Challenges to treat MDR TB

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2nd European Advanced Course in Clinical Tuberculosis
22-24 September 2014, Amsterdam
MDR-TB control; WHO Europe, 2012

- Estimated total: 76,000
- Estimated target: 66,000
- Notified as MDR-TB: 41,000
- Enrolled for treatment: 40,000
- Cured (2010): 13,000

ECDC, Surveillance Report, 2014

Global number of estimated M/XDR TB cases (2012) ~ 450,000
A.1.4 Classification based on drug resistance

Cases are classified in categories based on drug susceptibility testing (DST) of clinical isolates M. tuberculosis:

- **Monoresistance**: resistance to one first-line anti-TB drug only.

- **Polydrug resistance**: resistance to more than one first-line anti-TB drug (other than both isoniazid and rifampicin).

- **Multidrug resistance**: resistance to at least both isoniazid and rifampicin.

- **Extensive drug resistance**: resistance to any fluoroquinolone and to at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin), in addition to multidrug resistance.

- **Rifampicin resistance**: resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin, whether monoresistance, multidrug resistance, polydrug resistance or extensive drug resistance.
Republic of Estonia: Situation of TB

✓ Population – 1.32 million people
✓ 263 newly diagnosed and relapses TB cases in 2013
✓ TB incidence
  - 17.1 new cases per 100 000 population,
  - 21.8 all TB cases per 100 000
✓ 11.4% TB patients co-infected with HIV (n=30)
✓ 50% of them IDU-s (n=15)
✓ High rate of M/XDR-TB
  ~ 20% of newly diagnosed culture positive pulmonary TB are MDR
  ~50% of previously treated culture positive pulmonary TB cases are MDR
• There are Guidelines but few recommendations are based on a strong evidence
• The best Guidelines are useless if the drugs are not available
• The best drugs are useless if the patients do not tolerate them or poor case holding
Management of patients with multidrug-resistant/extensively drug-resistant tuberculosis in Europe: a TBNET consensus statement

Christoph Lange, Ibrahim Abubakar, Jan-Willem C. Alffenaar, Graham Bothamley, Jose A. Caminero, Anna Cristina C. Carvalho, Kwok-Chiu Chang, Luigi Codecasa, Ana Correia, Valeriu Crudu, Peter Davies, Martin Dedicoat, Francis Drobniewski, Raquel Duarte, Cordula Ehlers, Connie Erkens, Delia Goletti, Gunar Günther, Elmira Ibraim, Beate Kampmann, Liga Kuksa, Wiel de Lange, Frank van Leth, Jan van Lunzen, Alberto Matteelli, Dick Menzies, Ignacio Monedero, Elvira Richter, Sabine Rüscher-Gerdes, Andreas Sandgren, Anna Scardigli, Alena Skrahina, Enrico Tortoli, Grigory Volchenkov, Dirk Wagner, Marieke J. van der Werf, Bhanu Williams, Wing-Wai Yew, Jean-Pierre Zellweger and Daniela Maria Cirillo for the TBNET

ABSTRACT The emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis (TB) substantially challenges TB control, especially in the European Region of the World Health Organization, where the highest prevalence of MDR/XDR cases is reported. The current management of patients with MDR/XDR-TB is extremely complex for medical, social and public health systems. The treatment with currently available anti-TB therapies to achieve relapse-free cure is long and undermined by a high frequency of adverse drug events, suboptimal treatment adherence, high costs and low treatment success rates. Availability of optimal management for patients with MDR/XDR-TB is limited even in the European Region. In the absence of a preventive vaccine, more effective diagnostic tools and novel therapeutic interventions the control of MDR/XDR-TB will be extremely difficult. Despite recent scientific advances in MDR/XDR-TB care, decisions for the management of patients with MDR/XDR-TB and their contacts often rely on expert opinions, rather than on clinical evidence.
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ERS J. 2014; 44 (1) 23-63

