>HBV negative</td>
<td>ALT 30</td>
</tr>
<tr>
<td>HCV negative</td>
<td>AST 116</td>
</tr>
<tr>
<td>WBC 14.9</td>
<td>Alk Phos 87</td>
</tr>
<tr>
<td>Hgb 10.1</td>
<td>INR 2.0</td>
</tr>
<tr>
<td>PLT 32</td>
<td>Albumin 2.0</td>
</tr>
<tr>
<td>Creatinine 0.48</td>
<td></td>
</tr>
</tbody>
</table>
Case #2

Chest CT Imaging: “Right supraclavicular, right paratracheal, & subcarinal LAD concerning for lymphoma.” Normal lung parenchyma.

Lymph Node Bx: Extensive necrosis with occasional AFB. Culture grew *M. tuberculosis*.

Sputum for AFB & mycobacterial culture: negative
Case #2

What initial treatment regimen do you recommend for this patient with active, symptomatic MTB infection with alcoholic hepatitis and cirrhosis?

A) Delay therapy until alcoholic hepatitis resolves
B) Standard 4-drug regimen: INH, Rif, PZA, EMB
C) Modified Regimen: INH, Rif, Moxi, EMB
D) Regimen with 1 hepatotoxic drugs
E) Regimen with no hepatotoxic drugs
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C) Modified Regimen: INH, Rif, Moxi, EMB
D) Regimen with 1 hepatotoxic drugs
E) Regimen with no hepatotoxic drugs
### Tuberculosis and Cirrhosis

- Cirrhosis is a risk factor for tuberculosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>N (cirrhosis)</th>
<th>MTB with cirrhosis (vs. Gen Pop)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin YT 2014</td>
<td>Taiwan</td>
<td>41,076 (’98-’07)</td>
<td>416 / 100,000 (vs. 53 / 100,000)</td>
</tr>
<tr>
<td>Baijal 2010</td>
<td>India</td>
<td>667 (’03-’08)</td>
<td>73.8 / 1,000 (vs. 5.05 / 1,000)</td>
</tr>
<tr>
<td>Thulstrup 2000</td>
<td>Denmark</td>
<td>22,675 (’77-’93)</td>
<td>168.6 / 100,000 (vs. 8 / 100,000)</td>
</tr>
</tbody>
</table>
Tuberculosis and Cirrhosis

• Pathogenesis
  – Impaired immune defenses
    • Macrophages & neutrophils
      – impaired phagocytosis & chemotaxis
      – Reduced oxidative burst
    • Impaired T cell function
    • Reduced cytokine production (INFγ, TNFα)
    • Impaired toll-like receptor 2 (TLR-2) mediated immune response
  – Impaired reticuloendothelial system (RES) function
    • 90% of RES cells are found in the liver
    • Important in clearing bacteria
  – Malnutrition

MTB treatment in the setting of Cirrhosis

- No formalized guidelines are available (expert opinion)

General Concepts
- Risk for drug hepatotoxicity is higher in patients with cirrhosis
- Drug-induced hepatotoxicity can be life-threatening
- Must assess overall risk for hepatotoxicity
  - Assess status for HAV, HBV, HCV, HEV, HIV
  - Consultation with hepatology can be helpful
  - Risk is higher with decompensated versus compensated cirrhosis
- Avoid alcohol & other hepatotoxic drugs
- Fluctuations in LFTs due to liver disease can make monitoring challenging.
- Expert consultation is recommended

MTB treatment in the setting of Cirrhosis

• General Treatment Recommendations
  – Avoid regimens with 3 or more hepatotoxic drugs
  – 2 hepatotoxic drugs (compensated cirrhosis)
    • HRE x 2 months → HR x 7 months  9 month total
    • RPE x 2 months → RPE x 4 months  2 month total
  – 1 hepatotoxic drug (decompensated cirrhosis)
    • RIF (or INH) + EMB + FQ ± Streptomycin/Amikacin x 12 – 18 mo
  – 0 hepatotoxic drugs (unstable/decompensated liver disease)
    • EMB + FQ + Streptomycin/Amikacin (S/A) + 2nd line oral x 18-24 mo
    • EMB + FQ + Cycloserine + Capreomycin or S/A x 18-24 months
    • Note: some providers avoid aminoglycosides due to concerns for renal insufficiency or bleeding at the site of injection (especially with low platelets or significant coagulopathy).

