MDR and XDR Tuberculosis

DR. MOHAMMED AMDAD ULLAH KHAN

ASSISTANT PROFESSOR OF MEDICINE

MYMENSINGH MEDICAL COLLEGE

Multidrug-Resistant TB

“I have been treated several times over the past five years and I’m still coughing and can’t gain weight!”

Background

- Tuberculosis (TB) is a major public health problem in Bangladesh since long. Estimates suggest that daily about 880 new TB cases and 176 TB deaths occur in the country.
- Nearly one-third of the global population, i.e. **two billion** people, is infected with Mycobacterium tuberculosis and thus at risk of developing the disease. More than **nine million** people develop active TB every year and about **two million** die.

- More than 90% of global TB cases and deaths occur in the developing world, where 75% of cases are in the most economically productive age group (15-54 years). It is estimated that 480,000 peoples developed MDR TB in 2014 About 190,000 people died as a result of it.

Global status of TB

- Multidrug-resistant TB (MDR-TB) has emerged in nearly every country of the world.
- Extensively drug-resistant TB (XDR-TB) has been identified in **117** countries and in all geographical regions.
- The total number of new TB cases is still **rising** slowly as the case load continues to grow in the African, Eastern Mediterranean and **South-East Asia** regions.

The burden of illness

- Usually 1 in 10 infected people are in chance of developing disease
- Greater risk in poor, malnourished or co-morbities.
- Without treatment, there is more than a 50% chance death in TB.
- The overall goal of TB control is to reduce morbidity, mortality and transmission of TB.

