Drug Resistant Tuberculosis: Pearls and other Considerations

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Disclosures

- None
Objectives

- Describe factors responsible for delayed response and/or treatment failure
- Describe treatment and management strategies for multidrug-resistant TB
TB Therapy Drug Resistance Definitions

• **Poly-resistant TB**
  - Resistance to >1 drug
    - but not isoniazid and rifampin

• **Multi-Drug Resistant (MDR) TB**
  - Resistance to at least isoniazid and rifampin

• **Extensively Drug Resistant (XDR) TB**
  - MDR (INH & rifampin) + plus:
  - Resistance to a fluoroquinolone + plus:
  - Resistant to an injectable (kanamycin, streptomycin, amikacin)
MDR-TB Prevalence in the United States

- MDR TB cases
  - Totals
    - 1.4% (96 cases) in 2013
    - 1.3% (91 cases) in 2014

- Foreign born:
  - 31% (149 of 484) in 1993
  - 88% (80 of 91) in 2014.

Risk Factors for Drug-resistant TB

1. Previous TB therapy – especially with
   - Prior non-DOT based therapy
   - Patient non-compliance
   - Incomplete treatment, lack of documentation
   - Non-CDC, non-WHO endorsed standard regimens
     - Acknowledging for a patient – *TB therapy is difficult*
       - Prolonged treatment program
       - Many pills
       - Common drug intolerances

2. Contact with a patient with drug-resistant TB
3. Persons from countries with higher rates of drug-resistant/MDR TB cases

More than 6% of new TB cases are MDR-TB in these locations:
- Azerbaijan, Baku City (22.3%)
- Kazakhstan (20%)
- Republic of Moldova (19.4%)
- Ukraine, Donetsk (16%)
- Russian Federation, Tomsk (15%)
- Uzbekistan, Tashkent (14.8%)
- Estonia (13.3%)
- Russian Federation, Mary El (12.5%)
- Latvia (10.8%)
- Lithuania (9.8%)
- Armenia (9.4%)
- Russian Federation, Orel (8.8%)
- China, Inner Mongolia (7.3%)
- China, Heilongjiang (7.2%)
- Georgia (6.8%)

Risk Factors for Drug-resistant TB - cont’d

Other risk factors (international):

1. Prolonged hospitalization (endemic regions)
2. HIV co-infection
3. Lack of sustainable drug availability to patients through inadequate pharmaceutical supply chain and/or failure to provide free treatment
4. Overuse of fluoroquinolones in other infection syndromes that propagates fluoroquinolone-resistant TB
5. Delays in diagnosing drug-resistant TB

International challenges with TB Mgmt

• In 2008, ~ 20 % of the approximately 30,000 MDR-TB patients reported to the WHO were treated in GLC approved TB centers that adhered to published international guideline (WHO. Global tuberculosis control: a short update to the 2009 Global TB Report)

• Only 22% of countries routinely perform cultures and drug susceptibility testing
  • Only 48% of the 46 countries in the WHO Africa region have ever undertaken a drug-resistance survey (The Lancet. 2010;375:1830-1843)

• Furthermore in 2008 among the 27 WHO-identified high MDR-TB burden countries, only 1% of new TB cases and 3% of previously treated had DST performed (WHO. Multidrug and extensively drug-resistant TB (M/XDR-TB): 2010 global report on surveillance and response 2010.)
XDR-TB: A Global Dilemma

Countries that had notified at least one case of XDR-TB by the end of 2011

Problems of *Global* TB Containment

- Lack of Involvement of clinicians outside of public health TB control programs
  - E.g. private physicians
- Clinician deviation from standard internationally accepted DOTS TB management
- Under-use of sputum AFB smear microscopy
  - Over-reliance on CXRs
- Use of non-recommended TB drug regimens and combinations
- Mistakes in drug dosing and treatment duration
- Lack of supervised patient adherence

Hopewell. Lancet Inf Dis 2006;6:710
Problems of *Global* TB Containment-II

- Lack of mycobacteria culture lab facilities
- Lack of drug susceptibility testing
  - Phenotypic DST
  - MDDR
- Lack of newer agents:
  - Linezolid
  - Moxifloxacin/levofloxacin
  - BDQ
- Lack of surgical capacity
Second Line TB Medications

- Less effective
- More expensive
- More toxic
Second Line TB Medications

- Fluoroquinolones
  - Moxifloxacin, Levofloxacin
- Aminoglycosides
  - Streptomycin, Amikacin & Kanamycin
- Capreomycin
- Linezolid
- Ethionamide
- Cycloserine
- Para-Aminosalicylic Acid (PAS)
New and other novel drugs for use (MDR- & XDR-TB)

