Case Managing Side Effects

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Nurses Responsibilities

• Delegation
  – Outreach worker
    • Reports to the clinical staff
    • Trained to do directly observed therapy (DOT)
  – Medical staff (public health nurses, school nurse)
    • Clear instructions on DOT
    • Medical orders
    • Weekly communication
    • DOT documentation

• Nursing assessment
  – Assess all reports of side effects
  – Notify the treating physician when appropriate
  – Standing orders for labs
Assess

- Monitor patient’s clinical response to treatment
- Review other medical conditions and medications for possible drug interactions
- Assess for expected or unexpected side effects
- Provide education on how to manage minor side effects
- Review labs and ensure testing needed for specific medications
  - LFTs
  - Eye exams
  - Audiograms

Documentation

- Documentation is an integral part of all steps in the TB nurse case management process
- Documentation chronicles patient care outcomes and can be used to facilitate positive changes for both patients and health care providers
- The nurse case manager must ensure that documentation is completed regularly by all members of the multidisciplinary team and submitted to the appropriate people or agencies within the required time frame

“If it’s not documented, it did not happen!”
Directly Observed Therapy

- DOT/DOPT daily sheet
  - Observed taking medication
  - Side effects and intervention
  - Missed DOT and number of attempts to reach the patient
    - Why DOT appointment was broken and intervention to address
- DOT data collection form
  - Treatment adherence
  - Counting of doses (initial phase vs. continuation phase)
  - Hospital discharge date (do you count the doses from the hospital?)
  - Medication start date
  - Number of total doses counted toward treatment completion

DOT Report Form (Sample)
Most Common Side Effects

- Nausea
- Vomiting
- Rash
- Itching
- Joint Pain
- Tingling in hands or feet
- Trouble seeing
- Jaundice
- Fever/Chills
- Bruising
- Dark colored urine
- Other
The outreach worker is providing to DOT to a patient in the home and calls to tell you the patient has experienced nausea and vomiting.

• What would you tell the outreach worker to do?

When you arrive at the patient’s home for DOT, he reports he has no problems with his medications. Then his wife tells you she noticed he has a lot more bruises lately. What would you tell her?

A. This is not related to any of the medications he is taking
B. Get more information from the patient
C. Tell her to mind her own business because she is not the patient
D. Not sure
A patient calls to tell you their hair is falling out. What would you do?

A. Tell the patient this is not a side effect of the TB medications  
B. Ask the patient to continue with DOT but schedule them for a physician visit  
C. Ask them come into the clinic to get labs drawn  
D. Not sure

The patient had labs done at their physician visit. The results show an AST of 79 and the ALT is 100. What would you do?

A. Call the patient and instruct them to stop all medications  
B. Call the doctor to report these results  
C. Do nothing because the results are not high enough to be concerned  
D. Unsure
Questions?
Managing Adverse Effects of TB Medications

Henry S. Fraimow, MD

Objectives

- How we define and monitor for adverse drug reactions (ADRs) from TB medications
- Common types of ADRs
- Which 1st-line TB medications cause which problems?
- Practical approaches to the management of specific ADRs: gastrointestinal toxicity, hepatotoxicity, skin rashes, other
- That other complication of TB medications: Drug interactions in patient
Case 1

- A 63 y/o Chinese born woman is diagnosed with smear positive pulmonary TB and is started on TB therapy with RIPE via DOT. About 1 week into treatment course she complains to her clinic nurse that the medications are “making her sick” and she wants to stop them.

Questions

1) Is this woman having an adverse drug reaction (ADR) from her TB therapy?

2) If so, which medication is the culprit?

3) And if so, what do you do about it?
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”
• Side effects vs. ADRs
  – “Side effect” is a less precise term, often refers to milder, predictable effects of taking a medication

Question 1

• Which of the following new complaints would not be considered an ADR in a patient recently started on RIPE for pulmonary TB?
  1) Generalized itching
  2) Nausea but with normal liver enzymes
  3) Orange urine
  4) Gagging and choking on Ethambutol tablets
  5) Numbness in the feet
Monitoring for ADRs

- A process starting before initiating treatment and continuing through the entire treatment course
- Assessment for factors that may increase risk of developing an ADR
  - e.g., increased age, underlying medical conditions: liver disease, peripheral neuropathy
  - Concomitant medications and supplements
  - Behavioral risk factors: e.g., alcohol
  - Barriers to effective monitoring for ADRs: language/ cultural barriers, psychiatric issues

Prescribing TB Therapy: A Risk Benefit Analysis

- Treatment for LTBI
  - Weigh risks (toxicity) vs. benefits of treatment
  - Those at highest risk for progression to TB disease should be treated (e.g., HIV+, infant contacts, etc.) despite risks if at all possible
  - 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
Prospective Monitoring for ADRs

• Collaboration between patient, prescriber, and the TB program
• Patient education
  – Make sure patients are educated (but not terrified) about potential serious ADRs and the need to report symptoms
• Assessment for symptoms of ADRs from the patient at each and every interaction
  – Don’t assume that they will tell you, you have to ask!
  – Document them
• Multiple interactions and opportunities to assess

