TB Nurse Case Management
Davenport, Iowa
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Medication Administration
and Adverse Reactions
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• No conflict of interest.

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TB Drug Review
Side Effects and Adverse Reactions

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Objectives

• Describe the monitoring process for adverse drug events associated with anti-TB drugs.

• Discuss the nursing interventions and medical management of the most common adverse drug events seen in patients on first- and second-line anti-tuberculosis therapy.
Adverse Drug Reaction Definitions

• Side Effect
  – An *undesirable* response associated with use of a drug that either compromises therapeutic efficacy, enhances toxicity, or both.

• Adverse Reaction
  – *An unintended harmful reaction to a drug administered at normal dosage*

Side effects

Usually *predictable* or dose dependent effect of drug (that is not the principle effect) for which the drug was chosen

• Desirable

• Undesirable
Drug Management Goals

- Recognize adverse drug events
- Assess appropriately
- Intervene rapidly
  - Prevent further morbidity/mortality
  - Minimize treatment interruptions
  - Reduce opportunities for “medical mismanagement”
  - Avoid development of psychological intolerance

ANTITUBERCULOSIS DRUGS
(ATS/CDC/IDSA)

- First-Line drugs
  - Isoniazid
  - Rifampin
  - Rifapentene
  - Rifabutin*
  - Ethambutol
  - Pyrazinamide

- Second-Line Drugs
  - Cylcoserine
  - Ethionamide
  - Levofloxacin*
  - Moxifloxacin*
  - PAS
  - Streptomycin
  - Amikacin/Kanamycin
  - Capreomycin

*Not FDA approved for TB
ISONIAZID (INH)

- “Profound early bactericidal activity…” Accounts for the majority of early bactericidal activity of multi-drug TB regimens
- Excellent absorption and tissue penetration
- Adults: 5mg/kg (300 mg/daily), 20-30 mg/kg (900 mg) twice or three times weekly
- Children: 10-15 mg/kg daily, 20-30 mg/kg (900 mg) twice weekly

INH Hepatotoxicity

- Asymptomatic elevation of aminotransferases: 20% of patients
- Clinical hepatitis: 0.6% of patients
- Fulminant hepatitis (hepatic failure): Approximately 4/100,000 persons completing therapy (continued INH with symptoms of hepatitis, prior INH hepatotoxicity, malnutrition).
Isoniazid Hepatotoxicity: Pretreatment Evaluation
(AJRCCM, 2006; 174: 935-952)

- Standardized history form, including risks for hepatotoxicity
- Physical examination: liver tenderness, hepatosplenomegaly, jaundice, ascites, edema
- Screening for viral hepatitis: IV drug users, patients from endemic areas of the world

Treatment of LTBI
AJRCCM 2006, 174; 935

- Limit dispensed dose to 1 month supply
- Patients should be categorically told to immediately stop medications (INH) for nausea, vomiting, abdominal discomfort, or unexplained fatigue and to contact the clinic for further evaluation
- Document, document, document
Isoniazid Hepatotoxicity: Treatment Choice

(AJRCCM, 2006; 174: 935-952)

• “For those with ALT elevation more than 2.5 to 3 times the ULN, chronic alcohol consumption, or severe liver disease manifested by low albumin and coagulopathy or encephalopathy, the risks of LTBI may outweigh benefits. If LTBI is undertaken, close monitoring is indicated.”

• The decision to treat LTBI, or more likely defer, should be carefully made on a case-by-case basis

• Evaluate risk of progression from LTBI to active TB

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Treatment of LTBI

AJRCCM 2006, 174; 935

• If treatment is started (in patients with elevated ALT) some experts recommend measuring serum transaminases and bilirubin every 2 to 4 weeks for the first 2 to 3 months, and as necessary. The INR may also be followed periodically in patients with severe hepatic impairment.
RIFAMPIN (Rif)
(Rifamycins: rifampin, rifabutin, rifapentene)

• Bacteriocidal (highest sterilizing activity). Activity against rapidly dividing and against semi-dormant bacterial populations.
• Cornerstone of short course therapy
• Well absorbed, good tissue levels
• Adults: 10 mg/kg (600 mg) daily, twice weekly or three times weekly (dosing of rifampin being re-evaluated)
• Children: 10-20 mg/kg (600 mg) daily or twice weekly

Rifampin Toxicity

• Cutaneous Reactions: 6%, generally self-limited
• Orange discoloration of body fluids
• Gastrointestinal symptoms: nausea, anorexia, abdominal pain
• Flulike symptoms: < 1% of patients on intermittent therapy.
• Hepatotoxicity: nearly 0% as monotherapy, 2-3% with INH
Rifampin Drug Interactions