→ a few other “arrows in the quiver”

New drugs

• Bedaquiline
• Delamanid

Older / less active

• Clofazimine
• Carbapenem/clavulanate
Principles of Drug-Resistant TB Management

• A single new drug should never be added to a failing regimen

• MDR/XDR treatment regimens are based on expert opinion, not clinical trials

• Several regimens exist based on different sites/guidelines
  • CDC/ATS/IDSA 2003 TB Treatment Guidelines
  • New York City Dept. of Health, Clinical policies and protocols. *Bureau of Tuberculosis Control*, 2008
  • Francis Curry TB Center / UCSF
  • Union 2013: Int J Tuberc Lung Dis 2010; 14: 382–390
Treatment options, regimens and basic approaches for drug-resistant TB
Resistance to which 1st line anti-TB medication requires a prolongation in therapy (e.g. beyond 6 months)?

For a *pan-susceptible* MTB strain:

A. Isoniazid
B. Rifampin
C. Pyrazinamide
D. Ethambutol
E. B or C
F. A, B, or C
Monoresistance – Isoniazid

- Rifampin, PZA, Ethambutol x 6-9 months

- Considerations for more extensive disease:
  - Treat 9 months
  - Add fluoroquinolone (moxifloxacin, levofloxacin) or injectable (e.g. amikacin)

- Examples: ND, Wisc. TB outbreaks
Monoresistance - Rifampin

NYCHD

- Option 1: Induction - INH/PZA/EMB/inj/FQ x 2-3 mo. after culture conversion
  Continuation: INH/PZA/EMB+/-FQ x 12-14 mo. (18 total mo. preferred)

- Option 2: Induction - INH/PZA/SM+/-EMB 2-3 mo. after culture conversion
  Continuation - INH/PZA/SM+/-EMB x 3-5 mo. (9 mo. total)

Curry/UCSF

- Option 1: INH/EMB/PZA/FQ x 2 mo. then INH/EMB/FQ to complete 12-18 mo.
- Option 2: Option 1 +injectable for first 2 mo.
- Option 3: INH/PZA/SM( or other inj) x 9 mo.

CDC/ATS

- INH/PZA/EMB x 12-18 mo. (consider + FQ or Inj. if extensive disease)
- INH/PZA/SM x 9 mo.
Mono resistance to EMB, PZA, or SM

• Little impact on treatment efficacy
• Loss of EMB/SM does not change efficacy or treatment duration
• Loss of PZA: extend duration with INH/RIF by 3 mo. (9 mo. total)
Poly-resistant TB

- Resistance to >1 TB drug, but not INH & RIF
- Treatment should include as many 1\textsuperscript{st} line drugs as possible + FQ and in some cases injectable
  - Composition and duration of therapy depended upon specific drug resistance profile
Approach to MDR-TB Management

- Include any active 1st line drug, then add FQ and injectable (amikacin/kanamycin/SM/capreomycin)

- Add oral 2nd line drugs to compose 4-6 drug regimen
  - Note: When restarting or revising therapy, always try to use at least 3 previously unused drugs to which there is demonstrated in vitro susceptibility (1 should be injectable)

- If there are not 4-6 active drugs available, then consider 3rd line drugs (clofazimine, imipenem, high dose-Augmentin, high dose-INH)

- Surgery can be considered with complex cavitary disease or slow clinical response
Additional considerations

• “Low level” INH resistance
  • INH resistance at MIC 0.2 mg/L, but active at MIC 1.0mg/L
  • Consideration for 900 mg INH twice weekly
  • Would not count INH as an “active” drug in regimen

• ~10-15 % rifampin resistant MTB may be susceptible to rifabutin (in vitro)
  • Rifabutin can be considered, but would not count as active drug
Composing an Effective Drug Treatment Program for MDR-TB

**STEP 1**

Begin with any first-line agents to which the isolate is susceptible.

Add a fluoroquinolone and an injectable drug based on susceptibilities.