Treatment success rates of MDR/XDR-TB vary between 36% and 79% [5, 6]. The 2013 joint WHO and European Centre for Disease Prevention and Control (ECDC) surveillance report recorded only 31.6% successful treatment outcome for MDR/XDR-TB cases in the European Union (EU)/European Economic Area (EEA) region [7], comparable to the situation in the pre-antibiotic era [8]. It is estimated that, globally, <20% of patients with pulmonary MDR/XDR-TB are currently receiving adequate treatment [2]. The current high frequency of adverse drug events, suboptimal treatment adherence, high costs and low treatment success rates. Availability of optimal management for patients with MDR/XDR-TB is limited even in the European Region. In the absence of a preventive vaccine, more effective diagnostic tools and novel therapeutic interventions the control of MDR/XDR-TB will be extremely difficult. Despite recent scientific advances in MDR/XDR-TB care, decisions for the management of patients with MDR/XDR-TB and their contacts often rely on expert opinions, rather than on clinical evidence.
Main challenges in management of MDR/XDR TB

- Delay with diagnosis. Lack of QA laboratories
- Limited access to M/XDR-TB treatment
- Weak control over the use of second-line drugs
- High cost of SL drugs
- Problem of DR paediatric cases is often underestimated
- Increasing number of HIV infected DR cases
- Treatment of migrants (stigma, not regulated, high default rate)
- Lack of infection control measures (transmission in hospitals)
- Management of adverse effects needs more experience
- Poor adherence to treatment and too long treatment period
- The current use of new TB drugs is not regulated. Many countries are not ready to get access to these drugs
• Conditions and possibilities to treat MDR TB patients are different in low incidence countries and in high burden settings

• In several WHO EUR Region countries proper treatment of M/XDR-TB patients became available only 2-3 years ago and many of them are financially fully donor dependent

• Despite of WHO guidelines, there are still variability of treatment regimens often not effective
ERS-WHO e-Consilium (https://tbconsilium.org/)

- In order to improve the clinical management of difficult to treat TB and M/XDR-TB cases and support countries of the Region, WHO/Europe, in collaboration with the European Respiratory Society (ERS) has launched an electronic consilium adding to the programmatic benefits brought to you by the regional Green Light Committee/Europe (GLC).

- The e-consilium focuses on provision of scientifically sound and evidence-based clinical advice through internet to national consilium and individual practitioners on the management of MDR-TB and other difficult-to-treat TB cases, including TB/HIV and paediatric cases.
Anti-TB medications: first- second- and third line drugs:

**First-line Drugs**
- Isoniazid
- Rifampicin
- Pyrazinamide
- Ethambutol

**Second-line Drugs**
- Streptomycin
- Kanamycin
- Amikacin
- Capreomycin
- INJECTABLES
- Ciprofloxacin
- Ofloxacin
- Levofloxacin
- Moxifloxacin

**Third-line Drugs**
- Third-line Drugs (Unclear efficacy)
  - Cycloserine
  - PAS
  - Ethionamide
  - Prothionamide
  - Linezolid
  - Imipenem,
  - Meropenem
  - High-dose INH
  - Amoxicillin/ Clav. Acid
  - Clarithromycin
  - Clofazimine

**New drugs**: *Bedaquiline (Sirturo*) *Delamanide (Deltyba*)
Treatment was individualized in 26 studies with 5,985 patients, and standardized in six studies with 2,968 patients. A total of 200 patients in two centers received standardized regimens with first-line drugs only; all remaining patients received second-line drugs. In all but one study, the outcome definitions for treatment success and failure were judged the same or similar to the consensus definitions. Overall 4,934 (54%) of patients were judged to have treatment success, 732 (8%) failed or relapsed, 1,392 (15%) died, and 2,095 (23%) defaulted.

This individual patient data meta-analysis of 9,153 patients suggests that treatment of MDR-TB should include a later generation quinolone, and ethionamide or prothionamide, the optimal number of likely effective drugs appears to be at least four in the initial intensive phase, and at least three in the continuation phase.

