Medications for Drug Resistant Cases and Other Medication Issues

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Treatment of TB Disease

- Overall goals
  - Cure the individual patient
  - Minimize transmission within the community
  - Responsibility for successful treatment is assigned to public health department or private provider, not individual patient.
  - Health department ultimately responsible for ensuring adequate, appropriate treatment.

- 4 regimens approved for drug susceptible disease
- Recommendations for HIV-infected same with a few exceptions
  - Twice weekly options are not recommended for HIV+ patients with CD4+ cell counts less than 100
Antituberculosis Drugs Currently in Use in the United States

- **First-line Drugs**
  - Isoniazid
  - Rifampin
  - Rifapentine
  - Rifabutin*
  - Ethambutol
  - Pyrazinamide

- **Second-line Drugs**
  - Cycloserine
  - Ethionamide
  - Levofloxacin*
  - Moxifloxacin*
  - Gatifloxacin*
  - P-Aminosalicylic acid
  - Streptomycin
  - Amikacin/kanamycin*
  - Capreomycin

Treatment Pearls

- Ethambutol can be discontinued once susceptibility to INH and RIF demonstrated
- Must be on PZA
- Requires physician order
- PZA must be continued for full recommended course to qualify for short-course treatment
- DOT standard of care for all

Drug Regimens for Culture-Positive TB with Drug Susceptible Organisms

Regimen 1

- **Initial phase**
  - INH/RIF/PZA/EMB
    - 7 d/wk for 56 doses (8 weeks)
    - Option – 5 d/wk for 40 doses (8 weeks)
- **Continuation phase**
  - INH/RIF
    - 7 d/wk for 126 doses (18 weeks)
    - 5 d/wk for 90 doses (18 weeks)
    - Twice weekly for 36 doses (18 weeks)*
  - INH/RPT
    - Once weekly for 18 doses (18 weeks)*
Drug Regimens for Culture-Positive TB with Drug Susceptible Organisms

Regimen 2
- Initial phase
  - INH/RIF/PZA/EMB
    - 7 d/wk for 14 doses (2 weeks)
    - Then twice weekly for 12 doses (6 weeks)
    - OR
    - 5 d/wk for 10 doses (2 weeks)
    - Then twice weekly for 12 doses (6 weeks)
- Continuation phase
  - INH/RIF
    - Twice weekly for 16 doses (8 weeks)
  - INH/RPT
    - Weekly for 18 doses

Drug Regimens for Culture-Positive TB with Drug Susceptible Organisms

Regimen 3
- Initial phase
  - INH/RIF/PZA/EMB
    - Three times weekly for 24 doses (8 weeks)
- Continuation phase
  - INH/RIF
    - Three times weekly for 54 doses (18 weeks)

Drug Regimens for Culture-Positive TB with Drug Susceptible Organisms

Regimen 4
- Initial phase
  - INH/RIF/EMB
    - 7 d/wk for 56 doses (8 weeks)
    - OR
    - 5 d/wk for 40 doses (8 weeks)
- Continuation phase
  - INH/RIF
    - 7 d/wk for 217 doses (31 weeks)
    - 5 d/wk for 155 doses (31 weeks)
    - Twice weekly for 62 doses (31 weeks)
Drug resistant TB

- Choice of drugs depends on resistance pattern
- May require second line drug(s)
- Requires DOT
- Requires >>26 weeks of treatment
- Almost always requires daily therapy – 5 or 7 days/week
- Monitoring for culture conversion, clinical improvement, side effects/toxicity critical

Definitions

- **Primary drug resistance:**
  - Infected with TB which is already drug resistant
- **Secondary (acquired) drug resistance:**
  - Drug resistance develops during treatment