MTB treatment in the setting of Cirrhosis


<table>
<thead>
<tr>
<th>CTP Score (Child-Turcotte-Pugh)</th>
<th>Liver Disease</th>
<th>Number of Hepatotoxic drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 7</td>
<td>Stable</td>
<td>2</td>
</tr>
<tr>
<td>8-10</td>
<td>Advanced</td>
<td>1</td>
</tr>
<tr>
<td>≥ 11</td>
<td>Very Advanced</td>
<td>0</td>
</tr>
</tbody>
</table>

Hepatotoxicity Sx’s: Nausea, vomiting, anorexia, jaundice
Frequent monitoring of LFTs, CBC, INR are needed.
- weekly x 1 mo, every 2 weeks x 2 mo, once a month thereafter

Khumar et al. World J Gastroenterol 2013;20:5760-72

<table>
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<tr>
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<th>Liver Disease</th>
<th>Number of Hepatotoxic drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Stable</td>
<td>2 – INH/RIF</td>
</tr>
<tr>
<td>B</td>
<td>Advanced</td>
<td>1</td>
</tr>
<tr>
<td>C</td>
<td>Very Advanced</td>
<td>0</td>
</tr>
</tbody>
</table>
### MTB treatment in the setting of Cirrhosis

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Drug-Induced Liver injury (DILI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Park et al. 2010 (South Korea)</td>
<td>46 chronic hepatitis, 58 cirrhosis*</td>
<td>24% (11 / 46 – 8 of 11 on HRPE) 12.1% (7/58 – 4 of 7 on HRPE)</td>
</tr>
<tr>
<td>Sharma K et al. 2015</td>
<td>36 with cirrhosis**</td>
<td>11.1% (2/18) on 2HRE/7HR 0.00% (0 / 18) on 12HOE (O = ofloxacin)</td>
</tr>
<tr>
<td>Kaneko Y et al. 2008</td>
<td>107 chronic hepatitis</td>
<td>22.4% (13/58) on HRZ (controls 6.9%) 4.1% (2 / 49) on HR (controls 4.1%)</td>
</tr>
<tr>
<td>Ungo et al. 1998</td>
<td>40 with HCV</td>
<td>30% in patient on HRP (5x relative risk)</td>
</tr>
<tr>
<td>Hwang et al. 1997</td>
<td>31 HBsAg + (HBeAg -)</td>
<td>29% (9/31) in patients on HRP</td>
</tr>
</tbody>
</table>

*56 of 58 were CTP class A or B, whereas only 2 were CTP class C  
**all 36 patients with CTP class A or B

**No consensus on the definition of drug-induced hepatotoxicity in patients with liver dz:**

- **Schenker et al.**
  - Increase of AST or ALT 50 – 100 U/L above baseline

- **Park et al.**
  - Increase in ALP, AST, ALT 3x ULN or 1.5x baseline.

- **Sharma et al.**
  - Increase in AST or ALT 3x baseline or bilirubin by 2.5 mg/dL

- **Saigal et al.**
  - Increase of AST or ALT 5x above baseline or > 400 IU/L or increase in bilirubin by 2.5 mg/dL
Case #2

In collaboration with hepatology and following patient consent, a 4-drug regimen was started:

- INH 900 mg 3x/week
- Rifampin 600 mg 3x/week
- Moxifloxacin 400 mg daily
- Ethambutol 2000 mg 3x/week
- Vitamin B6 50 mg daily

LFT Monitoring: 2 x per week

Other recommendations: Avoid alcohol & QT prolonging medications
Case #2

Patient tolerated the 4 drug regimen well without significant rise in LFT’s or alterations in other labs. He was avoiding alcohol consumption. After 2 months of initiation therapy, moxifloxacin and ethambutol were stopped. Rifampin and INH were continued for consolidation therapy.
Case #2

12 days into consolidation therapy, he developed significant anemia requiring admission to the hospital.

