Recognizing and Managing Common Adverse Drug Reactions from Anti-tuberculous Therapy

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Objectives

• How do we define and monitor for adverse drug reactions (ADR)
• Common types of adverse drug reactions: minor to major
• Which drugs cause which problems?
• Practical approaches to the management of specific ADRs: gastrointestinal toxicity, hepatotoxicity, skin rashes, other
What is an ADR?

- Several different definitions used
- World Health Organization definition: “a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease”

“Significant” ADRs (ASHP)

- Requires discontinuing the drug
- Requires changing the drug therapy
- Requires modifying the dose
- Necessitates admission to a hospital
- Prolongs stay in a health care facility
- Necessitates supportive treatment
- Negatively affects prognosis
- Results in temporary or permanent harm, disability, or death
Monitoring for ADRs

- A process that starts before the initiation of treatment and continues throughout the entire treatment course
- Before prescribing anti-tuberculous medications, assess for factors that may increase risk of ADRs
  - e.g., increased age, underlying medical conditions such as preexisting liver disease, HIV, peripheral neuropathy and post partum state
  - Concomitant medications and supplements
  - Behavioral risk factors: e.g. alcohol consumption, illicit drugs.
  - Barriers to effective monitoring for ADRs: language and cultural barriers, psychiatric issues
- Baseline laboratory monitoring: depends on the drugs and patient population (TB infection vs. TB treatment)

Prescribing Anti-TB Therapy: A Risk Benefit Analysis

- Treatment for TB infection
  - Weigh risks (toxicity) vs. benefits of treatment
  - Those at highest risk for progression to TB disease should always be treated (e.g., HIV+, infant contacts, etc.) despite risks
  - Risks may outweigh benefits for other groups
- Treatment for TB disease
  - Benefits always outweigh the risks, but those at higher risk need more careful monitoring
Most Common Types of Drug Toxicity

- Gastrointestinal toxicity
- Hepatotoxicity
- Hypersensitivity (allergic) reactions
- Other dermatologic reactions
- Joint symptoms
- Neuropathy
- Visual symptoms
- Drug fever
- Hematologic and Other

Summary of Most Common ADRs to First Line Agents (and FQ)

<table>
<thead>
<tr>
<th>Reaction</th>
<th>INH</th>
<th>RIF</th>
<th>EMB</th>
<th>PZA</th>
<th>FQ</th>
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</table>
Case 1

• A 22 year old American born male who was diagnosed with TB after presenting with weight loss; evaluated in ER where he had an abnl CXR
• Started on RIPE. Treated as an outpatient after initiation of meds

Initial CXR
Social History

- Patient then arrested did not disclose disease
- Released with a P.O. and ankle bracelet
- Tracked down by PH department
- Living in unsafe unstable housing with questionable characters
- Failed to comply with therapy
- Menaced to LSH

- Started on RIPE 12/23/16
- Early satiety noted 3 weeks later
- Transaminitis noted with ALT > 5 times ULN
- Alk Phos minimally up, bili nl
- Next step
Is this man having an adverse drug reaction to his anti-TB therapy?

A. No, these are expected side effects of treatment and treatment should not be stopped as barely symptomatic
B. Yes, this is definitely an ADR and will require change in therapy
C. Can't tell, he will need further evaluation

Yes, this is a serious drug reaction even though symptoms are mild.
Risk factors in this patient

- From Slide 5 e.g., increased age, underlying medical conditions such as preexisting liver disease, peripheral neuropathy postpartum state
- Concomitant medications and supplements
- Behavioral risk factors: e.g. alcohol consumption
- Barriers to effective monitoring for ADRS:
  - Language and cultural barriers, psychiatric issues

- He was young so no risk factor there
- No known history of hepatitis
- HCV ab negative, no Hep B antigenemia
- Baseline LFT within normal limits
- HIV negative
- Inpatient so no IVDU or ETOH... did have psych issues

What is the next step?