The importance of what’s missing

- INH only
  - can treat with rifampin, EMB and PZA for 6 months
  - Fluoroquinolone may help if extensive disease
  - Ethambutol only
    - RIP for 2 months and IR for 4 months – 6 months total
  - PZA only
    - RIE for 2 months and IR for 7 months – 9 months total
  - Rifampin only
    - INH, EMB, fluoroquinolone and PZA for 1st 2 months
    - Total treatment 12-18 months
Step 1
Use any available
Begin with any first-line agents to which the isolate is susceptible
Add a fluoroquinolone and an injectable drug based on susceptibilities

First-line drugs
Pyrazamide
Ethambutol

Fluoroquinolones
Levofloxacin
Moxifloxacin

Injectable agents
Amikacin
Capreomycin
Streptomycin
Kanamycin

PLUS
One of these

Step 2
Pick one or more of these
Oral second line drugs
Cycloserine
Ethionamide
PAS

Step 3
Consider use of these
Third line drugs
Imipenem
Linezolid
Macrolides
Amoxicillin/Clavulanate

If there are not 4-6 drugs to which isolate is susceptible (which have not been used previously), consider 3rd line in consultation with MDRTB experts.
Completion of Treatment

- Determination made more accurately by total number of doses taken, not time period
- Goal is to deliver the recommended specified number of doses in a maximum time frame
  - Important in cases of non-adherence, toxicity
  - 6 month regimen should be completed in 9 months
  - 9 month regimen should be completed in 12 months
- Non-standard treatment due to drug resistance or intolerance – longer, more complicated
  - Depends on missing drug or drugs

Completion of Treatment – cont.

- Interruptions may have significant impact on duration of treatment
- Earlier in treatment and longer the duration, the more serious the effect.
- May need to restart treatment from beginning.

TB Medications
Monitoring for Adverse Reactions

- All medicines have potential negative effects on patients
- Frequency, severity, preventability vary

Types of Adverse Effects

- Side Effect - Uncomfortable but not dangerous effect of medications as properly administered
  - Most meds – nausea, other GI symptoms
    - usually can continue treatment – can be signs/symptom of hepatitis
    - Diarrhea less common but potentially important – can be marker for malabsorption, predict low blood/tissue drug levels
  - First line meds – non-specific itching
    - Itching, non-specific rash common – can be initial sign of hepatitis
    - Hives, extensive maculo-papular, purpura rare – require D/C meds, contact HCP, consider ER

- CNS/peripheral nervous system side effects
  - Irritability, sleepiness, insomnia common
  - Peripheral neuropathy – usually isoniazid; pyridoxine prevents
  - Optic neuritis – causes visual disturbances
    - feared w/ ethambutol, can be seen w/ other meds
  - Musculoskeletal –
    - PZA can cause non-specific muscle and joint pain
    - PZA elevates uric acid – can induce gout
  - “Flu-like” symptoms – can occur w/ rifampin
    - more common twice weekly treatment
  - Report to case manager immediately
Types of Adverse Effects

- Toxicity – Adverse effect on metabolic processes (e.g., enzyme systems, tissue replication or repair mechanisms); often dose related
  - INH – hepatitis, peripheral neuropathy
  - Rifampin – hepatitis
  - Ethambutol – retrobulbar neuritis
  - Aminoglycosides – ototoxicity, nephrotoxicity

Types of Adverse Effects

- Contraindicated - Known negative consequence of use in certain patients or situations
  - Streptomycin contraindicated in pregnancy: ototoxicity in fetus

Other TB Drug Effects

- Drug-drug interactions
  - May increase or decrease effective dose of either TB drug or other medication
    - Rifampicin
      - Rapid metabolism of methadone, warfarin, theophylline – may require increased doses
    - INH
      - May decrease concentrations of phenytoin, diazepam – require increased doses
Other TB Drug Effects

- Sub-therapeutic levels
- Unrecognized drug-drug interactions
- Malabsorption
  - Other disease
  - OTC meds
  - Food
  - Rapid transit through GI tract
- Incorrect dose