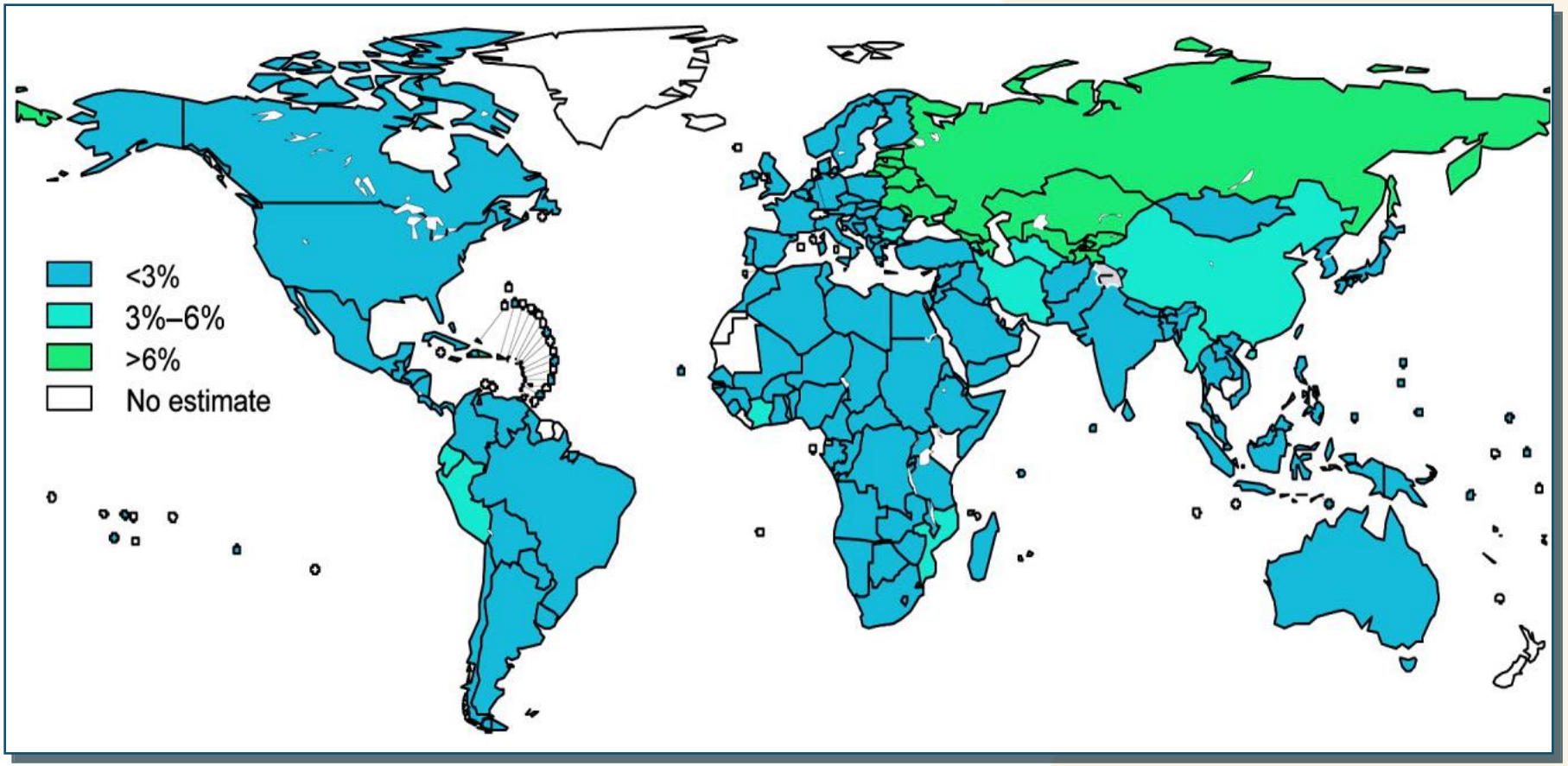
Drug-Resistant Tuberculosis

MDR-TB is a manmade problem… It is costly, deadly, debilitating and is a major threat to our current control strategies.

Drug-Resistant TB: Definitions

- **Multidrug-resistant (MDR):**
  In-vitro resistance to at least isoniazid and rifampicin
- **Extensively drug-resistant (XDR):**
  MDR plus resistance to fluoroquinolones and at least 1 of the 3 second-line injectable drugs (amikacin, kanamycin, capreomycin)