**Use any available**

**First-line drugs**
- Pyrazinamide
- Ethambutol

**PLUS**

**One of these**

**Fluoroquinolones**
- Levofloxacin
- Moxifloxacin

**PLUS**

**One of these**

**Injectable agents**
- Amikacin
- Capreomycin
- Streptomycin
- Kanamycin

Challenging
Composing an Effective Drug Treatment Program for MDR-TB

**STEP 2**

Add second-line drugs until you have 4–6 drugs to which the isolate is susceptible (and preferably which have not been used to treat the patient previously)

Pick one or more of these

**Oral second-line drugs**

- Linezolid
- Cycloserine
- Ethionamide
- PAS

More challenging
Composing an Effective Drug Treatment Program for MDR-TB

### STEP 3

If there are not 4–6 drugs available in the above categories, consider third-line drugs in consultation with an MDR-TB expert.

<table>
<thead>
<tr>
<th>Third-line drugs</th>
<th>Other / BDQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clofazimine</td>
<td>Imipenem</td>
</tr>
<tr>
<td>Amoxicillin/clavulanate</td>
<td>Macrolides</td>
</tr>
<tr>
<td>High-dose isoniazid</td>
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</tbody>
</table>

Most challenging
Extremely Drug resistant TB (XDR-TB)

• Resistance profile:
  • INH & rifampin = MDR strain) and:
  • A fluoroquinolone and:
  • One of injectables (kanamycin, streptomycin, amikacin)

• Similar approach to MDR TB but may need to use 3rd line drugs

• Surgery should strongly be considered

Other consideration:

• Delays in starting therapy until DST is occasionally considered:
  • Controversial
  • Stable disease in immunocompetent host
  • No vulnerable contacts at home
  • MDR or XDR-TB case when DST pending and construction of active regimen is in doubt
  • No flight risk

• Judgement call – high caution
The role of surgical resection

• Favorable results reported with resectional lung surgery in patients with MDR-TB

• Resective surgery considered for:
  • Patients with high-grade drug resistance (limited drug options)
  • Relatively localized lung disease
  • Lack of initial response

• NJMC, Denver with high experience
  • Dedicated surgeon / surgical team (Dr. M Pomeranz)
  • Pneumonectomy or lobectomy

Pomerantz et al. J of Thorac Cardiovasc Surg. 2001;121(3) 448-53
The role of surgical resection - timing

- When surgical resection is favored
  - e.g. cavitary disease, necrotic / avascular lung tissue

- Optimal timing for surgery can be difficult to determine

- Consider delaying surgery for a few months after start of combination drug therapy
  - Lower TB organism burden
  - Enhanced patient nutrition / weight gain
  - Improved postoperative tissue healing

Pomerantz et al. J of Thorac Cardiovasc Surg. 2001;121(3) 448-53
Successful MDR-TB outcomes not necessarily limited to surgical resection

• Inclusion of better 2\textsuperscript{nd} line drugs - e.g.:
  • Newer fluoroquinolones (Moxifloxacin / levofloxacin); Injectables (prolonged periods of time); Linezolid
  • Even better when PZA or EMB remain active

• Medical management a consideration when an active combination drug regimen can be composed
  • Inclusion of ≥ 5 drugs with in vitro activity

• Pushing serum levels to upper limits of therapeutic window (roles for TDM)

Principles for MDR and XDR-TB management

• Providers *need to be comfortable* asking for assistance
  • Most providers are not overly experienced in drug-resistant TB management
• Our Mayo TB Center practice utilizes Region-5 MDR-TB Team consensus with more complex TB drug-resistant cases
• Such patients may not have a “2nd chance” for treatment success
Principles for MDR and XDR-TB management - II

Co. and State Public health departments need to be involved for case management:

- Directly observed therapy (DOT) *is crucial*
- Heightened monitoring for treatment response and drug toxicities
- Contact investigations
Case Presentation:

My first patient as a new Mayo Clinic Staff

July 2000
Case Presentation: 33 yo Somali Woman

- 10/99 Abnormal CXR for LTBI screen – no follow-up
- 5/00 – Diagnosis with pulmonary tuberculosis
  RUL cavitary and multifocal disease
  - AFB smear and mycobacteria cultures both (+)
    - DST pending
  - Minimal cough
  - HIV negative (-); immunocompetent
- 7 months pregnant
Case Presentation – TB and pregnant:

Question # 2: What TB drugs to start?? - DST pending

A. INH/RIF/PZA/EMB; B6
B. INH/RIF/EMB; B6
C. INH/RIF/PZA; B6
D. INH/RIF/Streptomycin; B6
E. Delay therapy until after delivery

20% 20% 20% 20% 20%
Case Presentation – TB and pregnant:

