

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.

Treatment of TB Disease

- 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 (8weeks)
- 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 36 doses (18 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 **PLUS** One of these **PLUS** One of these

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	Fluoroquinolones	Injectable agents
Pyrazinamide Ethambutol	Levofloxacin Moxifloxacin	Amikacin Capreomycin Streptomycin Kanamycin

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Pick one or more of these

Add 2nd line drugs until you have 4-6 drugs to which isolate is susceptible (which have not been used previously)

Oral second line drugs
Cycloserine Ethionamide PAS

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Oral second line drugs
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Step 3

Consider use of these

If there are not 4-6 drugs available consider 3rd line in consult with MDRTB experts

Third line drugs
Imipenem Linezolid Macrolides Amoxicillin/Clavulanate

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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 sign/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 rashes common – can be initial sign of hepatitis
 - Hives, extensive maculo-papular, purpera rare – require D/C meds, contact HCP, consider ER

Types of Adverse Effects

- 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
 - Rifamycins
 - 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

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

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
 - Severe 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

Cycloserine



- 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

Moxifloxacin (Avelox)

- 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



Capreomycin – Streptomycin Amikacin - Kanamycin

- 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 amt food ok
 - Make sure they will finish amount you use!
 - Teach how to swallow meds
 - Tablets SINK – TILT HEAD UP
 - Capsules FLOAT – TIL 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????????