Minor vs. Serious Drug Reactions

• Mild reactions
• No lasting effects
• Usually do not require change in the TB regimen
• May respond to simple interventions e.g., taking pills with food; antihistamines
• E.g., gas, bloating, itching, HA
• More “severe”
• Require more intensive monitoring
• Potentially life threatening if ignored
• May require change in therapy
• May require hospitalization
• E.g., liver toxicity, severe skin reactions
Consequences of Severe ADRs

- Worst case scenarios: severe morbidity and even death; e.g., fatal hepatitis
- Need for more intensive clinical and laboratory monitoring
- Need for alternative, often more protracted and potentially less effective treatment regimen
- Potential impact of having an ADR on adherence and treatment outcome

Most Common Types of Drug Toxicity

- Gastrointestinal toxicity
- Hepatotoxicity
- Hypersensitivity (allergic) reactions
- Other dermatologic reactions
- Joint symptoms
- Neuropathy
- Visual symptoms
- Drug fever
- Other: nephrotoxicity, hearing loss
First Line TB Drugs (ATS/IDSA/CDC) Based on Efficacy, Cost, Toxicity
- Isoniazid INH
- Rifampin RIF
- Pyrazinamide PZA
- Ethambutol EMB
- Rifabutin RFB
- Rifapentine RPT

ADRs to First Line Agents (and FQ*)

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*Levofloxacin or Moxifloxacin
Incidence of Adverse Events During TB Treatment – Montreal Chest Institute

• Retrospective review of 403 adult patients
  ➢ 9.2% (37/403) patients had major ADRs that lead to drug discontinuation
    – 9 had second ADR (46 events)
• Rash/fever 4%, Hepatitis 2.9%, other GI 2%
• Risks:
  – Female > Male
  – Age > 60


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

Sex-related differences

Age-related differences

Management of Some Common ADRs to 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 1

• When further interviewed (using interpreter line) our patient says that when she takes her TB pills, she feels “sick to her stomach” like she might throw up and can’t eat. She has not vomited, does not have abdominal pain or dark urine. She has lost 2 lbs.
  – She has blood work done
  – ALT 51 (ULN 32, baseline was 23 before treatment); AST 38 (at the ULN), Bilirubin 0.9

Question 2

The most likely explanation for her symptoms is:
1) Gastrointestinal toxicity from INH
2) Hepatotoxicity from INH
3) Gastrointestinal toxicity from PZA
4) Gastrointestinal toxicity from any of her TB medications
Question 3

How would you try and manage her symptoms?
1) Stop TB medications and re-introduce them one at a time
2) Try giving medications with food or at a different time
3) Try giving medication with an anti-emetic
4) Stop the PZA and see if symptoms resolve

Gastrointestinal (GI) Toxicity

- Nausea
- Vomiting
- Diarrhea
- Bloating
- Anorexia
- Abdominal pain

➢ Overlap of GI symptoms and symptoms of hepatotoxicity- can’t tell without checking 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 Rx
- Hierarchy: 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 GI toxicity (exception: injectables)

Management of GI Symptoms (after excluding hepatotoxicity)

- Change the timing of the dose
- Give the meds with food
- Daily dosing with fewer pills rather than intermittent (3x per week) therapy
- Antacids 2hr before or after
- Anxiolytic if the nausea occurs prior to swallowing the pills
- Anti-emetics: ondansetron, promethazine, prochlorperazine, hydroxyzine
Question 4

What if our patient’s liver enzymes were elevated: **AST 732, ALT 444, Total Bili 3.4**

How should her symptoms be managed?
1) Stop all TB medications until LFTs return to 2X ULN
2) Stop INH and monitor LFTs
3) Stop INH and PZA and follow LFTs
4) Stop INH, RIF, and PZA, continue EMB and add 2 new, non-hepatotoxic TB agents

Hepatotoxicity

- Elevation in liver enzymes: ALT (AST, Bili)
- Confounders: Other drugs/supplements, alcohol, viral hepatitis, other liver/biliary tract disease
- Spectrum of hepatotoxicity
  - Symptomatic or asymptomatic disease
    - Asymptomatic AST elevation in up to 20% on INH
  - ATS symptom related threshold for stopping therapy: ALT 3x upper limit of normal
  - ATS asymptomatic threshold for stopping therapy: ALT 5x upper limit of normal
  - Fulminant Hepatitis (rare)
Some Risk Factors for Hepatotoxicity from anti-tuberculous Therapy

- Increasing age
- Malnutrition or hypoalbuminemia
- PZA in regimen
- Other hepatotoxic agents
- Alcohol
- Pregnancy or post-partum

- Elevated baseline ALT
- HIV infection
- Multiple medical problems
- Pre-existing chronic liver disease
- Chronic Hepatitis: B and/or C