• 5/12/00 started on INH/RIF/EMB
  • PZA avoided (in USA) during pregnancy
    • Lack of data during pregnancy to determine safety
    • PZA still used during pregnancy for following:
      • HIV (+) patient
      • Suspected drug-resistance
      • WHO (non-USA) recommendations (PZA given during pregnancy outside of USA)
  • Patient with some improvement over 1 month
  • Then susceptibility results……..
# Case Presentation – MDR TB

**Susceptibility data from Mayo:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Sensitivity</th>
<th>Drug</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>&gt; 0.1 Resistant</td>
<td>Kanamycin</td>
<td>8 Sensitive</td>
</tr>
<tr>
<td>Rifampin</td>
<td>&gt; 2 Resistant</td>
<td>Capreomycin</td>
<td>8 Sensitive</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>&gt; 100 Resistant</td>
<td>Ethionamide</td>
<td>4 Sensitive</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>&lt; 2.5 Sensitive</td>
<td>Streptomycin</td>
<td>&gt; 2 Resistant</td>
</tr>
</tbody>
</table>

**Additional susceptibility data from NJH:**

<table>
<thead>
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<th>Drug</th>
<th>Sensitivity</th>
<th>Drug</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>&lt; 2 Sensitive</td>
<td>PAS</td>
<td>8 Sensitive</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>&lt; 2.0 Sensitive</td>
<td>Cycloserine</td>
<td>60 Sensitive</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>&lt; 2.0 Sensitive</td>
<td>Linezolid</td>
<td>&lt; 4.0 Sensitive</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>&lt; 2.0 Sensitive</td>
<td></td>
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</tr>
</tbody>
</table>

Dr. J Wilson joins staff here ……………. Takes over patient care
Case Presentation – MDR TB

— all things considered – this could have been worse!!

Susceptibility data from Mayo:

- Isoniazid > 0.1 Resistant
- Rifampin > 2 Resistant
- Pyrazinamide > 100 Resistant
- Ethambutol < 2.5 Sensitive
- Streptomycin > 2 Resistant

- Kanamycin 8 Sensitive
- Capreomycin 8 Sensitive
- Ethionamide 4 Sensitive

Additional susceptibility data from NJH:

- Amikacin < 2 Sensitive
- Levofloxacin < 2.0 Sensitive
- Gatifloxacin < 2.0 Sensitive
- Ofloxacin < 2.0 Sensitive

- PAS 8 Sensitive
- Cycloserine 60 Sensitive
- Linezolid < 4.0 Sensitive

Dr. J Wilson joins staff here ……………… Takes over patient care
Question # 3: With DST results: How best to modify therapy during pregnancy?
MTB resistant to INH/RIF/PZA/SM; susceptible to EMB & 2nd line agents
Patient now 8 months pregnant (June, 2000)
No / min. symptoms (some improvement)

A. RBT/EMB/AMK/ETH/CYC; B6
B. EMB/AMK/ETH/CYC/PAS; B6
C. EMB/Levo/AMK/ETH/CYC; B6
D. EMB/Moxi/AMK/LZD/ETH; B6
E. Stop TB therapy until delivery (1 mo.)

20% 20% 20% 20% 20%
Drug Resistant TB: General Treatment principles

- Poly-resistant MTB disease
  - Use as many 1st-line agents as possible, plus a fluoroquinolone and (in some cases) an injectable agent (e.g. aminoglycoside)

- MDR-TB disease
  - Use a minimum of 4 or more drugs to which the MTB is susceptible (at least 3 drugs not used previously with in vitro activity, including injectable)
    - Begin with available 1st-line TB drugs
    - Add a fluoroquinolone (Moxi > Levo > Cipro)
    - Add injectable agent (AMK/Kana/SM/Capreo)

- XDR-TB – include above principles
  - May need to include 3rd-line drug (in vitro activity but limited clinical experience) – includes:
    - Clofazimine
    - Linezolid
    - Amox/Clavulanate
    - Imipenem
    - Macrolides
    - High-dose INH
Case Presentation – 33 yo Somali woman with MDR TB; 8 mo. pregnant

- Consultation with NJMC & MDH:
  - Medications stopped late/end May 2000 (Combination second-line MTB drug therapy delayed until after delivery of baby).
  - Newborn baby immediately separated from mother until mid 8/00 when pt. was Smear & culture negative)
  - Controversial – other treatment approaches can be very appropriate

- Late June, 2000, started: Ethambutol; IV Amikacin; Levofloxacin; Ethionamide; Cycloserine (B6)
  - Before wide usage of LZD, Moxi
Case Presentation – MDR TB; post-partum
- Started expanded TB drug therapy – June, 2000
- 3 months later developed hypothyroidism

Question # 4: Which drug is most suspect for hypothyroidism?