WBC 4.0, Hgb 4.6 (was 8.9), PLT 51, reticulocytes 0.0.5%, Haptoglobin < 8
Tbili 3.9, Direct Bili 1.9, Indirect Bili 2.0
AST 45, ALT 26, INR 1.59, LDH 184
Fecal Occult Blood Testing: Negative x 2
Blood Smear: Absence of microangiopathic changes (no schistocytes)
Bone Marrow Biopsy: Red blood cell aplasia
   No granulomas. No BM infiltration.
Parvovirus testing: Negative
Anemia & Tuberculosis Therapy

• Isoniazid
  – Pure red cell aplasia (PRCA)
    • Erythroblastopenia in BM with reticulocytopenia
  – Sideroblastic anemia
    • Erythroblastopenia in BM with reticulocytopenia &
      Ringed sideroblasts in the bone marrow

• Rifampin
  – Acute hemolytic anemia
    • More common with intermittent administration
    • Mediated by IgM & IgG antibodies
  – Thrombocytopenia
    • More common with intermittent administration
    • Mediated by IgM antibodies
  – Pure red cell aplasia (PRCA)

Case #2

INH and Rifampin were briefly stopped and anemia improved. New regimen started after stabilization of hemoglobin: Rifampin 600 mg daily
  Moxifloxacin 400 mg daily
  Ethambutol 1200 mg daily
Unfortunately, his hemoglobin declined 6.0 with WBC 2.9, and PLT 40, reticulocytes 0.3%, haptoglobulin < 8.
Case #2

Rifampin, Ethambutol, and Moxifloxacin were stopped. Following transfusion and stability of hemoglobin, the patient was started on: PZA 1500 mg daily
Levofloxacin 750 mg daily
ETH 1200 mg daily

Extensive work-up including repeat CT imaging and sputum cultures showed no evidence of relapsing infection. Thus, addition of streptomycin or amikacin was deferred to minimize the risk of aminoglycoside-induced renal failure, which could precipitate hepato-renal syndrome. Moreover, streptomycin can induce permanent vestibular toxicity.
Case #2

6 weeks into the new regimen, the patient developed increase in right supraclavicular lymphadenopathy, which fluctuated over the next 8 weeks until it began to drain purulent material. No fevers, chills, nightsweats, cough, or weight loss.

Routine evaluation by his ophthalmologist demonstrated progressive loss of peripheral visual field in the left eye since starting ethambutol (color blind at baseline).

While on levofloxacin, he developed bilateral tenderness in his Achilles tendons.
Case #2

What is the most likely scenario?
A) Progression of infection
B) Paradoxical reaction
C) Superinfection

What are next best steps?
A) Admission to the hospital
B) Bronchoscopy with BAL including AFB/Cx
C) AFB/Cx of the draining lymph node
D) Change in anti-TB regimen
Case #2

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   A) Progression of infection
   B) Paradoxical reaction
   C) Superinfection

What are next best steps?
   A) Admission to the hospital
   B) Bronchoscopy with BAL including AFB/Cx
   C) AFB/Cx of the draining lymph node
   D) Change in anti-TB regimen
Case #2

Patient was admitted to the hospital for expedited work-up. Right supraclavicular LN drainage was AFB positive (1-9/10 HPF) and PCR was positive for MTB. He underwent surgical drainage of the right supraclavicular LN with intra-operative samples negative for AFB. AFB stains of BAL and sputum X 2 were negative.

MDDR testing at CDC: INH – no mutations
  Rifampin – no mutations
  FQ – CGG to CTG (Arg75Leu)
Not enough material for other tests
Case #2

What is the next reasonable step in management of this patient’s tuberculosis considering history of cirrhosis, pure RBC aplasia, progressive decline in visual field testing, and tendon pain with levofloxacin?

A) Rifabutin + Moxifloxacin + PZA
B) INH + Moxifloxacin + Linezolid
C) Regimen A plus an injectable agent
D) Regimen B plus an injectable agent
Case #2

What is the next reasonable step in management of this patient's tuberculosis considering history of cirrhosis, pure RBC aplasia, progressive decline in visual field testing, and tendon pain with levofloxacin?

