Drug resistance of *Mycobacterium tuberculosis* in patients with new pulmonary tuberculosis in Lviv/UA

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Revised abstract

Background: Standardized drug therapy is one of the cornerstones of the current WHO strategy for the elimination of tuberculosis (TB), however, the emergence and transmission of drug-resistant strains of *Mycobacterium tuberculosis* (Mtb) is increasingly jeopardizing the success of this strategy. The availability of local drug resistance surveillance data is therefore of the utmost importance for guiding TB control programs. The STOP TB LVIV Study Group has recently collected Mtb isolates from 24 consecutive patients with new pulmonary TB in Lviv, Ukraine ("pilot study"). The drug susceptibilities of these isolates were tested in order to estimate the rate of primary drug resistance in Lviv.

Methods: Drug susceptibilities of Mtb isolates obtained from patients with new pulmonary TB were assessed by the Bactec MGIT 960 method (Becton-Dickinson, Germany). The following drugs were tested at the critical concentrations (mg/L) indicated: isoniazid (0.1; 0.4), rifampicin (1.0), pyrazinamide (100), ethambutol (5.0; 7.5), streptomycin (1.0; 4.0), and levofloxacin (1.0).

Results: To date, the drug susceptibility testing results of 24 isolates are available. Of these, 15 (63%) were susceptible to all the drugs tested. Two (7%) showed mono-resistance to isoniazid, and three (13%) were resistant to both isoniazid and streptomycin. Four (17%) isolates were resistant to at least isoniazid and rifampicin, i.e. were MDR-TB.

Conclusions: Our limited data set suggests that in Lviv approximately 80% of the patients with new pulmonary TB are amenable to cure by WHO's standard drug regimen or modifications thereof, whereas approx. 20% are not. Corroboration will require the study of a larger patient population. If these results are confirmed, upgrading the laboratory infrastructure and introducing assays for the rapid detection of MDR- and/or XDR-TB will be essential to effectively combat the current TB epidemic and to minimize the emergence of new drug-resistant strains.

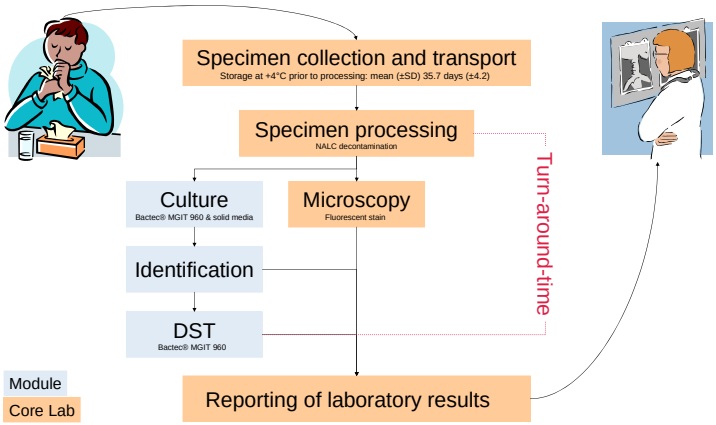
Background

Standardized drug therapy is one of the cornerstones of the current WHO strategy for the elimination of tuberculosis (TB), however, the emergence and transmission of drug-resistant strains of *Mycobacterium tuberculosis* (Mtb) is increasingly jeopardizing the success of this strategy. The availability of local drug resistance surveillance data is therefore of the utmost importance for guiding TB control programs. The STOP TB LVIV Study Group has recently collected Mtb isolates from 24 consecutive patients with new pulmonary TB in Lviv, Ukraine (see abstract #91148). The drug susceptibilities of these isolates were tested in order to estimate the rate of drug resistance in new cases of pulmonary TB in Lviv/UA.

Patients and procedures

Fifty consecutive patients with newly diagnosed pulmonary TB were enrolled between 16.06.08 and 02.07.08 Three sputum specimens per patient were collected, split (see abstract #91148) and processed as outlined in figure 1:

Figure 1. Specimen collection and processing scheme



Drug susceptibility testing (DST) of the following drugs at the concentrations (µg/ml) indicated was performed by Bactec® MGIT 960 (BD Diagnostics, Switzerland): isoniazid (0.1; 0.4), rifampicin (1.0), pyrazinamide (100), ethambutol (5.0; 7.5), streptomycin (1.0; 4.0), and levofloxacin (1.0).