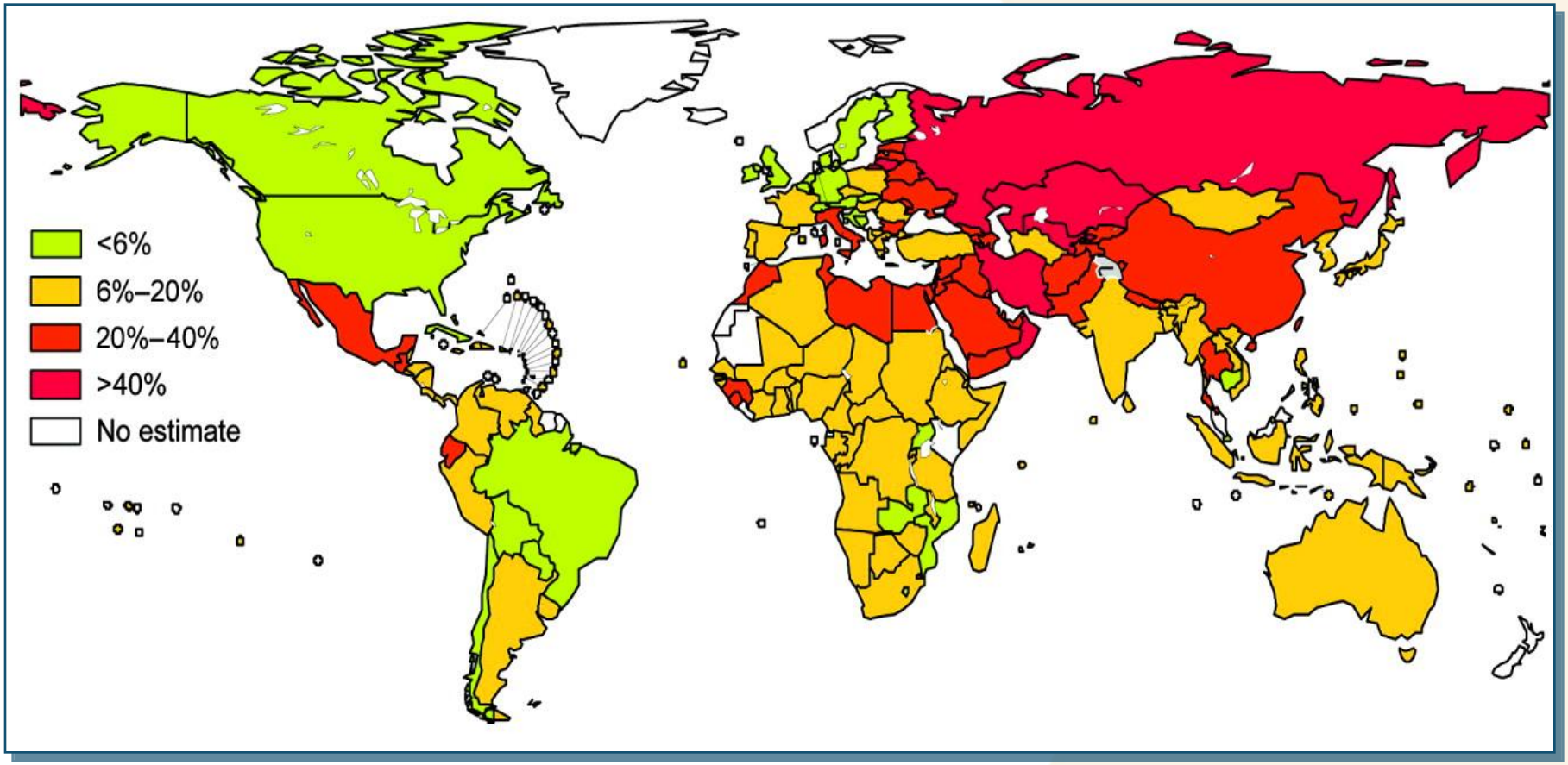
Distribution of MDR: No Prior Treatment



Distribution of MDR rates among new cases (previously untreated)

