TB Updates for the Physician
Rochester, Minnesota
June 19, 2009

XDR-TB: Epidemiology, Management and Control
G.B. Migliori
WHO Collaborating Centre for Control of TB and Lung Diseases, Fondazione S. Maugeri, IRCCS, Tradate, Italy

XDR-TB: epidemiology, management and control
Rochester, June 19th, 2009

G.B. Migliori
WHO Collaborating Centre for Control of TB and Lung Diseases, Fondazione S. Maugeri, IRCCS, Tradate, Italy
Objectives

To describe
- the epidemiology
- the management issues
- the control strategies
of XDR-TB in HIV-negative and positive individuals

Outline

- Introduction: XDR, a sexy topic
- Definition
- Epidemiology
- Management
- Control
Outline

• Introduction: XDR, a sexy topic
• Definition
• Epidemiology
• Management
• Control

XDR-TB in the News: 5/07-8/07

The flying lawyer

References Per Million

- News
- Business
- Entertainment
- Sports
- Other
- Total
In Italia la Tbc che resiste ai farmaci
Allarme dell’Oms: scoperti 8 casi del ceppo più pericoloso
Defining priorities: swine-origin H1N1 and the MDR-TB epidemic

In the response to the emergence of a novel H1N1 influenza virus and its subsequent spread worldwide, we would like to ensure that existing global health priorities are not neglected. Tuberculosis is a respiratory pandemic priority, affecting an estimated 9.27 million people and killing 1.77 million worldwide in 2007. Multidrug-resistant tuberculosis (MDR-TB; 511,000 cases, 150,000 deaths estimated in 2007) has a case-fatality rate of 294 per 1000 affected individuals, and extensively drug resistant tuberculosis (XDR-TB; 50,000 cases and 30,000 deaths estimated in 2007) has a case-fatality rate of 600 per 1000 affected cases. This means 1.13 daily deaths in Mexico and 0.1 in the rest of the world for influenza H1N1 and 410.9 and 82.2 daily deaths, respectively, for MDR-TB and XDR-TB. In the given situation, vigilance is important but the fight against the true priorities should continue. While the media reported extensively on the novel influenza virus, WHO and the US Centers for Disease Control and Prevention stopped using the term “swine flu” to prevent the collapse of the swine products market, WHO declared phase 5 (the current definition does not consider mortality), and the World Health Assembly was shortened, rescheduling and then reintroducing the planned discussion on the MDR-TB emergency. It seems that under media pressure, the scientific community has lost its capacity to keep priorities in check and to manage the new challenge in a collaborative and non-vertical manner...

Giovanni Battista Migliori, Giovanni Sotgiu, Christoph Lange, Gavin Macgregor-Skinner

giovannibattista.migliori@fsm.it
The STOP TB Strategy - 2009

1. **Pursue high-quality DOTS expansion and enhancement**
   a. Political commitment with increased and sustained financing
   b. Early detection, and diagnosis through quality-assured bacteriology
   c. Standardised treatment, with supervision and patient support
   d. An effective drug supply and management system
   e. Monitoring & evaluation system, and impact measurement

2. **Address TB-HIV, MDR-TB and other challenges**
   a. Scale-up TB/HIV collaborative activities
   b. Scale-up prevention and management of multidrug-resistant TB
   c. Address TB contacts, the poor and other highly vulnerable groups, prisoners, refugees, etc

3. **Contribute to health system strengthening**
   a. Participate in improvement of health policies, human resources, financing, supplies, service delivery, and information
   b. Innovate, introducing the Practical Approach to Lung Health (PAL), infection control, upgraded laboratory networks, etc
   c. Adapt successful approaches from other fields and sectors

4. **Engage all care providers**
   a. Involve all public, voluntary, corporate and private providers through Public-Private Mix (PPM) approaches
   b. Promote use of the International Standards for TB Care (ISTC)

5. **Empower people with TB, and communities**
   a. Pursue advocacy, communication, and social mobilization
   b. Foster community participation in TB care
   c. Promote the Patients' Charter for Tuberculosis Care

6. **Enable and promote research**
   a. Conduct programme-based operational research and introduce new tools into practice
   b. Advocate, and participate in research to develop new diagnostics, drugs and vaccines

---

New WHO Guidelines with focus on XDR-TB
Outline

• Introduction: XDR, a sexy topic
• Definition
• Epidemiology
• Management
• Control
**XDR** = HR + 1 FQ + 1 Injectable (KM or AMK or CM)

**1st-line oral**
- INH
- RIF
- PZA
- EMB
- (Rfb)

**Injectables**
- SM
- KM
- AMK
- CM

**Fluoroquinolones**
- Cipro
- Oflox
- Levo
- Moxi
- (Gati)

**Oral bacteriostatic 2nd line**
- ETA/PTA
- PASA
- CYS

**Unclear efficacy**
- Not routinely recommended, efficacy unknown, e.g., amoxacillin/clavulanic acid, clarithromycin, clofazamine, linezolid, imipenem/cilastatin, high dose isonizid
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Prevalence (%) of MDR-TB among new cases 1994-2007

* Sub-national coverage in India, China, Russia, Indonesia.