• Interactions due to induction of hepatic microsomal enzymes (cytochrome P-450, CYP, enzyme system) that accelerate metabolism of multiple drugs
• Major concern is reduction in serum concentrations of common drugs (BCP’s, warfarin, etc.) to ineffective levels
• Bidirectional interactions between rifamycins and antiretroviral agents

Managing & Monitoring Rifampin

• Monitor CBC monthly
• Advise women using hormonal contraceptive to use another form of control
• Reduction of methadone almost to an ineffective level
• Cannot use with some Anti-retroviral drugs
Common Rifampin Drug Interactions

- HMG-CoA reductase inhibitors
- Oral anticoagulants
- Oral contraceptives
- Cyclosporine/Tacrolimus
- Digoxin
- Glucocorticoids
- Itraconazole/ketoconazole
- Methadone
- Phenytoin
- Theophylline
- Verapamil/diltiazem
- Amiodarone
- Midazolam
- Thyroid hormone

Rifabutin

- A substitute for rifampin for patients who are receiving drugs, especially antiretroviral drugs, that have unacceptable interactions with rifampin.
- Adverse effects: Less severe induction of hepatic microsomal enzymes, therefore, less effect on the metabolism of other drugs
- Adult dose 5 mg/kg (300 mg daily, 2-3X/week). Adjust dose with some NNRTI’s, PI’s
Rifabutin Toxicity

- Hematologic toxicity: neutropenia and thrombocytopenia
- Drug interactions: less severe than rifampin
- Uveitis: Rare, < 0.01%
- GI Symptoms
- Polyarthralgias: 1-2% at standard doses
- Pseudojaundice
- Hepatotoxicity, flu-like syndrome

PYRAZINAMIDE (PZA)

- Bacteriostatic/sterilizing agent: Greatest activity against dormant or semi-dormant (slowly growing) organisms within macrophages or caseous foci (acidic environment).
- Necessary for 6 months treatment regimen
- Adults: 20-25 mg/kg (2.0 g) daily, 50 mg/kg (4.0 g) twice weekly
- Children: 15-30 mg/kg (2.0 g) daily, 50 mg/kg (2.0 g) twice weekly
Pyrazinamide (PZA) Toxicity

- Hepatotoxicity: ?Unusual at 25 mg/kg
- Gastrointestinal symptoms: nausea and vomiting mild at standard doses.
- Nongouty polyarthritis: Up to 40% of patients: not an indication to stop therapy.
- Asymptomatic hyperuricemia: Expected
- Acute gouty arthritis: Unusual except in patients with pre-existing gout.
- Rash/dermatitis: usually self limited

Ethambutol (EMB) Protector

- Included in first-line treatment regimens to prevent the emergence of Rif resistance when INH resistance may be present.
- Adults: 15 mg/kg daily, 50 mg/kg twice weekly (max dosage based on wt, AJRCCM, 2003; 167: 603-662)
- Children: 15-20 mg/kg daily, 50 mg/kg (2.5 g) twice weekly
Ethambutol Toxicity

- Baseline & monthly visual acuity test (Snellen chart)
- Baseline & monthly color discrimination test (Ishihara tests)
- Question pt regarding possible visual disturbances including blurred vision & scotomata (blind spots) Observe children for eye rubbing, excessive blinking, sitting close TV, difficulty with accurate grasping
  - Hold Rx
  - Refer for Ophthalmologic evaluation
  - Permanent vision impairment if Rx continued

Second-line Drugs

- Cycloserine
- Ethionamide
- Levofloxacin
- Moxifloxacin
- PAS
- Streptomycin
- Amikacin
- Kanamycin
- Capreomycin
Fluoroquinolones

- The FQ’s exhibit early bactericidal activity from days 0-2 slightly less than INH but greater extended EBA (days 2-7) compared with INH
- **Levofloxacin**: 750-1000 mg/day, no data to support intermittent dosing (dosing adjustment in renal insufficiency)
- **Moxifloxacin**: 400 mg/day, no data to support intermittent dosing (NO dosage adjustment with renal insufficiency).

Fluoroquinolones

- Preferred oral agents for treating drug resistant TB that is susceptible to this class of drugs or for patients intolerant of first-line drugs
- Activity against MTB: [Gati] > Moxifloxacin > levofloxacin > ofloxacin/ciprofloxacin
Fluoroquinolone Toxicity
Musculoskeletal

- Tendonitis/Tendon Rupture (*Black box* warning)
- If tendon inflammation is mild:
  - Rest the joint/NSAID’s
  - Reduce dose of FQ if possible
  - If symptoms progress, stop the FQ
- If tendon inflammation is moderate/severe
  - Stop the FQ
  - Rest the joint/NSAID’s
  - Risk/benefit evaluation of FQ continuation
- Tendon rupture (usually Achilles) is rare