A. Stop INH
B. Stop Rifampin
C. Stop Ethambutol
D. Stop PZA
E. Stop all drugs
F. Review need to avoid other hepatotoxic substances including ETOH
• ALT > 3 X ULN with nausea, vomiting, or abdominal pain
• ALT > 5 X ULN
• Interrupt treatment
• If moderate to severe TB, then continue at least 3 drugs
  • Rifamycin, EMB, fluoroquinolone
  • Hepatic sparing regimen: EMB, FQ, injectable
• Assess for confounders
  • Concomitant medications, OTC, supplements, herbals, EtOH
• Acute viral hepatitis testing:
  • IgM anti–Hep A Ab; hepatitis B surface Ag and IgM anti–Hep B core Ab; anti-HCV Ab and/or HCV RNA

Patient 1 Cont’d

• PZA only stopped
• Transaminases continued to rise
• Moxi and EMB started once LFTs normalized
• Rifabutin added next
• Last drug INH
• PZA not added back
Prospective Monitoring for ADRs

- Collaboration between patient and the TB program
- Patient education
  - Make sure they are educated about potential serious ADRs from their regimen
  - Make sure that they understand need to report them
- Staff education
  - Make sure they are aware of potential serious ADRs from the different TB medications
  - Make sure they assess for symptoms of ADRs from the patient at each interaction AND document them
- Interactions: Monthly medication pick ups, daily or twice weekly DOT visits, phone calls, any other interactions

Minor Drug Reactions
important because can impact compliance and provider patient bond.

**Mild reactions**
- No lasting effects
- Usually do not require change in the TB regimen
- May often respond to simple interventions e.g. taking pills with food, use of an antihistamine

**Some examples**
- Discoloration of body fluids
- Gas, bloating, mild nausea ( ?check for H Pylori)
- Itching and mild rash
- Photosensitivity
- Sleep disturbance
- Headaches
Serious Adverse Drug Reactions

- More “severe"
- Require more intensive monitoring
- Potentially life threatening if ignored
- May require change in therapy
- May require hospitalization

- Severe N/V/diarrhea
- Liver toxicity
- Electrolyte abnormalities
- Allergic reactions
- Severe skin reactions
- Vision loss
- Neurologic damage
- Kidney damage
- Hearing loss
- Death

Consequences of Severe ADRs

- Worst case scenario: severe morbidity and even death for example: fatal hepatitis
- Need for more intensive clinical and laboratory monitoring
- Need for alternative, usually more protracted and potentially less effective treatment regimen
- Potential impact on compliance and treatment outcome
A case of severe toxicity in TB infection

- Index case is 16 y.o. U.S.A. born student in a suburban high school
- Played a wind instrument in one of the largest high school bands in the state
- Presented with cough, fever, chest pain for more than 1 month duration
- CXR: RML pneumonia TX with Quinolone x 10 days with improvement. CXR 2 weeks later: resolving pneumonia

Several weeks later symptoms returned, hospitalized – pneumonia treated with Azithromycin, transferred to a medical center for IV antibiotics

- DX at Medical Center: SM (+) on bronchoscopy
- D/C on 5 drugs INH, RIF, PZA, EMB and Levo. INH resistance suspected (age 2 after trip to India TST positive given INH)
PH Detective Work!

- Period of infectiousness prior to diagnosis and treatment determined from symptom history
- School staff, parents and health care providers interviewed to determine possible school, home, social and work contacts
- Contacts classified into risk groups for recent exposure and previous infection
- Contacts interviewed to determine previous TST status
- Children US-born not likely to have a prior positive
• Band members stratified by instrument type and room position

• 7 contacts likely infected with MDR-TB started on at least 2 drugs based on known susceptibility of the source case isolate