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not be full agreement. © WHO 2006. All rights reserved.
Top 19 settings with MDR among new cases > 6% (1994-2007)

Indicates survey data reported in an earlier phase of the project

Trend of MDR-TB among new cases, Estonia, Latvia and... Tomsk Oblast, RF
The South African warning (2005-6)

- Msinga district: 1,539 TB, 542 C+, 221 MDR and 53 “possibile” XDR
- 52/53 XDR died (16 day median survival)
- All 44 cases tested HIV +
- 15 died in ARV treatment (2 staff)
- 26 XDR (51%): new cases
- 39/46 (85%) with genotyping had similar strains.

TB Treatment Outcomes, by Selected Drug Resistance Patterns, Latvia, 2000-2003*

(from N = 820 evaluated)

Number of MDR and XDR Cases, by Countries Submitting ≥ 1 M. tuberculosis Isolate to Participating SRLs, 2000–2004

Total MDR= 3,520; XDR= 347 (~ 10% of MDR)
Countries with confirmed XDR-TB cases as of January 2009

THE BEIJING "CALL FOR ACTION" ON TUBERCULOSIS CONTROL AND PATIENT CARE: TOGETHER ADDRESSING THE GLOBAL M/XDR-TB EPIDEMIC

We recognize that countries have not yet fully addressed the possible causes of M/XDR-TB:

- Causes related to inadequate treatment
- Causes related to transmission
- Causes related to the underlying social determinants
Outline

- Introduction: XDR, a sexy topic
- Definition
- Epidemiology
- Management: diagnosis
- Control
Table 4. Pooled summary estimates for rifampicin resistance

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Pooled Sensitivity (95% CI)</th>
<th>Pooled Specificity (95% CI)</th>
<th>Pooled LR+ (95% CI)</th>
<th>Pooled LR- (95% CI)</th>
<th>Pooled DOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All rifampicin emds (14)</td>
<td>98.7 (95.9–99.1)</td>
<td>98.7 (97.3–99.4)</td>
<td>78.0 (0.02)</td>
<td>4010.1 (1205.9–13335.2)</td>
<td></td>
</tr>
<tr>
<td>Only MTBDRplus assays (4)</td>
<td>98.4 (95.1–99.5)</td>
<td>98.9 (96.8–99.7)</td>
<td>95.3 (0.02)</td>
<td>6150.7 (1061.8–35289.9)</td>
<td></td>
</tr>
<tr>
<td>Only clinical specimens (9)</td>
<td>98.6 (95.5–99.6)</td>
<td>98.5 (96.9–99.3)</td>
<td>66.3 (0.01)</td>
<td>4659.3 (1064.6–20391.3)</td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; DOR, diagnostic odds ratio; LR, likelihood ratio

Figure 2. Forest plot of sensitivity & specificity estimates for rifampicin resistance (all 14 studies, regardless of specimen type or assay version)

Table 5. Pooled summary estimates for isoniazid resistance

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Pooled Sensitivity (95% CI)</th>
<th>Pooled Specificity (95% CI)</th>
<th>Pooled LR+ (95% CI)</th>
<th>Pooled LR- (95% CI)</th>
<th>Pooled DOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All isoniaizid studies (15)</td>
<td>84.3 (76.6–89.8)</td>
<td>99.5 (97.5–99.9)</td>
<td>190.6 (0.16)</td>
<td>1210.8 (175.3, 8301.5)</td>
<td></td>
</tr>
<tr>
<td>Only MTBDRplus assays (5)</td>
<td>88.7 (82.4–92.3)</td>
<td>99.2 (95.4–99.8)</td>
<td>112.6 (0.11)</td>
<td>986.8 (135.6, 7265.9)</td>
<td></td>
</tr>
<tr>
<td>Only clinical specimens (10)</td>
<td>84.5 (72.1–92.0)</td>
<td>99.2 (96.4–99.8)</td>
<td>110.1 (0.15)</td>
<td>706.6 (97.7, 5110.8)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 4. Forest plot of sensitivity and specificity estimates for isoniaizid resistance (all 15 studies, regardless of specimen type or assay version)

DL Ling, M Pai, ERJ 08
From Z-N to Fluorescence

FluoLED Amplified fluorescence by transmitted excitation of radiation
A revolutionary concept in fluorescence microscopy

FRAEN
Development of a standardized MDR/XDR-TB assessment and monitoring tool

Giovanni Battista Migliori*, Giovanni Sotgiu^, Ernesto Jaramillo#, Fuad Mirzayev#, Rosella Centis*, Charlotte Colvin†, M. D’Arcy Richardson†

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The MDR/XDR TB Assessment and Monitoring Tool was developed to standardize evaluations of country capacity, to prevent, diagnose, and treat MDR/XDR-TB and identify program gaps. It provides data to guide national plans; generates baseline data to measure progress; provides information for GLC and GFATM applications; guides technical assistance; and informs donor investment. In field testing, the tool scoring system performed equally well in high- and low-prevalence settings. This GLC endorsed tool supports global efforts to contain MDR/XDR-TB and is useful to develop national MDR/XDR-TB control strategies. It is available at http://www.path.org/publications/details.php?i=1678.