Management of Suspected Hepatotoxicity

1. Hold all meds and check LFTs
2. If no symptoms and LFTs ≤ 5X ULN:
   - Continue therapy
3. If no symptoms and LFT > 5X ULN:
   - STOP therapy
4. If symptomatic and LFT > 3X ULN:
   - STOP therapy

Note: Patients with underlying cirrhosis may not demonstrate typical elevations in ALT and AST, must rely on other clues
Re-challenge: Practical Aspects

• Can restart once ALT < 2 X ULN
• Many can return to original regimen
• Weigh risks based on severity of hepatotoxicity
• Different strategies:
  – Sequential re-challenge is most useful to sort out cause of hepatotoxicity if elevated LFTs do recur; re-introduce drug every ~7 days and careful monitoring of LFTs
    • RIF +/- EMB, INH, +/- PZA
    • If symptoms recur, LFTs go up → stop last drug added
    • If RIF and INH are tolerated, and hepatitis was severe, do not add back PZA

Figure 3. Monitoring for hepatotoxicity during treatment of TB disease. Dotted lines signify management according to physician's discretion. ALT = alanine aminotransferase; AST = aspartate aminotransferase; HCV = hepatitis C virus; HepBsAg = hepatitis B surface antigen

Role for Liver Bx?
Fulminant Hepatitis

- An uncommon but catastrophic event
- Idiosyncratic reaction
- Outcomes include death/need for liver transplant
- Rate of fatal hepatitis from older studies (pooled data) 0.43 per 1000
- Risks increased with alcohol use
- Can occur later into treatment course
- ? More common in women

Severe INH liver injuries among persons being treated for LTBI in US 2004-2008

MMWR 2010

- 17 cases reported to CDC (did 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 from RIF than with either INH or PZA
- Most common liver injury pattern is cholestatic hepatitis
  - Elevated bilirubin and Alk Phosphatase
  - Fever
  - Often other manifestation of hypersensitivity reaction

Case 2

- 74 y/o Vietnamese male with recently diagnosed pulmonary TB with positive AFB smears and GeneXpert® positive for MTB and negative for RIF resistance. He has history of diabetes mellitus, chronic kidney disease and coronary artery disease. He is 68 inches and weighs 134 lbs, Creatinine is 1.7 (Calc Cr.Cl ~35).
- He is started on INH 300 mg, RIF 600 mg, PZA 1500 mg and EMB 1200 mg and B6
Case 2

• He is seen in the clinic 2 weeks later. His cough is better, he gained 2 lbs, but complains of aches in knees and ankles.

• On exam his left knee is mildly swollen and tender. You also note a diffuse erythematous macular rash and he now says that he has been a bit itchy.

Question 1

How should our patient’s rash be managed?
1) Stop all anti-tuberculous medications until the rash subsides
2) Obtain more history about the rash
3) Treat with antihistamines and see if improves
4) Examine for fever, mucous membrane involvement or generalized erythema and, if any of these, stop her medications
5) Dermatology evaluation
Question 2

• Does it matter what the rash looks like?

Cutaneous Adverse Drug Reactions (CADRs) to TB 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
  – Montreal Chest Institute study: PZA > RIF > INH but in other studies EMB skin reactions also very common
• Severe CADRs more common in HIV+ and in those with multiple drug allergies
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

- Affects only a 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
- 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

Petechial Rashes

- Check platelet count
- If low: presume Rifampin thrombocytopenia, and stop Rifampin and monitor platelets
- Rifampin should not be restarted
Question 2
What about his joint complaints? What should we do about these?
1) Stop all TB medications until the joint pains subside
2) Check a uric acid level and start allopurinol if high
3) Reduce dose of PZA
4) Stop PZA
5) Start a non-steroidal anti-inflammatory agent (NSAID)

Joint Complaints: PZA and other

- Arthralgias common: 8% with joint symptoms, 2% will stop drug
  - Elevated uric acid
  - Treatment is NSAIDS, allopurinol not helpful
- PZA rarely can cause acute gout flares, history of gout a relative contraindication but an elevated uric acid alone is not

- Other drugs:
  - Arthralgia: INH, FQ (both much less than PZA)
  - Gout: EMB (rare)
  - Tendinitis and tendon rupture: FQ
  - RIF: joint pain as part of hypersensitivity syndrome
A Few Words About TB Drug Interactions

- It's almost always the Rifamycin
- ↑ metabolism of many drugs by induction of CYP3A or UDG1A1 or induction of P glycoprotein
  - In general Rifampin > Rifapentine > Rifabutin
- You still want to use a Rifamycin if at all possible!!
  - Monitor for clinical outcomes: e.g., decreased levels of BP meds, methadone, corticosteroids
  - Monitor labs/levels: e.g., warfarin, phenytoin, tacrolimus
  - Use Rifabutin when possible- less but still some eff
  - Change the interacting drug if possible: e.g., change in antiepileptic agent or change in antiretroviral regimen

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 as soon as possible, but all do not necessarily require stopping or changing therapy