• Contacts’ treatment and complication history tracked

<table>
<thead>
<tr>
<th>Patient</th>
<th>Exposure Type</th>
<th>PPD Size</th>
<th>Drugs</th>
<th>Complications</th>
<th>Drug Change</th>
<th>Disposition</th>
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<tbody>
<tr>
<td># 1</td>
<td>Teacher</td>
<td>25 mm</td>
<td>PZA, Levo</td>
<td>Uric acid elevated (11.1)</td>
<td>PZA, Tequin</td>
<td>Completed Rx</td>
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<td>PZA, Levo</td>
<td>Uric acid elevated</td>
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<td>PZA, Levo</td>
<td>Uric acid elevated (8.2)</td>
<td>PZA, Tequin</td>
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<td>Band</td>
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<tr>
<td># 5</td>
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<td># 6</td>
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<td>12 mm</td>
<td>PZA, Levo</td>
<td>Foot and joint pain with no elevation of Uric acid</td>
<td>PZA, Tequin</td>
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<td># 7</td>
<td>15 yo teenage girl</td>
<td>18 mm</td>
<td>PZA, Levo</td>
<td>Admitted with acute liver failure and listed for a liver transplant until liver functions improved</td>
<td>All TB drugs discontinued</td>
<td>Unable to complete Rx</td>
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Risk factors in this youngster

- No ETOH
- No illicit drugs
- No hepatitis
- NO OTC meds
- She was needle phobic so she declined monthly blood draws, acknowledged abdominal distress but said it was menstrual
- Presented to ED 2 days after a TB clinic visit with bili of 23!
- Remember severe toxicity can be idiosyncratic and PZA is hepatotoxic!!

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ADRs to 1st-Line Agents (and FQ) – Review of Slide 8

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*Thrombocytopenia* other penias
Case 2

- 11 year old youngster diagnosed with MDR-TB with resistance to all first-line meds
- Injectable started first 7 days a week then 5 days a week at a dose of 20/mg/kg
- Unclear when first hearing testing done
- Child went on to deafness

- Conventional dosing for injectables10-12 mg/kg when given IV
- Serial audiological testing is crucial as well as testing with simple exams for vestibulopathy
- These toxicities once they occur are not reversible
- First abnl one sees the audiology exams is high frequency loss, which will not be functionally limiting (perhaps if she were a violinist).
- That HF loss is the warning sign, would then proceed with caution switch to an additional p.o. medication and eliminate all together
- Consider inhaled meds such as amikacin (serum levels are not in range for hearing loss)
How Common are Adverse Drug Reactions During TB Treatment?

- Treatment for TB infection
  - Most data is for risk of INH toxicity
  - Comparative data from clinical trials comparing INH with other regimens
    - 9 mos of INH vs 12 weeks of INH plus Rifapentine
    - 9 mos of INH vs 4 mos of Rifampin
- Treatment for TB disease
  - Multi-drug regimens
  - More difficult to always assign “blame” for the ADR

Risk for INH Toxicity by Age Group:

Table 1. Hepatotoxicity rate, adjusted for compliance with therapy, by age groups.

<table>
<thead>
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<th>Age range</th>
<th>Adjusted incidence hepatotoxicity per 1000</th>
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<tr>
<td>0 – 19</td>
<td>0.8</td>
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<tr>
<td>20 – 34</td>
<td>2.8</td>
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<tr>
<td>35 – 54</td>
<td>9.1 (or 17.2*)</td>
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<tr>
<td>&gt; 54</td>
<td>31.0</td>
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Adjusted incidence by age group (criteria from Table 2 applied to age subgroups). References [28-36] were used.
*Reference [29] included in 35 – 54 group (based on mean age of participants = 50). If this study is excluded, rate for 35 – 54 is 17.2.

Forget and Menzies. Exp. Opinion in Drug Safety 2006
Overall incidence of adverse events during TB treatment

- Montreal Chest Institute retrospective review
- 403 patients
  - Mean age 40.3 years (17-94)
  - 65% male
  - >80% foreign born
- 37/403 (9.2%) patients had major adverse reactions
  - 9 had second adverse reaction (46 events)

Incidence of major adverse events: Montreal series

- Definitions:
  - Any event that led to drug discontinuation
  - Drug-induced hepatitis: transaminases > 5 X ULN, attributed
  - Rash and/or drug fever (4%)
  - Drug-induced hepatitis (2.9%)
  - Other GI side effects (2%)

Incidence of serious side effects by type and drug

Shaded columns, isoniazid; cross-hatched columns, rifampin; open columns, pyrazinamide; dotted columns, ethambutol.