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Outline

• Introduction: XDR, a sexy topic
• Definition
• Epidemiology
• Management: treatment
• Control

Cross-resistance

• Rifamycin, high cross-resistance
• FQ, variable cross resistance (but new generation may be susceptible when earlier generation is already lost; clinical significance??)
• Amika & Kana, high cross resistance
• Capreo & Vio, high cross-resistance
• Other aminoglycosides and polypeptides, low cross resistance
• Eth, cross resistance to H if inhA mutation present)
• TH, low cross-resistance to H, Eth, PAS
The challenge of XDR
7 steps of drug treatment in MDR/XDR-tuberculosis

1. Use drugs shown to be sensitive in *in vitro* drug sensitivity testing.
2. Drugs are added until \( n > 5 \)
3. Use any first line oral agent to which the organism is sensitive: Isoniazid, rifampin, ethambutol, pyrazinamide
4. Use an injectable drug (aminoglycoside or capreomycin) to which the organism is sensitive. Continue the injectable drug at least 6 months after culture conversion since it is frequently one of only two bactericidal components in the therapy
5. Use a fluoroquinolone. Consider use of moxifloxacin in cases of drug resistance to ciprofloxacin or levofloxacin
6. Add as many second line drugs as are needed to reach a number of \( \geq 5 \). Cycloserin and ethionamid are considered first choice. PAS and linezolid are used in cases with high-grade drug resistance
7. If the regimen does not contain \( \geq 5 \) adequate drugs consider the additional use of amoxicillin/clavulanic acid or clofazimine
Figure 7.3 Management guidelines for patients with documented, or almost certain, XDR-TB

1. Use any Group 1 agents that may be effective.
2. Use an injectable agent to which the strain is susceptible and consider an extended duration of use (12 months or possibly the whole treatment). If resistant to all injectable agents, it is recommended to use one the patient has never used before.*
3. Use a later-generation fluoroquinolone such as moxifloxacin.
4. Use all Group 4 agents that have not been used extensively in a previous regimen or any that are likely to be effective.
5. Use two or more agents from Group 5.
6. Consider high-dose isoniazid treatment if low-level resistance is documented.
7. Consider adjuvant surgery if there is localized disease.
8. Ensure strong infection control measures.
9. Treat HIV (as per Chapter 10).
10. Provide comprehensive monitoring (see Chapter 11) and full adherence support (see Chapter 12).
MDR-/XDR-TB treatment programme
Decentralised case management

Latvia, Side Effects – MDR Cohort 2000

✓ 86% of patients experienced side effects
✓ Median of 4 side effect reports per person
✓ Most common side effects
   • Nausea 73.0%
   • Vomiting 38.7%
   • Abdominal pain 38.2%
   • Dizziness 35.8%
   • Hearing problems 28.4%
✓ 61% changed or discontinued drugs during treatment owing to side effects
✓ 2 patients stopped treatment due to side effects
Results: Final Conversion Over Time

N = 129 patients who converted, Latvia
What was not known on XDR?

- Is the risk of death/probability of success different from that of MDR?
- Are their clinical characteristics different in HIV-negative patients?
- Is their infectiousness different?
- Has the XDR definition a clinical relevance? Which is the role of susceptibility to first-line drugs different from HR?
Epidemiology and clinical management of XDR-TB: a systematic review by TBNET


TABLE 3: Microbiological features in the studies reviewed

<table>
<thead>
<tr>
<th>First author [ref.]</th>
<th>Drugs to which strains were resistant n</th>
<th>100% SRL QA DST</th>
<th>All drugs tested</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MDR</td>
<td>XDR</td>
<td></td>
</tr>
<tr>
<td>Gakoni [9]</td>
<td>5*</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Migliori [10]</td>
<td>5*</td>
<td>5*</td>
<td>Yes</td>
</tr>
<tr>
<td>Migliori [11]</td>
<td>5*</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Kim [12]</td>
<td>5*</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Minnich [14]</td>
<td>5*</td>
<td>5*</td>
<td>Yes</td>
</tr>
<tr>
<td>Chai [17]</td>
<td>5*</td>
<td>5*</td>
<td>Yes</td>
</tr>
<tr>
<td>Kesshauk [16]</td>
<td>5*</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Ezler [18]</td>
<td>5*</td>
<td>5*</td>
<td>Yes</td>
</tr>
<tr>
<td>Koron [20]</td>
<td>5*</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Lai [21]</td>
<td>5*</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Banhuk [22]</td>
<td>5*</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Boskula [23]</td>
<td>5*</td>
<td>5*</td>
<td>Yes</td>
</tr>
<tr>
<td>Kim [24]</td>
<td>5*</td>
<td></td>
<td>Yes</td>
</tr>
</tbody>
</table>