Zignol M, et al. *JID* 2006; 194: 479-85

Distribution of MDR: Prior Treatment



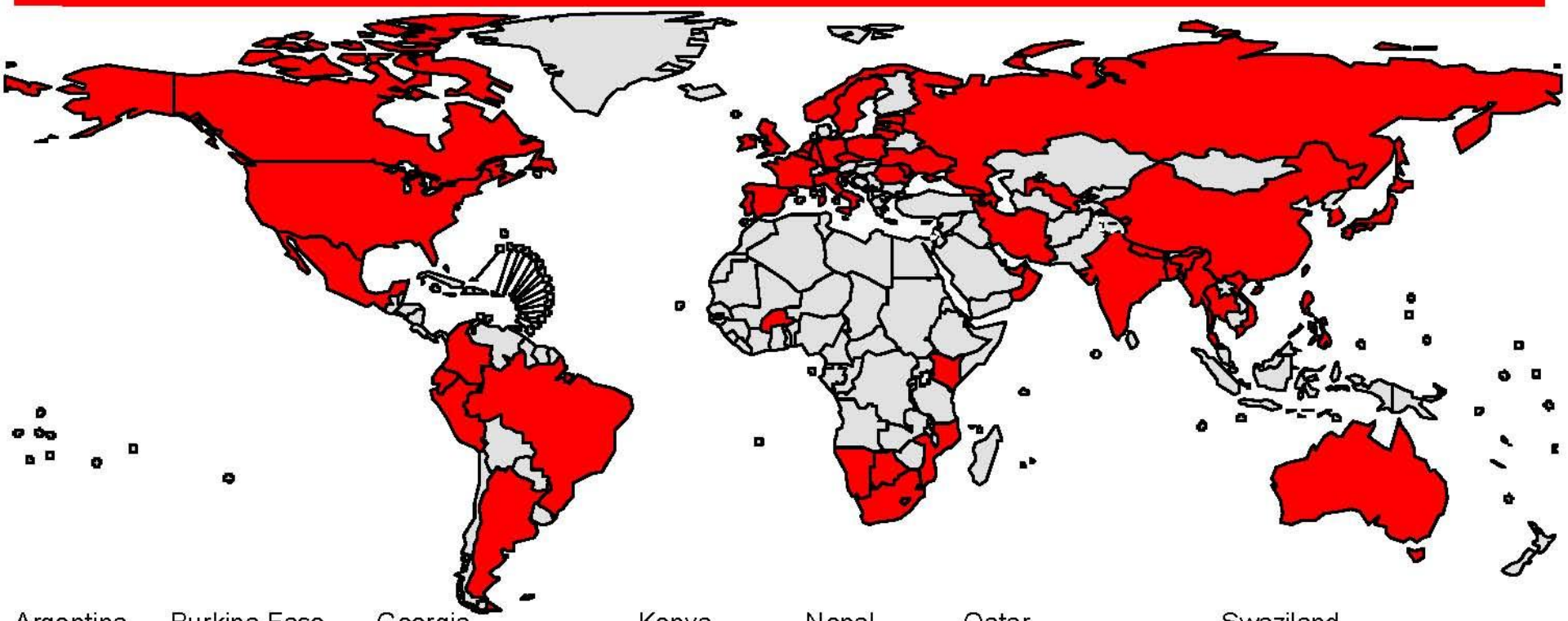
Distribution of MDR rates among previously treated cases

Zignol M, et al. *JID* 2006; 194: 479-85

Countries that had reported at least one XDR-TB case by September 2009

World Health Organization

THE STOP TB DEPARTMENT



Argentina
Armenia
Australia
Azerbaijan
Bangladesh
Belgium
Botswana
Brazil
Burkina Faso
Canada
China
Colombia
Czech Republic
Ecuador
Estonia
France
Georgia
Germany
India
Iran (Islamic Rep. of)
Ireland
Israel
Italy
Japan
Kenya
Latvia
Lesotho
Lithuania
Mexico
Mozambique
Myanmar
Namibia
Nepal
Netherlands
Norway
Oman
Peru
Philippines
Poland
Portugal
Qatar
Republic of Korea
Republic of Moldova
Romania
Russian Federation
Slovenia
South Africa
Spain
Swaziland
Sweden
Thailand
Ukraine
United Arab Emirates
United Kingdom
United States of America
Uzbekistan
Viet Nam

Individual Impact of MDR

- Average direct medical costs per case in the US: $27,752 [Burgos, et al. *CID* 2005; 40: 968-75]
- In BD it is about 15-20 lakh.
- Long treatment duration (18-24 months), often difficult and toxic
- Long periods of isolation may be necessary
- Depression is common
- Disease may be incurable (chronic)
- Higher rate of death

Factors that Lead to Drug Resistance

Causes of inadequate treatment:

- Patient-related factors
- Healthcare provider-related factors
- Healthcare system-related factors

Strategies to Prevent MDR

Common Causes	Interventions
Nonadherence, default	Patient-centered DOT, education, support, incentives
Management errors, lack of expertise	Consultation with experts, vigilant patient monitoring for treatment failure, provider training
Inadequate regimen in presence of drug resistance	Improved access to drugs and susceptibility testing

Diagnosis of MDR-TB

Diagnosis of MDR-TB

Appropriate diagnosis and timely treatment intervention for MDR-TB is facilitated by:

- Recognition of risk factors for MDR-TB
- Early recognition of treatment failure
- Drug-susceptibility testing (DST)