Principles of designing an MDR-TB treatment regimen

1. Include at least four second-line anti-TB drugs likely to be effective as well as pyrazinamide during the intensive phase. More than four SLD drugs is recommended if the effectiveness of some of drugs is uncertain.

2. The continuation phase should contain at least three SLD drugs (pyrazinamide should also be continued if extensive lung damage is present). More than three SLD drugs is recommended if the effectiveness of some of the drugs is uncertain.

3. Include a fluoroquinolone - a higher generation (levofloxacin or moxifloxacin) is strongly preferred.

4. Ethambutol can be included but is not counted as a core drug in the regimen.

5. Consider drug resistance data (of individual or region) and patient treatment history when designing a regimen.

6. The intensive phase should be at least 8 months and at least 4 months past conversion (whichever is longer).

7. Total duration of treatment should be at least 20 months and at least 18 months past conversion.
Possible treatment strategy

- Standard treatment for MDR-TB
  - Rapid diagnostic tests used
  - High risk groups of MDR-TB, in a certain population established

- Individual treatment for MDR-TB
  - High quality bacteriology laboratory is requested
  - Individualized treatment regimen designed on DST results of individual patient for \( I \) and \( II \) line drugs

- Empiric MDR-TB treatment (New cases with high risk of MDR-TB)
  - MDR-TB contacts
  - Rapid DST not available
  - Tx regimen according source case DST patterns
WHO recommended standard treatment regimen for MDR TB case

8ZKa(Ca, Am)LfxPtoCs (PAS) /12LfxPtoCs

(strong recommendation, low quality evidence)
Treatment of XDR-TB

- In the case of quinolone and injectable drug resistance, treatment choice are limited
- Linezolid and any remaining injectable become the main drugs of treatment, along with whatever oral medications are left to which there is in vitro susceptibility
- Include a higher generation fluoroquinolone - moxifloxacin despite of DST data (resistance to ofloxacin)
- Use of Bedaquiline or Delamanide
- Surgery if disease is localized
- Consider: some patients may not be treatable
• **The two strongest risk factors for XDR-TB:**

  – Failure of MDR-TB treatment regimen, which contains second line drugs including injectables and fluoroquinolones
  – Close contact with documented XDR-TB patients
Linezolid (Zyvoxid)

- Linezolid was found to be a good adjunctive medication when no other drugs are available.
- Excellent activity against *M. tb in vitro*.
- Recommended daily dose - 600 mg.
- High cost of therapy - can be reduce with useing generic formulas.
- Might have serious side effects - myelosuppression, peripheral neuropathy, changes in vision.
- There is a need for further clinical trials (on-going).

Linezolid seems highly active in combination treatment of MDR-TB.
Migliori GB, et al "Efficacy and tolerability of linezolid in the treatment of MDR-TB cases: a TBNET study in Germany and Italy" *ERS* 2008; Abstract 1356.
The key principles in the management of adverse effects