### TABLE 5: Treatment efficacy endpoints in the studies reviewed

<table>
<thead>
<tr>
<th>First author [ref.]</th>
<th>Time to conversion</th>
<th>Treatment success</th>
<th>Failure</th>
<th>Death</th>
<th>Follow-up months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MDR</td>
<td>XDR</td>
<td>MDR</td>
<td>XDR</td>
<td>p-value</td>
</tr>
<tr>
<td>Bouchon [9]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moore [10]</td>
<td>41 days</td>
<td>110 days</td>
<td>45 (55.7)</td>
<td>0</td>
<td>8 (63)</td>
</tr>
<tr>
<td>C: 58 days</td>
<td>C: 97.5 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moore [11]</td>
<td>56 days</td>
<td>110 days</td>
<td>168 (46.1)</td>
<td>22 (36.4)</td>
<td>32 (32.0)</td>
</tr>
<tr>
<td>C: 60 days</td>
<td>C: 96 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaw [12]</td>
<td>149 (89.8)</td>
<td>23 (5.8)</td>
<td>29 (17.3)</td>
<td>11 (5.4)</td>
<td>0.21</td>
</tr>
<tr>
<td>XDR: 43^*</td>
<td>MDR: 28^*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minder [16]</td>
<td>61 days</td>
<td>90 days</td>
<td>410 (86.3)</td>
<td>51 (81.6)</td>
<td>3 (2.1)</td>
</tr>
<tr>
<td>C: 96 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osen [17]</td>
<td>22.5</td>
<td>5</td>
<td>2.5</td>
<td>0.67</td>
<td></td>
</tr>
<tr>
<td>Wittenberg [18]</td>
<td>2 months</td>
<td>2 months</td>
<td>316 (86.7)</td>
<td>14 (40.3)</td>
<td>49 (8)</td>
</tr>
<tr>
<td>C: 7 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In [19]</td>
<td>53.5 days</td>
<td>88 days</td>
<td>105 (39.3)</td>
<td>4 (57.1)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>C: 61.5 days</td>
<td>C: 117 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nishi [20]</td>
<td>64 (65)</td>
<td>18 (67)</td>
<td>0.24</td>
<td>0.24</td>
<td></td>
</tr>
<tr>
<td>Le [21]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baverley [22]</td>
<td>98.5 days</td>
<td>195 days</td>
<td>54 (96)</td>
<td>7 (41.3)</td>
<td>80 (15)</td>
</tr>
<tr>
<td>C: 110 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bonacca [23]</td>
<td>3 months</td>
<td>26 months</td>
<td>372 (73.5)</td>
<td>10 (16.7)</td>
<td>90 (13)</td>
</tr>
<tr>
<td>C: 70 days</td>
<td>C: 180 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kuo [24]</td>
<td>61 (46.2)</td>
<td>26 (55.9)</td>
<td>43 (4)</td>
<td>12 (18)</td>
<td>124 (60.9)</td>
</tr>
<tr>
<td>C: 81 days</td>
<td>C: 117 days</td>
<td></td>
<td></td>
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</tbody>
</table>

XDR: a death sentence?
XDR compared with MDR, Italy-Germany

- Death rate: 36.4% vs 6.3% (RR 5.45)
- Longer hospitalization (241.2±177.0 vs. 99.1±85.9 days) → Cost?
- Longer treatment duration (30.3±29.4 vs. 15.0±23.8 months) → Cost?
- Bacteriological conversion in 4/11 XDR-vs. 102/126 MDR-TB cases (median: smear: 110 vs. 41 days; culture: 97.5 vs. 58 days) → Cost of new infections?

Emerging Infectious Diseases 2007

![Graph showing the estimated proportion of treatment success for various categories of drug-resistant tuberculosis cases.](image)

**Figure 1.** A Kaplan-Meier plot showing estimated proportion of treatment success (cure plus treatment completion) according to the drug-resistance profile in Estonia, Germany, Italy, and the Russian Federation. --- other multidrug-resistant tuberculosis (MDR-TB) cases; ... MDR-TB cases resistant to all first-line drugs; ---: extensively drug-resistant tuberculosis cases.

Eur Respir J 2007
Table 3. Treatment outcomes among patients with multidrug-resistant tuberculosis (MDR-TB), including those with extensively drug-resistant tuberculosis (XDR-TB).

<table>
<thead>
<tr>
<th>Treatment outcome</th>
<th>No. (%) of patients with treatment outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total MDR-TB (n = 211)</td>
</tr>
<tr>
<td>Treatment success</td>
<td>132 (62.6)</td>
</tr>
<tr>
<td>Cure</td>
<td>107 (50.7)</td>
</tr>
<tr>
<td>Completed</td>
<td>25 (11.9)</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>65 (30.8)</td>
</tr>
<tr>
<td>Relapse</td>
<td>6 (2.8)</td>
</tr>
<tr>
<td>Failure</td>
<td>40 (19.0)</td>
</tr>
<tr>
<td>Death</td>
<td>19 (9.0)</td>
</tr>
<tr>
<td>Other*</td>
<td>14 (6.6)</td>
</tr>
</tbody>
</table>

* Excluded from further analysis.