Results

A total of 24 patient isolates were tested. Patients' characteristics are shown in table 1:

Table 1. Patients' characteristics

Characteristic	All subjects (n = 50)	
Age, mean (SD), yr	47.1	(16.6)
Men, n (%)	36	(72%)
Foreign born, n (%)	0	(0%)
Prior TB therapy, n (%)	0	(0%)
HIV positive, n (%)	0	(0%)

Results, contd.

Figure 2 delineates the Bactec® MGIT 960 DST patterns of four clinical Mtb patient isolates and the respective turn-around-times (TAT), i.e. the intervals between the start of sample processing and the availability of the DST results.

Figure 2. Bactec® MGIT 960 DST patterns

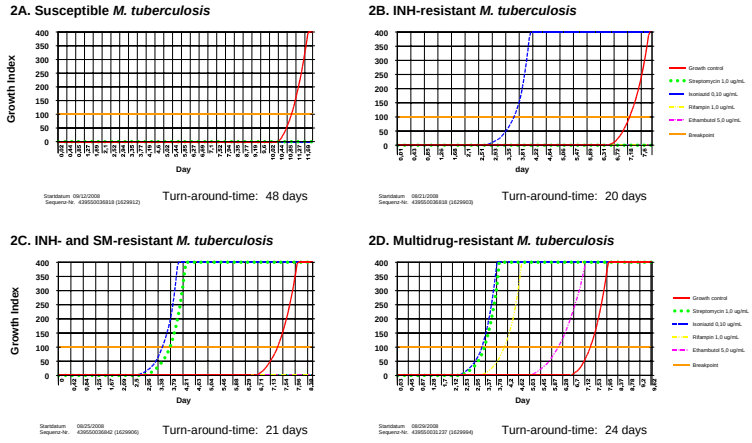


Figure 3. Association of microscopy results and turn-around-time (TAT)

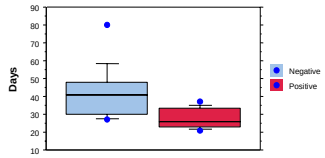


Figure 3 shows the distribution of TAT in smear-negative (median, 41 days) and smear-positive specimens (median, 26 days), respectively. In the latter, 90% of the DST results were available within 35 days (5 weeks).

Table 2 summarizes the Bactec® MGIT 960 DST results of the 24 Mtb patient isolates. One patient isolate was resistant to the fluoroquinolone tested.

Table 2. DST results and treatment options

Resistance	N	%	Regimen	Duration	Comments
None	15	63	HREZ; HR	2 mo; 4 mo	-
H / HS	5	20	RZE	6-9 mo	consider FQ*
HR (MDR-TB)	4	17	**	**	1 FQ-resistant***

H, isoniazid; E, ethambutol; R, rifampicin; S, streptomcin; Z, pyrazinamide; FQ, fluoroquinolone
*for patients with extensive disease; **individualised treatment on the basis of individual DST results (adapted from Ref 2); ***XDR TB ?

Conclusions

- Our results suggest that among HIV-negative patients with newly diagnosed pulmonary TB in Lviv/UA
  - o approx. 4 out of 5 patients were amenable to treatment with the standard drug regimen or modifications thereof (2)
  - o approx. 1 out of 5 patients was infected by MDR TB and would thus require individually tailored treatment on the basis of personal DST results (2)
  - o XDR TB may be an issue, since one FQ-resistant MDR TB isolate was detected
- The availability of timely and reliable DST results can
  - ✓ improve treatment outcomes
  - ✓ reduce the emergence of additional drug resistance
  - ✓ improve patient compliance (fewer drugs, less drug interactions/side effects)
  - ✓ reduce overall cost (better outcomes, fewer drugs)
- At this stage of the local TB epidemic implementation of the Bactec® MGIT 960 system for primary culture and DST will probably be most cost-effective for the diagnosis of new, sputum smear-positive patients, as here 50% and 90% of the DST results were available within 26 and 35 days, respectively ("TB Fast Track").

References
1. Dye, C. Doomsday postponed? Preventing and reversing epidemics of drug-resistant tuberculosis. Nature Rev. Microbiol. 2009; **7**: 81-87.
2. WHO emergency update 2008. Guidelines for the programmatic management of drug-resistant tuberculosis.

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