A. Ethambutol
B. Amikacin
C. Levofloxacin
D. Ethionamide
E. Cycloserine
Case Presentation – MDR TB; post-partum
- Started expanded TB drug therapy
- 3 months later developed hypothyroidism

Ethionamide – also can cause gynecomastia, alopecia, impotence and worsening hyperglycemia in pts with diabetes

- Both Ethionamide and PAS require sTSH monitoring – additive effect when used in combination.
Case Presentation – MDR TB

Started on Synthroid – continued ethionamide 5 months into treatment – developed asymptomatic high-frequency hearing loss via audiology testing:

Question # 5: Which drug is most suspect?

A. Ethambutol
B. Amikacin
C. Levofloxacin
D. Ethionamide
E. Cycloserine
Case Presentation – MDR TB

Amikacin – aminoglycosides can produce irreversible CN8 toxicity
  • Audio toxicity: AMK, KAN
  • Vestibular toxicity: SM
Case Presentation – MDR TB

-Amikacin stopped
-Para-aminosalicylic acid (PAS) granules started
-6 months into treatment – patient developed mild visual disturbance (decreased acuity):

Question # 6: Which is the most suspect drug?

A. Ethambutol
B. PAS
C. Levofloxacain
D. Ethionamide
E. Cycloserine
Case Presentation – MDR TB

**Ethambutol** – optic neuritis; red-green color discrimination and visual acuity

Edema of optic disc  
Mild temporal pallor
Case Presentation – MDR TB

• Stopped ethambutol
• Continued levofloxacin, ethionamide, cycloserine and PAS
• Later re-developed severe GI distress

Question # 7: Which is most likely drug?
Case Presentation – MDR TB

• GI distress – N/V, upset stomach, ache

Common with most TB drugs (early in therapy) but most problematic with ethionamide

• GI upset also common with PAS
Dose Escalation Strategies: Ethionamide, Cycloserine, PAS

- Relevant Drugs:
  - Ethionamide
  - Cycloserine
  - Para-aminosalicylic acid

- Purpose:
  - Improved patient tolerance (gradual dose escalation)
  - More precise dosing for acceptable serum drug levels
Dose Escalation Strategies: 
Ethionamide, Cycloserine, PAS

• Ethionamide & cycloserine
  • Start with 250 mg daily x a few days
  • Increase to 250 mg bid x a few days
    • Check serum level
  • Increase to 250 mg/qAM and 500 mg q/PM

• PAS (Paser granules, sachet packets)
  • Start with 2 gm bid x a few days
  • Increase to 2 gm/qAM and 4 gm qPM x few days
  • Increase to 4 gm bid
    • Check serum level
Linezolid usage

• An oxazolidinone

• Toxicities – significant (> 50%) and include:
  • Neuropathies - peripheral & optic
  • Myelosuppression
  • Hyperlactatemia
  • Risk of serotonin syndrome with SSRIs

• Bacteriostatic; binds rRNA; inhibits protein synthesis

• Dosing: 600 mg daily successfully used

Linezolid usage

- Dosing of 300 mg /d can be effective for MDR-TB
  - Possibly lower adverse effects compared to 600 mg daily or bid
- 300 mg/d dosing can achieve serum concentrations greater than MIC values (≤0.25 mg/L)
- Favorable penetration into pulmonary & soft tissues

Bedaquiline (Situro) – a new diarylquinoline

- Inhibits mycobacterial ATP synthase
- Spectrum of activity includes: *M. tuberculosis* and select NTM (including MAC)
- Indications: treatment of pulmonary MDR-TB in pts ≥ 18 yo when optimal TB drug program cannot be constructed
- BDQ dosing: 400 mg daily x 2 weeks, then 200 mg TIW x 22 weeks – then off
Bedaquiline – concerns and limitations

- Increased risk of death (11.4% vs. 2.5% in comparator group)
- Elevated QTc (although not felt to be a major risk by CDC group meeting)
  - May be additive with other QTc prolonging drugs - *caution by FDA
- Higher hepatic adverse reactions
- Drug interactions via Hepatic CYP 3A
  - M2 is major metabolite (4-6x less potent)
  - BDQ does not increase or decrease 3A4 activity
  - Rifampin will decrease BDQ levels (via accelerated 3A4 metabolism)
- Limited data in HIV co-infected patients