NOTE: OR 4.46 (P=0.057) from comparison of treatment success and treatment failure by \( \chi^2 \) test between XDR-TB and non-XDR-TB.

**Extensively Drug-Resistant Tuberculosis is Worse than Multidrug-Resistant Tuberculosis: Different Methodology and Settings, Same Results**

**Clinical Infectious Diseases 2008; 46:959-9**

Giovanni Battista Migliori, Christoph Lange, Enrico Garrib, Rosalia Centis, Giorgio Bescaini, Kol Klinman, Johannes Ortmann, Alberto Mattiello, Antonio Spacapalo, and Daniela M. Cittadino, and the SMIRA/TBNET Study Group

Table 1. Comparison of outcomes of patients with extensively drug-resistant (XDR) and multidrug-resistant (MDR) tuberculosis (TB).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. (%) of patients</th>
<th>Univariate analysis</th>
<th>P</th>
<th>No. (%) of patients</th>
<th>Univariate analysis</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>XDR TB (n = 43)</td>
<td>MDR TB (n = 168)</td>
<td>RR (95% CI)</td>
<td>P</td>
<td>XDR TB (n = 43)</td>
<td>MDR TB (n = 301)</td>
</tr>
<tr>
<td>Treatment success</td>
<td>23 (53.5)</td>
<td>109 (64.9)</td>
<td>3.42 (1.69-6.92)</td>
<td>.002</td>
<td>33 (76.7)</td>
<td>165 (64.9)</td>
</tr>
<tr>
<td>Cured</td>
<td>23 (53.5)</td>
<td>84 (50.0)</td>
<td>1.69 (0.92-3.06)</td>
<td>.067</td>
<td>19 (44.2)</td>
<td>134 (44.2)</td>
</tr>
<tr>
<td>Treatment completed</td>
<td>...</td>
<td>25 (14.9)</td>
<td>3 (12.7)</td>
<td>.878</td>
<td>3 (14.2)</td>
<td>31 (10.3)</td>
</tr>
<tr>
<td>Overall</td>
<td>19 (44.2)</td>
<td>46 (27.4)</td>
<td>1.69 (1.00-2.95)</td>
<td>.067</td>
<td>28 (40.6)</td>
<td>76 (25.3)</td>
</tr>
<tr>
<td>Relapse</td>
<td>2 (4.7)</td>
<td>4 (2.4)</td>
<td>1.69 (0.92-3.06)</td>
<td>.067</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Failure</td>
<td>11 (25.6)</td>
<td>29 (17.3)</td>
<td>1.58 (1.04-2.42)</td>
<td>.067</td>
<td>12 (28.6)</td>
<td>32 (10.9)</td>
</tr>
<tr>
<td>Death</td>
<td>6 (14.0)</td>
<td>13 (7.7)</td>
<td>1.69 (0.92-3.06)</td>
<td>.067</td>
<td>14 (32.6)</td>
<td>43 (11.0)</td>
</tr>
</tbody>
</table>

NOTE: RR, relative risk.
Fluoroquinolones: are they essential to treat multidrug-resistant tuberculosis?

G.B. Migliori\textsuperscript{1}, C. Lange\textsuperscript{1}, E. Ciccarelli\textsuperscript{1}, R. Cornetti\textsuperscript{1}, G. Bonazzi\textsuperscript{1}, K. Kliman\textsuperscript{1}, L.R. Codecasa\textsuperscript{2}, A. Spavelli\textsuperscript{2}, D.M. Castillo\textsuperscript{1} and the SMIRANET Study Group\textsuperscript{1,2}

TABLE 1

<table>
<thead>
<tr>
<th>Risk of death and failure in fluoroquinolone (FQ)-resistant versus FQ-susceptible multidrug-resistant tuberculosis cases from Estonia, Germany, Italy and the Russian Federation among cases achieving a final outcome (treatment success, death and failure)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>-------------------------------------</td>
</tr>
<tr>
<td>Subjects n</td>
</tr>
<tr>
<td>Treatment success</td>
</tr>
<tr>
<td>Death\textsuperscript{a}</td>
</tr>
<tr>
<td>Failure\textsuperscript{a}</td>
</tr>
</tbody>
</table>

Data are presented as n (%), unless otherwise indicated. Cases not achieving a final outcome (default, still on treatment) were excluded from the analysis. RR: relative risk; CI: confidence interval. \textsuperscript{a} comparison of treatment success and treatment failure/death between FQ-resistant and FQ-susceptible multidrug-resistant tuberculosis cases.

Eur Respir J 2018; 51: 904–913

1966, the last TB drug discovered...