AJRCCM 2003;167(11): 1472-1477
Demographic differences in adverse events: Female > Male, Older > Younger

Some other studies

- Tuberc and Lung Disease, 1996 (UK)
  - 5.1% had ADRs requiring treatment modification
  - Increase with increasing age 2.3% 0-19, 8.3% over 60; female > male
- PLOS 1, 2011 (Lima, Peru)
  - Risks for ADRs (in the multivariate analysis)
    - Age, Obesity, anemia, smoking
Management of Some Common ADRs to Anti-TB Therapy

“Don’t take any of these red pills, and if that doesn’t work, don’t take any of the blue ones”

Case 3

• 18 year old recently arrived from Haiti
• Pulmonary infection first noted while in Haiti
• Presents with cough
• Brought in by uncle who is concerned about her health
Small children in house so patient admitted
Patient discovers shockingly she is HIV positive
CD4 350
Patient started on RIPE and discharged back to community after about 3 to 4 weeks
PHN saves the day

- One month into therapy, patient tells PHN everything is blurry
- PHN calls MD

What is next step?

A. Stop all drugs
B. Stop INH
C. Stop EMB
D. Stop Rifampin
E. Stop PZA
F. Continue all drugs
• Presents to TB clinic
• Vision < 20/200
• Patient horribly depressed about HIV
• In addition, BF who infected her denies his culpability and "dumps her"

• Patient has been very depressed
• In retrospect, had lost significant weight in the hospital and an additional 7 kgs since her last visit
• EMB now dosed much too high for weight
• Creatinine nl
• Ophtamology exam reveals optic neuritis
Will she regain her sight?

A. Yes
B. No

- Ethambutol was stopped almost immediately thanks to the vigilance of the PH nurse

- As a result, her visual acuity did return to 20/20 uncorrected within the next month
Case 4

• 55 year old AA male, born in US but served overseas; was hospitalized at VA with TB
• Patient with long standing hypertension and renal failure on peritoneal dialysis times several years
• Patient treated at out of state VA for >2 months and transferred to LSH
• Patient on daily meds at conventional doses including EMB, despite peritoneal dialysis
• Patient had noted visual acuity loss for same time period but no one took notice
• Patient arrived at LSH VA LP only O.U.

What is the likely problem?

A. INH
B. Rif
C. EMB
D. PZA
Will patient regain his vision?

A. Yes
B. No

What went wrong?

- Patient 4 never recovered any functional vision, he was left with awareness of light only
- In patient number 3, issue was dosing. Higher dosing, especially dose for weight, greater chance of toxicity
- In patient 4, it's a clearance issue. EMB must be dosed for GFR or in this case dialysis.
- These cases reinforce importance of patient education, staff education, and minimum monthly VA/color in patients on EMB
Second Line Drugs

- Quick point about Linezolid as we now use it more and more
- Optic neuritis is a known ADR and patients should be monitored accordingly; if caught early vision is preserved

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Case 5

- 23 year old college student from China misdiagnosed for 7 months
- Eventually diagnosed with MDR-TB resistance to all first-line meds
- One month into therapy with CS, Moxi, Amikacin, Linezolid and PASER saw constant halos and had blurry vision
- Did not tell PHN but picked up early
- Vision nl within one month
Gastrointestinal Toxicity

- Nausea
- Vomiting
- Diarrhea
- Bloating
- Anorexia
- Abdominal pain
- Overlap of gastrointestinal symptoms and symptoms of hepatic toxicity - need to check LFTs (ALT, AST and bilirubin)
Which drugs are most likely to cause GI toxicity (and when?)

