Drug Resistant Tuberculosis: Pearls and other Considerations

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Disclosure

• none
Objectives

- Describe factors responsible for the delayed response and/or treatment failure
- Describe the treatment and management strategies for multi-drug 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)
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

Seaworth B. IDCNA Vol 16, No. 1, 73-105. March 2002
MDR-TB Prevalence in the United States

• Primary MDR-TB cases 1.3% (98 cases) of all primary TB cases in 2011
  • 82.7% (81 of 98) in 2011 were in foreign-born persons

• Among patients with previous TB history, there were 26 MDR-TB cases
  • 25/26 occurred in foreign-born persons

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%)

MDR-TB Underreporting in Africa

A. Data from Third Global report on Anti-TB Drug Resistance in the World, WHO, 2004

B. Data from WHO publications, peer-reviewed journal articles and WHO’s Fourth Global report

C. Formulaic estimates JID 2006;194:479

Emerg Inf Dis 2008, 14(9): 1345
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
  - Moxi/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)
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
    • [http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5211a1.htm](http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5211a1.htm)
  • New York City Dept. of Health, TB Section, 2008:
  • Francis Curry TB Center / UCSF:
    • [http://www.currytbcenter.ucsf.edu/drtb/drtb_ch3.cfm](http://www.currytbcenter.ucsf.edu/drtb/drtb_ch3.cfm)
Treatment options, regimens and basic approaches for drug-resistant TB
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 1<sup>st</sup> line drug, then add FQ and injectable (amikacin/kanamycin/SM/capreomycin)

• Add oral 2<sup>nd</sup> 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 3<sup>rd</sup> 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**
  - Levofloxacin
  - Moxifloxacin

**PLUS**

- **One of these**
  - 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.

Consider use of these third-line drugs:

- Clofazimine
- Imipenem
- Amoxicillin/clavulanate
- Macrolides
- High-dose isoniazid
- Other / BDQ

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

Expanded Treatment Regimen

- Used initially when suspicion of drug-resistant TB is high
  - In cases of relapse (esp. self-administered or inappropriate therapy), severe disease, or impaired immunity
  - Treatment failure
  - Close contact with MDR-TB case
  - High suspicion of MDR-TB based on country of origin/residence

- Start with all 4 first line drugs
  - Add 2 (or more drugs)-including FQ and injectable
  - For treatment failure, preferably add 3 new drugs
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 $\geq 5$ 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
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
  • Increase to 250 mg/qAM and 500 mg q/PM
    • Check serum level

• 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

Discovery
- Diaryquinolines
- InhA inhibitors
- LeuRS inhibitors
- Mycobacterial gyrase inhibitors
- Pyrazinamide analogues
- Riminophenazines
- Ruthenium (II) complexes
- Spectinamides
- Translocase 1 inhibitors

Preclinical development
- Preclinical development
- GLP toxicology

Clinical development
- Phase I
- Phase II
- Phase III

Chemical classes
- Fluoroquinolone
- Nitroimidazole
- Rifamycin
- Diaryquinoline
- Oxazolidinone
- Benzothiazinone

Nature Reviews | Drug Discovery
## Remodelling the Existing Antibacterial Drug Classes

<table>
<thead>
<tr>
<th>Antibiotic class</th>
<th>Parent scaffold</th>
<th>Derivatized scaffolds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoroquinolones</td>
<td>Nalidixic acid</td>
<td>Gatifloxacin, Moxifloxacin</td>
</tr>
<tr>
<td>Nitroimidazoles</td>
<td>Metronidazole</td>
<td>PA-824, 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>
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New drugs on the horizon

- OPC – 67683 (Delaminid)
  - 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?
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:

- 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

→ *all things considered – this could have been worse!!*

## Susceptibility data from Mayo:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Resistance Level</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></td>
<td></td>
</tr>
<tr>
<td>Streptomycin</td>
<td>&gt; 2 Resistant</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Additional susceptibility data from NJH:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Sensitive Level</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>
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Dr. J Wilson joins staff here..................Takes over patient care
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
  Ethambutol; IV Amikacin; Levofloxacin; Ethionamide; Cycloserine (B6)

- 3 months later developed *hypothyroidism*
- *cause?*
Case Presentation – MDR TB; post-partum

- Started expanded TB drug therapy
  Ethambutol; IV Amikacin; Levofloxacin;
  Ethionamide; Cycloserine (B6)

- 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:
• Cause?
Case Presentation – MDR TB

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

**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):
• Cause?
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
Case Presentation – MDR TB

- GI distress – N/V, upset stomach, ache
- Most likely cause?
  - (levofloxacin, ethionamide, cycloserine and PAS)
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
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