Resistance to second-line injectables and treatment outcomes in multidrug-resistant and extensively drug-resistant-tuberculosis cases

G.B. Migliori\textsuperscript{1}, C. Lange\textsuperscript{1}, R. Cornetti\textsuperscript{1}, G. Bonazzi\textsuperscript{1}, K. Kliman\textsuperscript{1}, L.R. Codecasa\textsuperscript{2}, A. Spavelli\textsuperscript{2}, D.M. Castillo\textsuperscript{1} and the SMIRANET Study Group\textsuperscript{1,2}

A logistic regression analysis was used to compare outcomes for cases susceptible versus resistant to each of the injectable agents. Resistance to capreomycin was the only independent variable significantly associated with unfavourable outcome (OR 3.51, 95% CI 1.67–7.36: p = 0.001), while resistance to amikacin (OR 1.76, 95% CI 0.91–3.39; p = 0.09) and kanamycin (OR 1.87, 95% CI 0.96–3.67; p = 0.047) achieved borderline significance. After adjustment for covariates (country, sex,
Long-term moxifloxacin in complicated tuberculosis patients with adverse reactions or resistance to first line drugs

Luigi Ruffo Codecasa*, Giovanni Ferrara, Maurizio Ferrarese, Maria A. Morandi, Valeria Penati, Carla Lacchini, Patrizia Vaccarino, Giovanni B. Migliori

Villa Maruzi Inc, Niguarda Hospital, Regional Reference Centre for TB, Viale Zara #1, 20159 Milan, Italy

Received 24 September 2005; accepted 2 January 2006

Summary

Study objective: To test safety and tolerability of long-term moxifloxacin in resistant tuberculosis (TB) patients and patients with intolerance to first line anti-TB drugs.

Design: Clinical evaluation of adverse events (AEs) during prolonged moxifloxacin treatment.

Settings: TB Unit of the Regional TB Reference Center, Villa Maruzi Institute, Niguarda Ca Granda Hospital, Milan, Italy.

Patients and interventions: Patients treated with moxifloxacin, 400 mg orally once daily for 6 months in the Villa Maruzi Institute from January 2001 to December 2003 were enrolled.

Results: Thirty-eight patients were treated with moxifloxacin at the Villa Maruzi Institute in the study period, for multidrug-resistant (MDR) TB (n=195) or MDR/TB patients (n=177). MDR-TB patients reported at least one AE due to moxifloxacin, whereas 14 (7.3%) patients with intolerance to first line anti-TB drugs (ITR+LZD) had AEs (n=65). The mean duration of moxifloxacin treatment was 26.3±3.2 months. Seventy-five percent (n=63) of the patients reported at least one AE due to moxifloxacin, including gastrointestinal symptoms (21.3%), general symptoms (13.2%) and central nervous system (3%). Two (4%) AEs (n=10) were recorded. Most of the patients (n=65) reported a treatment success, even if the success rate was lower in MDR TB patients (8/14, 57%).

Study population

- 195 MDR/XDR-TB
- 177 MDR-TB
- 18 XDR-TB

Safety analysis

- Lzd 600 mg OD (n=28)
- ITR+Lzd (n=85)
- Lzd 600 mg BD (n=97)

Efficacy analysis

- ITR+Lzd -cases-
- Definitive outcomes (n=45)
- 41 MDR-TB
- 4 XDR-TB
- ITR -cases- (n=110)
- 102 MDR-TB
- 8 XDR-TB
Safety, tolerability analysis

- LNZ administered for a mean period of 221 ± 250 days.
- AE after 69 days (median)
- 35/85 (41.2%) patients experienced 52 episodes of AE, 27 requiring LNZ discontinuation.
- The proportion of major AE lower for 600 mg OD (p=0.0004), although efficacy was similar

<table>
<thead>
<tr>
<th>Patients affected by</th>
<th>600mg OD (n=28)</th>
<th>600 mg BD (n=57)</th>
<th>P</th>
<th>Total (n=85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nº AE (%)</td>
<td>24/28 (85.7)</td>
<td>26/57 (45.6)</td>
<td>0.0004</td>
<td>50</td>
</tr>
<tr>
<td>Minor (%)</td>
<td>-</td>
<td>8/57 (14)</td>
<td>-</td>
<td>8</td>
</tr>
<tr>
<td>Major (%)</td>
<td>4/28 (14.3)</td>
<td>23/57 (40.4)</td>
<td>0.01</td>
<td>27</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
<td>57</td>
<td>-</td>
<td>89</td>
</tr>
</tbody>
</table>

Efficacy Analysis

- Cases significantly more severe than controls (drug resistance profile, number of previous treatments and drugs prescribed)
- Comparable treatment outcomes (p=0.88).
- Stratifying per resistance patterns, proportion of SS and C converters > in cases than in controls for > 7 resistances (p>0.005).
### Variables