- MDR TB patients have side effects even better medical care is provided.
- The majority of side effects are not severe and can be managed without discontinuation of therapy.
- Some side effects and toxicities are life-threatening if not recognized and treated promptly.
- If side effects are not well managed, there is a higher risk of default and treatment failure.
- Strategies must be in place to support such patients and to avoid potential refusal of treatment due to adverse drug effects.
- If adverse drug effects occur, ancillary drugs should be available.
- Permanent discontinuation of one or more drugs or replacement with other drugs may be required.
<table>
<thead>
<tr>
<th>Substance</th>
<th>Common adverse effects</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group I</strong></td>
<td></td>
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</tr>
<tr>
<td>Ethambutol</td>
<td>Optic neuropathy</td>
<td>Inform the patient to report decreased vision immediately. Discontinue and refer to an ophthalmologist if vision deteriorates. More likely to occur in patients with renal impairment. For hepatotoxicity, stop the drug; reintroduce in an escalating dose over several days. Discontinue drug if hepatotoxicity reoccurs. For rash, manage symptomatically; if extensive, stop drug and consider reintroduction. Discontinue if rash reoccurs. For gout, reduce dose initially and consider starting allopurinol when acute attack has settled.</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Hepatotoxicity, rash, gout</td>
<td></td>
</tr>
<tr>
<td><strong>Group II</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amikacin</td>
<td>Ototoxicity, nephrotoxicity</td>
<td>Monitor levels, hearing and renal function monthly. If problems occur, consider reducing dose frequency to three times a week. Discontinue if problems persist, but balance risk of cure versus deafness. Monitor levels, hearing and renal function monthly. If problems occur, consider reducing dose frequency to three times a week. Discontinue if problems persist, but balance risk of cure versus deafness. Monitor levels, hearing and renal function monthly. If problems occur, consider reducing dose frequency to three times a week. Discontinue if problems persist, but balance risk of cure versus deafness.</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>Ototoxicity, nephrotoxicity</td>
<td></td>
</tr>
<tr>
<td>Kanamycin</td>
<td>Ototoxicity, nephrotoxicity</td>
<td></td>
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<tr>
<td><strong>Group III</strong></td>
<td></td>
<td></td>
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<tr>
<td>Levofoxacin</td>
<td>GI disturbances, tendinitis, insomnia</td>
<td>QT interval prolongation may be potentiated with other drugs</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>GI disturbances, tendinitis, insomnia</td>
<td>QT interval prolongation may be potentiated with other drugs</td>
</tr>
<tr>
<td><strong>Group IV</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAS</td>
<td>Nausea and vomiting, gastritis, hepatotoxicity, hypothyroidism</td>
<td>Rehydrate if necessary. Give antiemetics 30 min before the medication; several classes of antiemetic may need to be tried. Twice or three times a day divided dose may help. Gastritis can be helped by administering the drug with a small amount of food or giving an antacid or H2 blocker. For hypothyroidism, check TFT. As above. Depression can be treated with an antidepressant if other causes excluded. Give high-dose pyridoxine, up to 50 mg for every 250 mg of drug. If neuropathy progresses, discontinue drug. Discontinue if psychosis develops. Seizures can be managed with anticonvulsants, but drug may need to be discontinued.</td>
</tr>
<tr>
<td>Prothionamide/ethionamide</td>
<td>GI disturbances, depression, hepatotoxicity, hypothyroidism</td>
<td></td>
</tr>
<tr>
<td>Terizidone/cycloserine</td>
<td>Neurotoxicity, peripheral neuropathy</td>
<td></td>
</tr>
<tr>
<td><strong>Group V</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin/clavulanic acid</td>
<td>Hypersensitivity, GI disturbances</td>
<td>Not suitable for patients with penicillin allergy. Inform the patient about discoloration of skin and body fluids. Monitor blood count. Monitor blood count; avoid prolonged use, when possible. Stop if peripheral neuropathy or haematological problems occur. Give with pyridoxine. Give with pyridoxine.</td>
</tr>
<tr>
<td>Clofazimine</td>
<td>Skin discolouration, GI disturbances</td>
<td></td>
</tr>
<tr>
<td>Imipenem</td>
<td>Hypersensitivity, neurotoxicity</td>
<td></td>
</tr>
<tr>
<td>Meropenem</td>
<td>Hypersensitivity, neurotoxicity</td>
<td></td>
</tr>
<tr>
<td>Linezolid</td>
<td>Neuropathy, anaemia</td>
<td></td>
</tr>
<tr>
<td>Isoniazid [high dose]</td>
<td>Peripheral neuropathy, hepatotoxicity</td>
<td></td>
</tr>
</tbody>
</table>
Rationale and Indications for surgery

- Remove pulmonary tissue which serve as source for bacterial infection
- Medications have inadequate penetratation into dead, fibroses or cavitary tissue
- Surgery is an important adjunct to cure certain patients with cavities, damaged lung tissue and high-grade resistance
- Localized cavities or extensive but focal pulmonary damage
- At least 3 effective drugs is still available
- Hemoptysis or other sequelae of pulmonary destruction (e.g. Aspergillumoma, bronquiectasia, broncho-pleural fistula, empyema)
Need for shorter regimens - Yes