Fluoroquinolone Toxicity

- Gastrointestinal disturbance: nausea/bloating 0.5-2%
- Neurologic effects: dizziness, insomnia, tremulousness, headache 0.5%
- Cutaneous reactions: rash, puritis, photosensitivity 0.2-0.4%
- Arrhythmias: QT prolongation (congenital, medications, MI)
- Avoid in pregnancy
Fluoroquinolone Caveats and Controversies

• Fluoroquinolone use for community acquired pneumonia and risk for developing fluoroquinolone resistant TB:
  – Multiple courses of fluoroquinolone
  – Prolonged courses of fluoroquinolone

Cycloserine

• Bacteriostatic agent
• Rapid, nearly complete GI absorption
• Widely distributed in most body fluids and tissues including CSF and breast milk
• Excretion is primarily renal, half life is longer in renally impaired patients
• Not recommended for patients with ESRD
Cycloserine Reactions

• Reactions
  – Behavior changes / Aggressive behavior / Irritability
  – Confusion
  – Dysarthria
  – Elevated liver transaminases
  – Headache
  – Hyper-reflexia / Tremors
  – Impaired memory
  – Rash
  – Somnolence
  – Vertigo

Second-Line TB Drugs

• Cycloserine
  – Central Nervous System Effects: headaches, restlessness, suicidal ideation psychosis, seizures (3% 500 mg/day). May exacerbate underlying seizure disorders or mental illness. Pyridoxine at 100-200 mg/day may help prevent neuro-toxic side-effect.
  – Administer with caution to alcoholics, patients with hx of mental illness or seizures
  – Peripheral neuropathy
  – Rash
Second-Line TB Drugs

• Cycloserine
  – Dosing can be split if necessary
  – Single dosing facilitates drug level determinations
  – **Drug levels are necessary**
    • (peak levels 20-35 mcg/ml)

Second-Line TB Drugs

• Ethionamide
  – Metabolized almost exclusively in the liver, no dosage adjustment necessary for renal insufficiency
  – Little effect of food or anti-acids, the drug can be administered with food if drug tolerance is a problem
  – Widely distributed throughout body tissues and fluids
  – May increase levels of INH and cycloserine
Second-Line TB Drugs

• Ethionamide
  – Gastrointestinal Effects: “commonly causes profound GI side-effects”. Symptoms may improve if taken with food or at hs
  – Hepatotoxicity: 2% of patients
  – Neurotoxicity: Peripheral neuritis, optic neuritis, depression, psychosis
  – Endocrine Effects: blood glucose abnormalities hypothyroidism, gynecomastia,

Second-Line TB Drugs

• P-Aminosalicylic acid (PAS)
  – Bacteriostatic drug
  – AUC increased by administering PAS with food
  – 80% of the drug excreted in the urine
  – Contraindicated for patients with serious renal disease (build up of toxic metabolites)
p-Aminosalicylic acid (PAS)

Common Reactions
- Abdominal pain
- Diarrhea
- Hepatitis
- Nausea / Vomiting

Serious Reactions
- Hypothyroidism
- Hypokalemia
- Thrombocytopenia

Second-Line TB Drugs
- P-Aminosalicylic acid (PAS)
  - Gastrointestinal Distress: 11% of patients, less with lower doses
  - Hepatotoxicity: 0.3% of patients (including jaundice)
  - Malabsorption syndrome
  - Hypothyroidism: common with prolonged administration or concomitant ethionamide
  - Rash, lymphadenopathy, leukocytosis, arthralgia
Monitoring and Management

PAS

• Monitor abdominal pain diarrhea
  – Diarrhea improves with time (self limiting)

• Management
  – Mix with acidic juice or apple sauce

• Monitor Thyroid function
  – TSH

Amoniglycosides

• Streptomycin
  – Ototoxicity: vestibular and hearing disturbances, risk increased with age, lasix, dose and cumulative dose
  – Neurotoxicity: perioral parasthesias
  – Nephrotoxicity: 2% of patients, less common than with amikacin or capreomycin
Antituberculous Drugs in Renal Disease

• Monitoring Streptomycin Therapy
  – Baseline audiogram, vestibular testing, Romberg testing and creatinine
  – Renal function and questions about auditory and vestibular symptoms monthly
  – Repeat audiogram or vestibular testing if symptoms develop

Second-Line TB Drugs

• Amikacin
  – Ototoxicity: hearing disturbances, less vestibular dysfunction than Strep
  – Nephrotoxicity: 3.4-8.7% of patients, increased risk with pre-existing renal disease, higher doses, other nephrotoxic drugs
  – Rash
  – Electrolyte disturbances: hypoklema, hypomagnasemia (cardiac dysrhythmias)
Second-Line TB Drugs

• Capreomycin
  – Ototoxicity
  – Nephrotoxicity
  – Electrolyte disturbances: hypoklemia, hypomagnasemia, cardiac dysrhythmias
  – Rash