CDC RTMCC meeting January 14-15, 2013
Current Global Pipeline of New Tuberculosis Drugs

Diagram showing the pipeline with stages: Discovery, Preclinical development, GLP toxicology, Phase I, Phase II, Phase III. Chemical classes are also shown: Fluoroquinolone, Rifamycin, Oxazolidinone, Nitroimidazole, Diarylquinoline, Benzothiazone.
Remodelling the Existing Antibacterial Drug Classes

<table>
<thead>
<tr>
<th>Antibiotic class</th>
<th>Parent scaffold</th>
<th>Derivatized scaffolds</th>
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</thead>
<tbody>
<tr>
<td>Fluoroquinolones</td>
<td>Nalidixic acid</td>
<td>Gatifloxacin</td>
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<tr>
<td></td>
<td></td>
<td>Moxifloxacin</td>
</tr>
<tr>
<td>Nitroimidazoles</td>
<td>Metronidazole</td>
<td>PA-824</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OPC-67683</td>
</tr>
<tr>
<td>Oxazolidinones</td>
<td>Linezolid</td>
<td>PNU-100480</td>
</tr>
<tr>
<td>1,2-ethylene diamine</td>
<td>Ethambutol</td>
<td>SQ109</td>
</tr>
</tbody>
</table>

New drugs on the horizon

- OPC – 67683 (Delamanid)
  - Nitro dihydro imidazoxoazole
- PA-824; nitroimidazole
  - Combinations with PZA and moxifloxacin
- AZD 5847; oxazolidinone
Remember – the negative stigma of drug-resistant TB is not simply abroad
• Drug resistant TB can be challenging to manage
• Some things in life seem very ‘unnatural’
• But if a basset hound can actually run……then together we can eliminate drug resistant TB!

The End

Questions?
Second Line Anti-TB drugs

Properties and dosing
Fluoroquinolones

• Preferred oral agents for drug-resistant TB if sensitive to this drug or for drug intolerance of any first line agents

• Mechanism of action: DNA gyrase inhibitors

• Potency: moxifloxacin, levofloxacin > ofloxacin, ciprofloxacin

• Avoid in pregnancy

• Better tolerated compared to other 2nd-line agents
  • Adverse effects: GI disturbance, tendinopathy, peripheral neuropathy

• Dose: Levofloxacin 750 - 1,000 mg/day
  Moxifloxacin 400 mg /day
Aminoglycosides

- Resistance Patterns
  - Resistance to amikacin = resistance to kanamycin
  - MTB resistant to streptomycin usually susceptible to amikacin / kanamycin
  - Resistance to amikacin / kanamycin can sometimes induce resistance to streptomycin (variable frequency)

- IM / IV administration; Renal metabolism
- Vestibular/ototoxicity/nephrotoxicity
- Avoid in pregnancy - can cause auditory nerve and renal damage in fetus
Capreomycin

- Polypeptide antibiotic
  - Usually no cross-resistance with aminoglycosides
  - Bactericidal
  - Only available IM/IV
  - Usually given 5-7 times/week
- Auditory/vestibular/renal toxicity
- Do not use in pregnancy
Ethionamide

• Near complete oral absorption
  • Hepatic metabolism

• Avoid in pregnancy - teratogenic

• Concomitant administration of pyridoxine (B6) recommended - similar structure & mechanism as INH

Adverse reactions:

• GI intolerance – (high likelihood) N/V, diarrhea, dysgeusia; metallic taste

• Arthralgias; peripheral neuropathy

• Hypothyroidism; Glucose intolerance
  • Coadministration with PAS increases risk
Cycloserine

- Mechanism: interferes with bacterial cell wall synthesis
- Good CNS penetration
- Oral drug; excreted in urine
- Adverse effects: CNS (headaches, seizures, psychosis, depression), vertigo, peripheral neuritis (give pyridoxine)
  - Avoid in pregnancy unless no alternatives
Para-aminosalicylic acid (PAS)

• Bacteriostatic agent

• Oral: delayed-release granules (acid-resistant outer coating)
  • CSF penetration: 10 - 50%
  • 50% - Hepatic metabolism, 80% - Renal excretion

• Adverse reactions:
  • Bulky, unpleasant taste
  • GI disturbance - anorexia, nausea, vomiting, abdominal discomfort
  • Hypothyroidism, goiter (PAS has anti-thyroid effect)
    • Caution when administering with Ethionamide
  • Hepatic dysfunction
  • Hypersensitivity reaction / skin rash