- Almost any drug can potentially cause GI toxicity
- Often occurs early (first few weeks) of treatment
- PZA > INH > RIF > EMB
- Fluoroquinolones can also cause GI toxicity but less commonly than PZA or INH
- Many of the other 2nd line drugs cause gastrointestinal toxicity (exception: injectables)

Management of GI Symptoms

- Initial options after excluding hepatotoxicity:
  - Change the timing of the dose
  - Give the meds with food
  - Daily dosing with fewer pills rather than intermittent therapy
  - Antacids 2hr before or after
  - Anxiolytic if the nausea occurs prior to swallowing the pills
  - Antiemetics
Antiemetic Options

- Ondansetron (Zofran®)
  4 to 8 mg PO twice daily prn
- Promethazine (Phenergan®)
  12.5 to 25 mg every 6 hours prn
- Prochlorperazine (Compazine®)
  5 to 10 mg every 6 hours prn
- Hydroxyzine (Vistaril® or Atarax®)
  25 to 50 mg every 6 hours prn

Case 6

- 40 year old alcoholic gentleman born in Nepal, works at Whole Foods
- He presents hypotensive in extremis to OSH
Patient admission CXR
• Patient emergently underwent pericardiocentesis

• Ultimately grew TB from pericardium, sputum and pleural fluid; PS

• Did well after one month platelets falling to 50K

How should his findings be managed?

A. Stop all anti-TB
B. Stop INH
C. Stop Rif
D. Observe
• Over the course of the next few months, rifampin and rifabutin added and d/c each time with thrombocytopenia and fevers to 102 with introduction and quickly resolving with discontinuation of the rifamycins
• The inability to use a rifamycin prolongs therapy in the fragile alcoholic

Case 7

• 40 year old HIV positive individual with smear positive, culture positive TB and a surprisingly nl CXR
Patient with untreated HIV (felt confidentiality compromised at TP office)

- Started on 4 drug therapy with RIPE
- Developed abnl LFTs with elevated alk phos>
  elevated bili> transaminases
- Not yet on HIV meds
She is mildly symptomatic, abdominal distress. What is your next step?

A. Stop all meds  
B. Stop none and observe  
C. Stop INH and PZA  
D. Stop Rifampin

• Abnl LFTs felt to be related to Rifamycin which were reintroduced several times each time with either fever or LFT abnl so decision made to treat without RIF  
• Again this has implications for therapy as one cannot treat for less than 1 year, frequently 18 months if I/E only. She received I/E and Moxi  
• 14 months into therapy she complained of severe arthralgias, Moxi alone was D/C with prompt improvement in symptoms
Hepatotoxicity

- Elevation in liver enzymes: ALT more specific for liver than AST
- Rifamycins tend to result in a more cholestatic picture
- I,Z a more pure transaminitis
- In patients with a history of gout, PZA will likely be a problem
- In pansensitive pulmonary disease, if one does not use PZA then therapy is prolonged for 9 months
- If one does not use a Rifamycin, even longer and no less than 12 months

Re-challenge: Practical Aspects

- Once ALT < 2 X ULN
- Many can return to original regimen
- Weigh risks based on severity of hepatotoxic event
- Different strategies:
  - Sequential re-challenge is most useful to sort out cause of hepatotoxicity if elevated LFTs recur: re-introduce drug every 7 days and monitor LFTs
    - RIF +/- EMB, INH, +/- PZA
    - If symptoms recur or LFTs increase ➔ stop last drug added
    - If RIF and INH are tolerated, and hepatitis was severe, do not add back PZA - assume PZA was responsible
Severe INH liver injuries among persons being treated for LTBI in US 2004-2008

- 17 cases reported to CDC (do not have data to determine a rate)
- 5 died, 5 required liver transplantation
- Can occur anytime in treatment
- 9/17 beyond the 3rd month
- Can occur in children: 2/17
- Diagnosed by other than prescribing physician: 10/17
- Did NOT STOP the medication when symptoms developed: 8/17