Auditory Toxicity

Perform audiometry at baseline and repeat monthly
  – Identify pre-existing hearing loss
  – Refer for evaluation if any decrease from baseline

• Fullness, ringing, roaring, hissing, or “buzzing” in ears
• Generally reversible
Second-Line TB Drugs

• Linezolid
  – Excellent penetration into bronchial mucosa and bronchoalveolar fluid
  – Does not require dosage adjustment with renal insufficiency
  – Optimal dose unknown

Linezolid for Treatment of Tuberculosis

- Very active in vitro against drug susceptible and drug resistant MTB
- Can be given orally (optimal dose unknown)
- Frequent, severe adverse events:
  bone marrow suppression- dose dependent/ reversible
  Peripheral Neuropathy- Not dose dependent
  ? not reversible
  Optic neuritis
  GI disturbance/Rash
Second-Line TB Drugs

- Linezolid
  - Myelosuppression
  - Peripheral Neuropathy
  - Optic Neuritis
  - Gastrointestinal Disturbance
  - Rash

TB Disease: Baseline Testing and Monitoring
AJRCCM 2006; 174: 935-952

- Baseline transaminases, bilirubin, alkaline phosphatase, creatinine and platelet count for all adults beginning TB therapy
- Routine measurements during treatment: baseline abnormalities, chronic alcohol consumption, other hepatotoxic drugs, viral hepatitis or history of liver disease, HIV infection, prior DILI
- Screen for viral hepatitis in at risk patients
- Assess the patient prior to each DOT dose and monthly, at a minimum, in a face-to-face encounter with the health care provider
Antituberculous Drugs in Pregnancy

- Used with caution: rifabutin, cycloserine, para-Aminosalicylic acid
- Contraindicated: ethionamide, amikacin, streptomycin, kanamycin, capreomycin, quinolones
- Unknown: rifapentine

Case Studies
Hepatotoxicity

38 y.o. male diagnosed with PTB during incarceration

- Mar. 13: started standard RIPE regimen
  - Baseline laboratory values: ALT 42, AST 63

- April 15: changed to BIW dosing; EMB d/c’d when susceptibility results showed isolate to be susceptible to INH/RIF

- June 4: F/U laboratory values: ALT 304, AST 97
  - Asymptomatic for hepatitis

Hepatotoxicity Cont.

What is the appropriate response?

- Hold TB medications!
  ALT ≥ 5x ULN in asymptomatic patient, or ≥ 3X ULN in patient with signs/symptoms consistent with hepatitis
Hepatotoxicity

When can therapy be safely restarted?

Once ALT is < 2X ULN

Hepatotoxicity Cont.

Should other TB therapy be started?

If it is likely there will be a delay of > 2-3 wks consideration can be given to starting a “liver friendly” regimen (EMB, fluoroquinolone, aminoglycoside) while waiting for LFT’s to normalize
Hepatotoxicity Cont.

What treatment should be considered when ALT returns to < 2X normal?

• RIF/EMB X 3-7 day
  Monitor LFT’s twice weekly

• If LFT’s stable after 3-7 days, add INH
  Continue to monitor LFT’s twice weekly

Ophthalmic Toxicity

21 y.o. male diagnosed with PTB in October

• **February-May:** Incarcerated in county jail
  – May: onset of illness (fever, chills, productive cough, chest pain, night sweats, wt. loss)

• **October 7:** Initial Clinic Visit
  – CXR: LUL cavitary infiltrate
  – AFB smear + (1-10/HPF), sent for culture

• **October 12:** Started RIPE standard regimen

• **November 9:** Isolate reported INH/SM resistant
Ophthalmic Toxicity

What do we do next?

• Pt. improving: afebrile, 6 lb wt. gain, night sweats resolved, cough improving

• INH discontinued; continued on RIF, PZA, EMB to complete 9 mo. treatment

Ophthalmic Toxicity

• March: pt. c/o difficulty driving, reading road signs

What do we do?

– Advised by LHD nurse to see “eye doctor”

  March 21: seen by optometrist and given RX for corrective lenses

– EMB continued
Ophthalmic Toxicity

- **May 3:** Pt. c/o worsening vision
  - Visual acuity: 20/200 both eyes
    - Baseline visual acuity (October): 20/20 both eyes

  **What would you do?**

- **May 5:** **EMB discontinued:** continued on RIF, PZA and Levo added to regimen to complete 9 mo of tx.

- Referred to retinal specialist

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**Follow-up**

- Seen by retinal specialist in May and June
  - DX: EMB optic neuritis
  - Central scotoma on right and parascotoma on left
  - Vision uncorrected: 20/200
  - Vision best corrected: 20/60

- Nurse admitted not performing visual acuity screening (Snellen chart), only color discrimination testing (Ishihara plates)
References

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