- Bangladesh Regimen (success rate: 87%)

**Am J Respir Crit Care Med Vol 182. pp 684–692, 2010**

- STREAM trial
  - STREAM is a randomised controlled trial currently being conducted in Ethiopia, South Africa and Vietnam
  - The control regimen is the locally used WHO recommended regimen in the participating countries
  - The study regimen is closely similar to the regimen used in Bangladesh with the exception that high dose moxifloxacin replaces high dose gatifloxacin

**Successful 9-month Bangladesh regimen for MDR-TB among over 500 patients.**

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<table>
<thead>
<tr>
<th>Drug</th>
<th>Months**</th>
<th>Drug doses by weight group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kanamycin*</td>
<td>1-4</td>
<td>&lt; 33 kg</td>
</tr>
<tr>
<td>Isoniazid (H)</td>
<td>1-4</td>
<td>15 mg per kilogramme body weight</td>
</tr>
<tr>
<td>Prothionamide</td>
<td>1-4</td>
<td>300 mg</td>
</tr>
<tr>
<td>Clofazimine</td>
<td>1-9</td>
<td>250 mg</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>1-9</td>
<td>50 mg</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>1-9</td>
<td>400 mg</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>1-9</td>
<td>800 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1000 mg</td>
</tr>
</tbody>
</table>

* Kanamycin 3 times/week in month 4
** The intensive phase can be extended to 6 months

www.controlled-trials.com/ISRCTN78372190/STREAM
Case: Female, 29 years

- Patients with cavitary PTB, sputum smear positive, new case, HIV -, 55 kg
- Admitted to the hospital in June 2013
- Patient had close contact with MDR-TB patients, good clinical condition
- HAIN MTBDR sl + MGIT
- Resistance to S, H, R, E, Z,OF, Pt
- Susceptible to Ka, Am, Ca, Mfx, Lzd (not tested to Cy, PAS)
- Treatment started on June 21, 2013

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capreomycine</td>
<td>1,0</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>1,5</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>0,4</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>0,5</td>
</tr>
<tr>
<td>PAS</td>
<td>8,0</td>
</tr>
<tr>
<td>Linezolide</td>
<td>0,6</td>
</tr>
</tbody>
</table>
Case, female, 29 y

- During next 3 months she had several serious side effects related to Ca, Am, PAS, Z and Mfx
  - high grade of allergy with rash
  - diarrhoea, severe headache
  - temperature 39-40

- Final adapted regimen from 09.2013:
  Ka 1,0; PT 0,5; CY 0,5; Lfx 0,75; Lzd 0,6

- Patient defaulted in Nov, 2013

- Refused any treatment, still sm+/c+
Case, Female, 29 y 55 kg

- Forced isolation from (according to law, by court order)
  18.11.2013 - 05.2014
- New treatment:
  Ka 1,0 (3x week); PT 0,5; CY 0,5; Lfx 1,0; Lzd 0,6; **Bedaquiline** 400mg-200 mg (3x week)
- Smear conversion from Dec, 2013 and culture conversion from March, 2014 (after 8 m of Tx)
- Current treatment:
  - Cy 0,5; PAS 8,0 Lfx 1,0
Conclusions

• DR-TB poses a serious challenge to TB care and prevention
• Standardized Tx of susceptible TB is priority to prevent MDR cases
• MDR/XDR-TB treatment needs special skills and expertize
• MDR-TB treatment programs must address potential barriers to treatment adherence (e.g. patient side effects, socioeconomic factors)
• Availability of rapid molecular tests that can detect DR to SLDs and availability of new generation of TB drugs are very positive trends
• There is a need for shorter and more effective treatment
• Last moment to set up strict rules how to use new drugs and to avoid the development of further drug resistance
Thank You!