Monitoring for Adverse Effects

- Part of case management plan
- Monitoring starts before treatment starts
  - Medical history
    - Known liver or renal disease
    - Risk factors for Hep B, Hep C, HIV
  - Other medications (prescription and OTC)
  - Alcohol/drug use
  - Allergies to medications
  - Pregnancy/postpartum/breast feeding
- Awareness of record and alert for changes

Managing the Medications

- Review non TB meds (OTC and prescription) regularly
  - Ask if prescriptions changed if recent appointment
  - Complaining? Ask about self treatment and OTC medications
- Food – last food before dose
- OTC antacids
Isoniazid

**Preparation**
- 50 mg, 100 mg, and 300 mg tablets
- Suspension (can cause diarrhea and cramping)
  - Only commercially prepared suspension
  - Must be kept at room temperature

**Administration tips**
- Can be cut or crushed
- Mix with food just before administering
- Do not take with large fatty meal
- If upsets stomach, take with small amount of food
- Avoid alcohol or OTC meds such as Tylenol or other pain relievers
- No antacids within 1 hour

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Isoniazid

**Adverse Reactions and Side effects**
- Hepatitis
- Loss of appetite
- Tiredness, weakness
- Stomach pain, nausea, vomiting
- Yellow skin or dark colored urine
- Can cause flushing with some fish or cheeses
- Peripheral neuritis
- Numbness or tingling in hands or feet
- Arthralgias
- Optic neuritis

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Rifampin

**Preparation**
- 150 mg and 300 mg capsules

**Administration tips**
- Store at room temperature – humidity can affect
- Powder from capsules can be mixed with liquid or soft food
- Must be administered immediately after mixing
- Be careful in opening capsules!
Rifampin

- Adverse Reactions and Side effects
  - Orange staining of body fluids – fast!
  - Will stain soft contact lens
  - Rash
  - GI upset, flu-like syndrome
  - Liver toxicity
    - Unusual tiredness or loss of appetite
    - Sever abdominal pain
    - Fever chills

Ethambutol

- Preparation
  - 100 mg and 400 mg tablets
- Administration tips
  - Store at room temperature
  - Can be taken with food
  - Can be split or crushed and mixed – used immediately

Ethambutol

- Adverse Reactions and Side effects
  - Visual disturbances – vision changes, blurring, color blindness, trouble seeing, eye pain
  - Swelling of face
  - Rash, hives, trouble breathing
  - Numbness, pain or tingling of hands/feet
  - Joint pain
  - Fever chills
  - Nausea, vomiting, poor appetite, abdominal pain
  - Headaches, dizziness
Pyrazinamide
- Preparation
  - 500 mg tablets
- Administration tips
  - Store at room temperature
  - May be taken with food
  - Can be split or crushed
  - Use immediately following mixing with food

Pyrazinamide
- Adverse Reactions and Side effects
  - Can cause rash after sun exposure – limit sun exposure
  - Gout-like symptoms (pain swelling in joints) and arthralgias
  - GI upset
  - Liver toxicity –
    - yellow skin/dark urine
    - nausea/vomiting
  - Skin rash, severe itching, hives

Rifabutin
- Preparation
  - 150 mg capsules
- Administration tips
  - Store at room temperature – humidity can affect
  - Powder from capsules can be mixed with liquids or small amount of food
  - Must be administered immediately after mixing
  - Be careful opening capsules!
Rifabutin

- Adverse reactions and side effects
  - Rashes and skin discoloration
  - Uveitis and other eye toxicities
  - Liver toxicity similar to rifampin
  - Joint pains
  - Drug interactions

Ethionamide

- Preparation
  - Coated tablets – 250 mg
- Administration tips
  - Should be taken with food
  - Client should be on high-dose B6 (pyridoxine) while on drug

Ethionamide

- Adverse reactions and side effects
  - GI upset and anorexia
  - Metallic taste
  - Hepatotoxicity
  - Endocrine effects – breast enlargement, hair loss, acne, impotence, menstrual issues
  - Neurotoxicity – may be worse if also on cycloserine
Cycloserine