<table>
<thead>
<tr>
<th></th>
<th>Linezolid</th>
<th>No Linezolid</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, mean ± S.D.)</td>
<td>36.4 ± 13.7</td>
<td>36.8 ± 13.7</td>
<td>0.86</td>
</tr>
<tr>
<td>Males (%)</td>
<td>33/45 (73.3)</td>
<td>82/110 (74.5)</td>
<td>0.89</td>
</tr>
<tr>
<td>Immigrants (%)</td>
<td>41/45 (91.1)</td>
<td>94/110 (85.5)</td>
<td>0.31</td>
</tr>
<tr>
<td>HIV+ (%)</td>
<td>2/45 (4.4)</td>
<td>7/110 (6.4)</td>
<td>0.61</td>
</tr>
<tr>
<td>MDR-TB (%)</td>
<td>41/45 (91.1)</td>
<td>102/110 (92.7)</td>
<td>0.83</td>
</tr>
<tr>
<td>Resistance* (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptomycin</td>
<td>43/45 (95.6)</td>
<td>93/110 (84.5)</td>
<td>0.06</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>35/44 (79.5)</td>
<td>65/108 (60.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>28/44 (63.6)</td>
<td>37/109 (33.9)</td>
<td>0.0007</td>
</tr>
<tr>
<td>Amikacin</td>
<td>10/28 (35.7)</td>
<td>15/36 (26.8)</td>
<td>0.39</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>2/13 (66.7)</td>
<td>4/14 (28.6)</td>
<td>0.05</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>15/42 (35.7)</td>
<td>7/78 (9.1)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>15/34 (44.1)</td>
<td>21/85 (24.7)</td>
<td>0.03</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>9/42 (21.4)</td>
<td>11/100 (11)</td>
<td>0.11</td>
</tr>
<tr>
<td>Average N of drugs to which isolates were resistant</td>
<td>4.3</td>
<td>3.8</td>
<td>0.002</td>
</tr>
<tr>
<td>First-line drugs</td>
<td>1.5</td>
<td>0.9</td>
<td>0.02</td>
</tr>
<tr>
<td>Second-line drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N of retreatment patients (%)</td>
<td>30/45 (66.7)</td>
<td>60/110 (54.5)</td>
<td>0.48</td>
</tr>
<tr>
<td>Average number of treatment regimens prescribed (&gt; 1 month) in retreated patients</td>
<td>4.5</td>
<td>2.3</td>
<td>0.07</td>
</tr>
</tbody>
</table>

### Efficacy endpoints

#### Proportion of converters (%)

<table>
<thead>
<tr>
<th>N° of drugs (resistance)</th>
<th>Sputum smear conversion</th>
<th>Culture conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases (LZD treated)</td>
<td>Cases (LZD treated)</td>
</tr>
<tr>
<td></td>
<td>Controls (LZD not treated)</td>
<td>Controls (LZD not treated)</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td>p-value</td>
</tr>
<tr>
<td>&lt;5 6/9 (66.7)</td>
<td>35/59 (59.3)</td>
<td>0.68</td>
</tr>
<tr>
<td>5-7 16/26 (61.5)</td>
<td>23/43 (53.5)</td>
<td>0.51</td>
</tr>
<tr>
<td>&gt;7 9/10 (90)</td>
<td>1/8 (12.5)</td>
<td>0.0009</td>
</tr>
<tr>
<td>TOTAL 31/45</td>
<td>59/110</td>
<td>86/110</td>
</tr>
</tbody>
</table>
### Treatment outcome (%)

<table>
<thead>
<tr>
<th></th>
<th>Linezolid (n = 45)</th>
<th>no Linezolid (n = 110)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cured</strong></td>
<td>23/45 (51.1)</td>
<td>75/110 (68.2)</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Treatment completed</strong></td>
<td>13/45 (28.9)</td>
<td>15/110 (13.6)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Failure</strong></td>
<td>-</td>
<td>1/110 (0.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td>9/45 (20)</td>
<td>19/110 (17.3)</td>
<td>0.65</td>
</tr>
</tbody>
</table>

### Culture conversion time (days, mean ± S.D.)

<table>
<thead>
<tr>
<th></th>
<th>Linezolid (n = 45)</th>
<th>no Linezolid (n = 110)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SS conversion</strong></td>
<td>102.9 ± 74</td>
<td>65.4 ± 80.1</td>
<td>0.007</td>
</tr>
<tr>
<td>time</td>
<td>n = 31 (69%)</td>
<td>n = 59 (54%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Culture</strong></td>
<td>109 ± 71</td>
<td>69 ± 63</td>
<td>0.0007</td>
</tr>
<tr>
<td>conversion</td>
<td>n = 39 (87%)</td>
<td>n = 86 (78%)</td>
<td></td>
</tr>
<tr>
<td>time</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### SS conversion time

<table>
<thead>
<tr>
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<th>Linezolid (n = 45)</th>
<th>no Linezolid (n = 110)</th>
<th>P</th>
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<tr>
<td><strong>SS conversion</strong></td>
<td>102.9 ± 74</td>
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<tr>
<td>time</td>
<td>n = 31 (69%)</td>
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<td></td>
</tr>
</tbody>
</table>

### Extensively Drug-Resistant TB (XDR TB) Summary Report

From DOTS to DOTS Strategy

37th UNION World Conference on Lung Health

31 Oct 2006

Extensively Drug-Resistant TB (XDR TB)

Kenneth G. Castro, M.D.* for

The First Global XDR TB Task Force

9-10 October 2006, Geneva, Switzerland

* Centers for Disease Control and Prevention
U.S. Department of Health and Human Services
Global Policy: MDR-TB and XDR-TB