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B) INH + Moxifloxacin + Linezolid
C) Regimen A plus an injectable agent
D) Regimen B plus an injectable agent
Case #2

Supraclavicular LN cultures: No growth

Diagnosis: Paradoxical Reaction

Treatment Regimen:
INH + Moxifloxacin + Linezolid
↓
INH + Moxifloxacin
Peripheral Tuberculous Lymphadenitis

• Epidemiology
  < 10% of TB cases in USA – most are foreign born
  Peak age: 30 – 40 y.o.
  Can be associated with HIV (IRIS)

• Clinical Presentation
  Slowly progressive swelling of a group of LN
    Median LN size 3 cm, but can be up to 8-10 cm
    Usually unilateral (80-85%)
    Tenderness in 10-35%
    Draining sinus 4-11%
  Site of involvement
    Cervical chain #1 (40-70%)
    Supraclavicular #2 (12-26%)
Peripheral Tuberculous Lymphadenitis

• Clinical Presentation
  
  Systemic Manifestations:
  
  more common in HIV + patients
  
  Fever 18-60% (up to 80% with HIV)
  
  Weight loss 16%

  Concomitant pulmonary tuberculosis: 18 – 42%

  Disseminated disease: 8% (38% if HIV +)

• Diagnosis / Work-up
  
  Culture, PCR, Histopathology – Excisional biopsy and needle aspiration

  Granulomas, AFB +/-, culture negative

  PA & Lateral CXR

  Labs: CBC with diff, Creatinine, LFTs, HIV, HAV, HBV, HCV

  Sputum specimens for AFB & mycobacterial culture
Peripheral Tuberculous Lymphadenitis

- **Treatment**
  
  6 months of therapy: 2HRPE → 4 HR

- **Paradoxical Reaction (Paradoxical Upgrading Reaction)**
  
  - Occurs in < 5 - 23%
  
  - Time of onset: 1.5-3.5 months
    
    - In a subset of patients, can onset after completion of therapy
  
  - Duration of reaction: 2 – 4 months
  
  - Clinical Manifestations
    
    - Enlarged LNs  32-68%
    - New LNs  27-36%
    - Draining sinuses  12-60%
Peripheral Tuberculous Lymphadenitis

- Paradoxical Reaction (Paradoxical Upgrading Reaction)
  Management
  
  Continue with anti-TB therapy
  Use of steroids is controversial
  Surgical therapy – indications not well defined
  Tense, fluctuant lymph nodes
  Significant pain or discomfort
Take Home Points

• **Cirrhosis**
  Cirrhosis is a risk factor for tuberculosis
  No formalized guidelines – Individualized treatment
  Treatment regimen based on hepatotoxicity risk & underlying severity of liver disease

• **Tuberculous Lymphadenitis**
  < 10% of TB cases in USA
  Cervical and supraclavicular LN chains
  Paradoxical reaction < 5 – 23% (during & after therapy)

• **Hematologic Toxicity**
  INH and Rifampin have different hematologic toxicities
70 y.o. Hmong male with a history of COPD and previously treated LTBI (1 yr INH) was diagnosed with active pulmonary TB in the Fall of 2015. CXR showed right upper lobe cavitary lesion. Culture grew INH-Rifampin-Ethambutol-Streptomycin resistant TB. He was started on Moxifloxacin, PZA, Linezolid, Amikacin (15 mg/kg/d), cycloserine and ethionamide at an outside facility.

As part of monitoring labs, a uric acid level was checked and was elevated at 10.6 (normal 3.2-8.0 mg/dL). Allopurinol was started by an outside provider.
Case #3

Approximately 9 days after initiation of allopurinol, he developed fever, shortness of breath, and rash.

<table>
<thead>
<tr>
<th>WBC</th>
<th>15.9</th>
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<tbody>
<tr>
<td>Eosinophils</td>
<td>2,890</td>
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<td>Hgb</td>
<td>11.9</td>
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<tr>
<td>PLT</td>
<td>173</td>
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<tr>
<td>Na</td>
<td>137</td>
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<tr>
<td>K</td>
<td>4.4</td>
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<tr>
<td>Creatinine</td>
<td>1.15</td>
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<tr>
<td>Total bili</td>
<td>0.5</td>
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<tr>
<td>AST</td>
<td>207</td>
</tr>
<tr>
<td>ALT</td>
<td>98</td>
</tr>
<tr>
<td>AP</td>
<td>387</td>
</tr>
<tr>
<td>INR</td>
<td>1.3</td>
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</table>
Case #9

What is your diagnosis?