- Preparation
  - 250 mg capsules
- Administration tips
  - Best taken on empty stomach - decreases absorption
  - Avoid large amounts of fatty foods
  - Avoid alcohol
  - Must be on high-dose B6(pyridoxine) while on drug

Adverse reactions and toxicity
- Serious central nervous system effects
  - Inability to concentrate and lethargy
  - Seizures
  - Depression
  - Psychoses
  - Suicidal thoughts
- Nerve issues in hand/feet
- Skin changes including rashes, hives

Linezolid (Zyvox)

- Preparation
  - Coated tablets – 400 mg and 600 mg
  - Intravenous solution
  - Oral powder for suspension
- Administration tips
  - May be taken with or without food
  - Avoid tyramine containing foods – aged cheeses, dried meats, sauerkraut, soy sauce, tap beers and red wines
Linezolid (Zyvox)

- Adverse reactions and side effects
  - Visual disturbances
  - Pain, numbness, tingling or weakness in extremities
  - Diarrhea
  - Headache
  - Nausea and vomiting

Levoquin

- Preparation
  - Coated tablets – 250 mg, 500 mg, 750 mg
  - Solution for injection
  - Oral suspension

- Administration tips
  - Can be taken with food
  - Drink plenty of beverages
  - Avoid caffeinated foods and beverages
  - May cause sensitivity to sun
  - Do not take within 2 hours of antacids or multivitamins

Levoquin

- Adverse reactions and toxicities
  - Nausea and bloating
  - Headache
  - Dizziness
  - Insomnia
  - Rare tendon rupture
  - Joint pain
  - Rashes, hives, blistering
Moxifloxacin (Avelox)

- Preparation
  - Tablets – 400 mg
  - Solution for IV injection
- Administration tips
  - Keep at room temperature
  - Can be taken with food, but not milk-based products
  - Do not take within 2 hours of antacids or vitamin supplements

Adverse reactions and toxicity
- Nausea and diarrhea
- Headache and dizziness
- Rare tendon rupture
- Rare hepatitis
- Joint pains

Para-Aminosalicylate (PAS) - Paser

- Preparation
  - 4 gm packets
- Administration tips
  - Packets should be kept in refrigerator or freezer
  - Sprinkle over applesauce or yogurt or swirl in acidic juices (tomato, cranberry, apple, or orange)
  - Do not chew
  - May be taken with food
  - Do not use if packet expanded or granules discolored
Para-Aminosalicylate (PAS) - Paser

- Adverse reactions and toxicity
  - GI upset and diarrhea improve over time
  - Shells of granules may be seen in stool
  - Skin rash, severe itching
  - Nausea, vomiting
  - Unusual tiredness
  - Loss of appetite
  - Black stools or bleeding
  - Rare hepatotoxicity

Capreomycin – Streptomycin
Amikacin - Kanamycin

- Preparation
  - 1 gm vials for reconstitution
  - Vials of solution for injection

- Administration tips
  - IM or IV use
  - Options for longer term administration

- Adverse reactions and toxicity
  - Kidney toxicity
  - Hearing loss
    - Risk increases with length and age of client
    - May not be reversible
  - Local pain at injection site
  - Electrolyte abnormalities
Monitoring and Reporting

- Observe and question patient, and document findings at each encounter
- Report changes or new findings immediately to case manager before dose administered
- If case manager not available and reaction seems severe, refer immediately to medical provider or emergency room

Miscellaneous Comments

- Difficulty swallowing pills
  - Patient may not tell you
  - Crushed pills, administered in small amount food ok
    - Make sure they will finish amount you use!
  - Teach how to swallow meds
    - Tablets SINK – TILT HEAD UP
    - Capsules FLOAT – TILT HEAD DOWN

Summary

- TB is treated with multiple drugs for a prolonged period of time
- Drug resistance generally extends treatment – length depends on missing drug(s)
- All anti-TB drugs have side effects and toxicities
- Second-line drug side effects are usually worse
- Regular monitoring for side effects and toxicities is critical!
Questions????????