1. Strengthen basic TB control, to prevent M/XDR-TB
2. Scale-up programmatic management and care of MDR-TB and XDR-TB
3. Strengthen laboratory services for adequate and timely diagnosis of MDR-TB and XDR-TB
4. Ensure availability of quality drugs and their rational use
5. Expand MDR-TB and XDR-TB surveillance
6. Introduce infection control, especially in high HIV prevalence settings
7. Mobilize urgently resources domestically and internationally
8. Promote research and development into new diagnostics, drugs and vaccines

THE BEIJING “CALL FOR ACTION” ON TUBERCULOSIS CONTROL AND PATIENT CARE: TOGETHER ADDRESSING THE GLOBAL M/XDR-TB EPIDEMIC

We recognize the key barriers to effective management of M/XDR-TB lie throughout the health system and beyond…

We therefore commit ourselves to accelerate efforts to prevent M/XDR-TB through effective TB care and control, and to scale-up the diagnosis and treatment of M/XDR-TB:

- universal access to diagnosis and treatment of M/XDR-TB by 2015
- equitable access
- comprehensive framework for management and care
- HR, laboratories
- coordination among public and private sectors
- infection control
- drug supply
- improved surveillance, M&E
- addressing social determinants
- ACSM
Laboratory room in Eastern Europe
Clinical case

- S.A. female, born in Poland 1984 (claiming to be Moldovian)

Past medical history

Healthy till 2002
- 2002: 1°episode PTB: unknown therapy for few months in Poland
- 2006: 2° episode of PTB: unknown therapy for 6 months in Greece with 4 drugs
- 2000-2006: IDU (cocaine, heroine), smoke (>15 sig/die)
- 19 March 07: arrived in Italy: admitted at hospital in XX
March 19th

Hospitalized in XX

Signs and symptoms: no fever, eupnoic, weight loss 10 Kg in the last two yrs, abdominal pain, productive cough

Med exam: weight 57Kg, height 186 cm. Thorax (auscultation): physiological sounds reduced, dry sounds on upper right lobe

Lab data: Hb 9.6 g/dL; WBC 14,439 (N%: 81%), PCR 98, albumine 22 g/L; gamma globuline increased.

VDRL +; HCV Ab +; HBcAb pos, Ab HbsAg +; HBsAg neg; HIV neg

Clinical suspicion of PTB

What is there?
What to do now?

CXR: “Large infiltrate in the left lower lobe, infiltrate in the right lobe, upper and lower. Mediastinal stretched towards left”

Clinical case management, March 20th

- Sputum smear **positive** for AAFB, culture in progress

Cat 1 regimen started:
- R 600 mg/die
- E 500 mg x 3/die
- Z 500 mg x3/die
- H 300 mg/die

Metadone 30 mg x 5/die
Akineton, Serenase, Zoloft, Tavor
March 28, CT Scan: what is there?
Clinical case management

After CT scan (28/3/07)
2 drugs added:
• Strepto 1000 mg/die
• Moxi 400 mg/die

Unchanged clinical picture
Sputum smears: persistently positive for AAFB until 18/4/07

....still DST was pending

Transferred to Sondalo, April 20th
- Moxi and Strepto stopped
- Treatment with R,H,E,Z continued
- Sputum: still smear positive
On 27 April 2007 DST results from XX arrive:

Mycobacterium tuberculosis RESISTANT to:
- RIFAMPICIN
- ISONIAZID
- STREPTOMYCIN
- PYRAZINAMIDE
- ETHAMBUTOL

DST for second line in progress......
- Treatment modified including second-line drugs

In Sondalo, April 27th...

2nd line started with 5 drugs
- Ethionamide
- Terizidon
- PAS
- Moxifloxacin
- Amikacin

Clinical case management
In Sondalo, May 25th

Significant worsening of general clinical conditions
- urgent CXR …
- Blood examination: (30,860 WBC, N 92%, 800 TLC); PCR 123
HeGA: pH 7.29; paCO2 70, PaO2 113

25/5/07 CXR
In Sondalo, May 25th

- Transferred to Intensive Care

ICU, May 28th

The second line DST shows resistance to:
- Cycloserin
- Ciprofloxacin
- Ethionamide
- Amikacin

\[ \text{XDR TB!!} \]

 Added to the regimen:
- Imipenem
- Linezolid

- Mechanical ventilation started
- General conditions further worsened
- EGA pH 7.119, paCO₂ 141, PaO₂ 64, Sat Hb 82%.
Clinical case death

28 May 07: Death (Respiratory Failure)
Clinical case: caveat

1. Treatment history not well defined
2. Language difficulties
3. Risk factors for low compliance (IDU..)
4. Country of origin → high risk of MDR-TB
5. Mis-management: moxi only added to a failing regimen (quinolones-Resistance developed after 40 d of monotherapy..)
6. Late DST (first line drugs) → 19/3-27/4!
“Nobody wants me around..”

Interventions over time: old weapons might be useful again to manage XDR
XDR and TB control: which future?