Clinical Suspicion for MDR-TB

Recognition of risk factors:

- History of prior therapy (most powerful predictor)
- History of non-adherence, default
- Residence in an MDR-endemic area
- Exposure to known or suspected MDR-TB case (“incurable” TB or TB requiring multiple treatment courses)
- HIV infection (in some settings)

Clinical Suspicion for MDR-TB (2)

Early recognition of treatment failure:

- Cough should improve within the first two weeks of effective treatment
- **Signs of failure might include:**
  - lack of sputum conversion,
  - persistent or recurrent cough,
  - continued fever and/or night sweats, and
  - failure to gain weight

Laboratory Diagnosis of MDR

Drug-susceptibility testing should be prioritized when:

- Risk factors for MDR are present
- There is evidence of treatment failure

Results can both:

- Confirm diagnosis of drug resistance
- Guide treatment choices

Drug-Susceptibility Test Limitations

- Identification of MDR may take 4–8 weeks, and second-line drug sensitivity testing 6–12 weeks for results
  - 2–4 weeks for initial culture to become positive
  - Additional 2–4+ weeks to get 1st-line susceptibilities
  - Additional 2–4+ weeks (sent to reference laboratory) to get 2nd-line susceptibilities

➡ In view of this inherent delay, don't wait to treat with an augmented regimen if MDR suspicion is high and resistance pattern can be predicted

Treating drug-resistant and MDR-TB

Standard 12: Management of Drug-Resistant TB

- Patients with MDR/XDR TB organisms should be treated with specialized regimens containing 2nd line anti-TB drugs.
- The regimen chosen may be standardized or based on suspected or confirmed DST.
- **At least 4 drugs** to which the organisms are known or presumed to be susceptible, **including an injectable agent**, should be used and treatment should be given for at least **18-24** months beyond culture conversion

Standard 12: Management of Drug-Resistant TB (2)

- Patient-centered measures, including observation of treatment, are required to ensure adherence
- Consultation with a provider experienced in treatment of patients with MDR/XDR tuberculosis should be obtained

Conditions to be consider before treatment

- Malnutrition
- Diabetes mellitus
- Renal insufficiency
- Liver disease
- Thyroid disease
- Mental illness
- Pregnancy
- Seizure
- HIV infection

Treatment Strategies

Recommended MDR-TB treatment approaches:

- *Standard regimen*
  - Settings where **DST is not readily available**
  - Based on drug-resistance surveillance data or history of drug usage in country
- *Individualized treatment regimen*
  - Based on patient's past history of drug use and on DST results
  - Ideal, but resources must be considered

WHO/HTM/TB/2009.420

Anti-tuberculosis Drug Groups

Group 1 **First-line drugs:** isoniazid, rifampicin, ethambutol, pyrazinamide

Group 2 **Injectable agents:** streptomycin, kanamycin, amikacin, capreomycin

Group 3 **Fluoroquinolones:** ofloxacin, levofloxacin, moxifloxacin

Group 4 **Oral bacteriostatic agents:** ethionamide, protionamide, cycloserine, para-aminosalicylic acid (PAS)

Group 5 **Agents with unclear role in drug-resistant treatment**: Amoxicillin/clavulanate, linezolid, clofazimine, imipenem/cilastatin, high-dose INH

Treatment Principles

- Use direct observation of treatment (DOT)
- Use daily, not intermittent, administration
- Treatment duration of a minimum of 18-24 months
- When possible, continue injectable for at least six months post-culture conversion
- Continue at least three oral drugs for full treatment duration

Standardized Treatment Regimens

Intensive Phase
(minimum 8 months)

- kanamycin
- Ethionamide
- PZA
- Levofloxacin
- (Ethambutol)
- cycloserine

Continuation Phase
(minimum 12 months)

- Ethionamide
- Levofloxacin
- PZA
- cycloserine
- (Ethambutol)

Use ethambutol in both phases of treatment if strains are still susceptible.