A) Disseminated TB with cutaneous involvement
B) **DRESS** (Drug Reaction with Eosinophilia and Systemic Symptoms)
C) Rheumatic fever
D) Lupus
Case #9

What is your diagnosis?

A) Disseminated TB with cutaneous involvement
B) DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms)
C) Rheumatic fever
D) Lupus
DRESS

- Incidence: unknown
- Onset: 2 wks – 3 months
- HLA association: HLA-B*5701, 5801, 1301
- Major offending agents
  - Anticonvulsants* #1
  - Allopurinol #2
  - Sulfonamides**
  - Minocycline
  - Dapsone
  - Abacavir
  - Nevirapine
  - Raltegravir

* Carbamazapine, Phenytoin, Phenobarbital, Lamotrigine
** Sulfasalazine, Sulfamethoxazole
# DRESS, Allopurinol, Ethnicity

## HLA-B*5801

<table>
<thead>
<tr>
<th>Study</th>
<th>Ethnicity</th>
<th>SCAR*</th>
<th>General Pop</th>
<th>OR</th>
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<tbody>
<tr>
<td>Hung SL et al.</td>
<td>Han Chinese</td>
<td>100% (51/51)</td>
<td>10.4 – 20%</td>
<td>580.3</td>
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<tr>
<td>Tassaneeyakula W</td>
<td>Thai</td>
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<td>8.6%</td>
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<td>Kang HR</td>
<td>Korean</td>
<td>92% (23/25)</td>
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<tr>
<td>Tohkin M et al.</td>
<td>Japanese</td>
<td>28% (10/36)</td>
<td>0.6%</td>
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</table>

*SCAR = severe cutaneous adverse reaction = DRESS, SJS, TEN

DRESS

• Clinical Features

1) **Cutaneous drug eruption**
   Morbilliform rash that becomes confluent and involves more than 50% of the body. Face, trunk & extremities involved. Due to intense cutaneous edema, vescicles & bullae/blisters can form.

2) **Eosinophilia** $> 0.7 \times 10^9$/mL or atypical lymphocytes

3) **Systemic involvement**
   - Fever
   - Interstitial pneumonia/pleuritis
   - Myocarditis/pericarditis (eosinophilic)
   - Hepatitis with AST/ALT $> 2x$ ULN
   - Interstitial nephritis – 10 – 30%
   - Lymphadenopathy – 30-60% with diffuse lymphadenopathy
DRESS

• Diagnostic work-up
  – CBC with differential and peripheral smear
  – Liver function testing
  – Testing for HAV, HBV, HCV
  – Serum creatinine and UA
  – Skin biopsy
  – Blood PCR for EBV, CMV, HHV-6, HHV-7 reactivation.
Case #3

Patient transferred to UWHC for further management and opinion regarding initiation of high-dose steroids to treat DRESS. What are your recommendations?

A) Stop allopurinol
B) Start high-dose steroids
C) Stop allopurinol & start high-dose steroids
Case #3

Patient transferred to UWHC for further management and opinion regarding initiation of high-dose steroids to treat DRESS. What are your recommendations?

A) Stop allopurinol
B) Start high-dose steroids
C) Stop allopurinol & start high-dose steroids
**DRESS**

- **Management**
  - Stop the offending medication
  - Avoid introducing new medications
  - DRESS without severe organ involvement
    - Skin + Liver with ALT/AST < 3x ULN
    - Topical steroids for rash & pruritus
  - DRESS with severe organ involvement
    - Skin + AST/ALT > 3x ULN + Lung or Renal involvement
    - Systemic steroids 0.5 – 2 mg/kg/d with 8-12 wk taper
    - Role of antiviral agents (HHV-6, CMV) uncertain
Clinical Case #3

Methylprednisolone 60 mg IV started, then converted to prednisone 60 mg x 2 weeks followed by a 10 week taper (12 weeks total). Atovaquone given for pneumocystis prophylaxis.