Rifampin Hepatotoxicity

- Transaminitis much less common than with INH or PZA
- Most common liver injury pattern is cholestatic hepatitis
  - Elevated Bilirubin and Alk Phosphatase
  - Fever
  - Manifestation of hypersensitivity reaction
Cutaneous Adverse Drug Reactions (CADRs) to Anti-tuberculous Drugs

- Can be confined to the skin or part of a systemic hypersensitivity syndromes
- Epidemiology and rates of CADRs less well defined than for other toxicities
  - Yee study: PZA > Rif > INH but in other studies EMB reactions also very common
- Severe CADRs more common in HIV+
  - Rifampin reactions more common in HIV+

Skin Reactions and Anti-TB Drug Associations

- Acne (INH)
- Photosensitivity (PZA,FQ)
- Urticaria (any)
- Purpura (RIF,INH)
- SLE-like syndrome (INH)
- Pellagra (INH)
- Exfoliative dermatitis (Any)
- Toxic epidermal necrolysis (Any)
- Stevens-Johnson syndrome (Any)
Minor Rashes

- Limited area
- The itching may be worse than the actual rash
- Not progressing over time

Management
- Generally treat symptoms with anti-histamine or a topical steroid
- Continue anti-TB medications
- Follow for any worsening

Generalized Erythematous Rashes

- Any drug can cause this
- Stop all drugs immediately
  - Especially if fever and/or mucous membrane involvement
  - Concern for toxic epidermal necrolysis/Steven Johnson syndrome
- If severe TB, use three new drugs
- Once rash significantly improved
  - Re-challenge serially
  - Reintroduce new drug every 2 – 5 days
    - R, H, E, (Z)
- Adjuvant testing: CBC (eosinophil count)
- Skin Biopsy
Peripheral Neuropathy

- Most common cause: INH
- Dose/duration of treatment related
- Incidence: Overall < 0.2%
- Risk Factors:
  - EtOH, Diabetes, renal failure, pregnancy, other peripheral neuropathies, other neurotoxic drugs, ? Slow metabolizers
  - Prevention: Pyridoxine 25-100 mg/day
- Very rarely reported with EMB

Ocular Toxicity

- Ethambutol optic (retrobulbar) neuritis:
  - Decreased visual acuity
  - Decreased red-green discrimination
  - Can be asymptomatic
  - Risk is increased with renal insufficiency - appropriate dosage adjustment in the elderly
    - Creatinine clearance < 30 → 3 x per week dosing
  - Generally does not cause pain, usually bilateral.
  - Rarely INH can cause
Monitoring and Management

- Baseline/ monthly
  - Visual acuity test (Snellen chart)
  - Color discrimination test (Ishihara tests- web app available)

- Patient education

- Monthly symptoms
  - blurred vision, etc.

- Hold medication – for any symptoms, but Ophthalmology evaluation ASAP

Rifampin Hypersensitivity Syndromes

- “Flu-like” syndrome: fever, chills, headache, myalgias
  - 1-2 hrs after dose, resolves spontaneously after 6-8 hrs
    - Associated with intermittent and higher doses
    - If mild, consider daily dosing (including weekend)

- Other severe immunologic reactions – rare, each < 0.1% patients: All require stopping of drug
  - Low platelet count
  - Renal dysfunction
  - Hepatotoxicity
  - Hemolytic anemia
  - Thrombotic thrombocytopenic purpura
“Possible Hypersensitivity” to Rifapentene was most Common Drug related ADR in the PREVENT TB Trial

Key Points

• ADRs are common in patients on treatment for LTBI and TB disease and range in severity from minor to major

• Severe, idiosyncratic ADRs are rare but have significant implications

• Monitoring for ADRs requires risk assessment, Patient (and staff) education, open communication and careful documentation

• All suspected ADRs need to be addressed, but all do not necessarily require stopping or change in therapy