Bangladesh short course regimen

- Total treatment duration -9 to 12 months
- **Initial phase(4-6 months):**

  Kanamycin, moxifloxacin, prothionamide, clofazamine, pyrazinamide, high dose of isoniazide , ethumbutol
- **Continuation phase(5 months)**
  Moxifloxacin, clofazimine,pyrazinamide ethumbutol

Cross-Resistance: WHO

- **All rifamycins:** high level cross-resistance
- **Fluoroquinolones:** variable, but probably should be assumed to be cross-resistant
- **Amikacin and kanamycin:** generally highly cross-resistant, but both should be tested
- **Capreomycin and aminoglycosides:** occasional cross-resistance, susceptibilities should be tested

Drug Contraindications: WHO

- Known severe drug allergy
- Unmanageable drug intolerance
- Risk of severe toxicity, with symptoms such as renal failure, hepatitis, hearing loss, depression, and psychosis
- Drugs of unknown quality.

Directly Observed Treatment

Effect on Resistance and Relapse

	Self-RX N = 407 (pre 1987)	**DOT** N = 581 (1987 +)
Primary R	13.0%	6.7%
Secondary R	10.3%	1.4%
Relapse	20.9%	5.5%
MDR relapse	6.1%	0.9%

* $P < 0.001$

Weis SE, et al. *NEJM* 1994; 330(17): 1179-84

Monitoring

- Collect sputum specimens for smear and culture **monthly during treatment until culture negative** then periodically until treatment completed
- Obtain **end-of-treatment sputum** specimen for smear and culture
- Clinical evaluation **monthly** until culture conversion then every 2-3 monthly
- Perform chest radiograph periodically during treatment and at end of treatment
- **Post-treatment:** monitor quarterly during first year, then every 6 months during second year

Treatment of XDR TB (Standard Regimen)

- **Intensive phase(12 months):**
  - Capreomycin, pyrazinamide, moxifloxacin,para-aminosalicyclic acid, cycloserine, amoxicillin/clavulanate, linezolide,cofazimine
- **Continuation phase(12 months):**
  - Pyrazinamide, moxifloxacin, para-aminosalicyclic acid, cycloserine, amoxicillin/clavulanate, linezolide,cofazimine

Common Adverse Effects

Adverse Effect	Potentially Offending Drug
G.I. complaints	Ethionamide Cycloserine PAS Fluoroquinolones Clofazimine
Hepatotoxicity (early symptoms are anorexia and malaise, then abdominal pain, vomiting, jaundice)	Ethionamide PZA PAS Fluoroquinolones

Common Adverse Effects (2)

Adverse Effect	Potentially Offending Drug
Peripheral neuropathy	Ethionamide Cycloserine Linezolid
Rash	All
Headache	Fluoroquinolones Cycloserine Ethionamide Ethambutol
Seizures	Cycloserine

Common Adverse Effects (3)

Adverse Effect	Potentially Offending Drug
Hypothyroidism	Ethionamide, PAS
Hearing loss, Vestibular toxicity	Aminoglycosides, Capreomycin
Behavioral changes	Cycloserine, Ethionamide, Fluoroquinolones
Visual changes	Ethambutol, Rifabutin, Linezolid
Renal failure Hypokalemia, Hypomagnesemia	Aminoglycosides, Capreomycin

Summary

- Treatment of MDR-TB is complex and costly. It is much easier to prevent than to treat
- Expert consultation should be obtained when MDR-TB is suspected
- Patients can be treated with a standardized or an empiric regimen
- Ideally the regimen should be guided by drug-susceptibilities

Summary……

- Considerable attention must be paid to treatment supervision and support
- A patient-centered approach to DOT is an important element of successful care
- Adverse effects of second-line drugs are common and may be severe. Monitoring for these effects is essential!


Thank You!