TB Guidelines MMWR 2003 for Pericarditis: (11 weeks total)
Prednisone 60 mg/d x 4 weeks, 30 mg/day x 4 weeks, 15 mg/day x 2 weeks, 5 mg/day, off.

<table>
<thead>
<tr>
<th>Site</th>
<th>Length of therapy (mo)</th>
<th>Rating (duration)</th>
<th>Corticosteroids†</th>
<th>Rating (corticosteroids)</th>
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<td>Lymph node</td>
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<td>AI</td>
<td>Not recommended</td>
<td>DIII</td>
</tr>
<tr>
<td>Bone and joint</td>
<td>6-9</td>
<td>AI</td>
<td>Not recommended</td>
<td>DIII</td>
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<tr>
<td>Pleural disease</td>
<td>6</td>
<td>All</td>
<td>Not recommended</td>
<td>DI</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>6</td>
<td>All</td>
<td>Strongly recommended</td>
<td>AI</td>
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<tr>
<td>CNS tuberculosis including meningitis</td>
<td>9–12</td>
<td>BII</td>
<td>Strongly recommended</td>
<td>AI</td>
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<tr>
<td>Disseminated disease</td>
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<td>All</td>
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<td>DIII</td>
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<tr>
<td>Genitourinary</td>
<td>6</td>
<td>All</td>
<td>Not recommended</td>
<td>DIII</td>
</tr>
<tr>
<td>Peritoneal</td>
<td>6</td>
<td>All</td>
<td>Not recommended</td>
<td>DIII</td>
</tr>
</tbody>
</table>
Clinical Case #3

Readmitted 6 weeks later with altered mental status, pulmonary infiltrates, worsening rash, acute renal insufficiency. MTB regimen: Amikacin, Cycloserine, Moxifloxacin, PZA, Linezolid. Prednisone 5 mg/day. Atovaquone prophylaxis against Pneumocystis.

HHV-6 PCR negative. CMV PCR 18,000.

Hearing loss due to Amikacin, Depression from cycloserine.

All TB meds temporarily held
High-dose steroids restarted.
Clinical Case #3

Slow re-introduction of TB regimen
  Linezolid 600 mg/day over 1 week
  PZA 1000 mg/day over 1 week
  Moxifloxacin 400 mg/day over 2 weeks
  Bedaquilline 400 mg daily x 2 weeks → 200 mg TIW x 22 wks
  Prednisone 75 mg x 2 wks -> 70 mg x 4 weeks -> 14 week taper
Two cases of tuberculosis with multiple drug hypersensitivity after drug-induced hypersensitivity syndrome

Here, we report 2 cases of drug-induced hypersensitivity syndrome (DIHS) caused by salazosulfapyridine and allopurinol during tuberculosis treatment. Both patients also developed multiple drug hypersensitivity (MDH) to several antituberculosis drugs that were used at around the period of DIHS onset, and thus, the treatment could not be successfully completed. Our cases show that MDH can easily occur after development of DIHS. Considering that treatment for tuberculosis requires long-term management with several drugs, it is important to refrain from administering drugs that can cause DIHS during tuberculosis treatment.

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<th>Dec / 1997</th>
<th>Jan / 1998</th>
<th>Fcb</th>
<th>Mar</th>
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<tr>
<td><strong>Allopurinol</strong></td>
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<tr>
<td>Methylprednisolone</td>
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<td>Skin rash</td>
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<tr>
<td>Fever 38°C</td>
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<td>37°C</td>
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</tbody>
</table>
Case of drug-induced hypersensitivity syndrome involving multiple-drug hypersensitivity

(a) (b)

Ogawa K et al. J Dermatol 2012;39:945-946
Take Home Points

• **Pyrazinamide (PZA)**
  Routine uric acid measurements not recommended
  Asx hyperuricemia does not require treatment
  Avoid use of allopurinol during MTB therapy

• **DRESS**
  Uncommon complication in patients with MTB
  Organ involvement requires use of steroids
  Steroid treatment for DRESS requires prolonged taper
  Don’t forget about prophylaxis against Pneumocystis
  Avoid sulfonamides for PJP prophylaxis