In vitro susceptibility testing and totally drug-resistant tuberculosis

To the Editor:

We find the article by MIGLIORI *et al.* [1], on extensively drug-resistant tuberculosis (XDR-TB), very informative and would like to commend them for the excellent meta-analysis. Without any doubt, XDR-TB is an extensive global problem; the use of the lower susceptibility breaking points that we recently suggested [2] mean that the burden of XDR-TB could be even higher. Although there are recent reports of ''totally drug-resistant (TDR)'' TB, the World Health Organization does not recognise this term [3]. There is already a social stigma attached to having TB in many parts of the world and a label of TDR poses further challenges for patients. Antibiotic susceptibility testing is ideal for all patients, and is even more of a requirement when a patient is not responding to the anti-TB therapy. Lessons from other infectious diseases suggest that an even better approach would be to record actual minimum inhibitory concentrations (MICs), but clearly these are difficult to perform for TB in many laboratories and need further standardisation. Management of TB always involves a combination therapy, whereas drug sensitivity is measured for a single drug and not for the combination of drugs used for the treatment. Therefore, there is a possibility that even though the bacteria is resistant to the drug *in vitro*, combination therapy may still work, as evidenced by the results of the present report [1], and another article by UDWADIA and VENDOTI [4]. This is because there could be a number of other factors beyond ''resistance'' or MIC that lead to the unfavourable response to the treatment. These include, but are not limited to, the interindividual differences in pharmacokinetics as well as genetic makeup of an individual [5]. While there is no quick measure to prevent the emergence of resistance, knowledge acquired from scientific research should be translated to develop new tools to improve patient care. We suggest that patients with suspected or confirmed XDR-TB should be subjected to therapeutic drug monitoring (TDM) to make sure that the desired drug concentration is achieved with the administration of the prescribed drug doses. For those drugs with a good therapeutic window, and for drugs without concentration driven toxicity, higher doses can then be administered. Such doses can also be customised to achieve concentrations above those that define drug resistance or above the MIC, a solution already applied to other bacterial infections. We recognise that TDM for treatment of TB is in its infancy, and is potentially costly in resource limited settings. Nevertheless, it is a logical solution for these resistance patterns that are clearly associated with high mortality, as shown by the analysis of MIGLIORI *et al.* [1]. Although drug susceptibility testing provides valuable information on the resistance pattern and remains an important tool to design therapeutic regimens, we should not give up by labelling patients as having ''totally'' drug-resistant TB, but instead continue with the XDR-TB label.

@ERSpublications
What's in the name: totally drug-resistant or extremely drug-resistant tuberculosis?
http://ow.ly/kslPb

Shashikant Srivastava[1], Carleton Sherman[1] and Tawanda Gumbo[1,2]

[1]Dept of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, and [2]Office of Global Health, University of Texas Southwestern Medical Center, Dallas, TX, USA.

Correspondence: S. Srivastava, Dept of Internal Medicine, 5323 Harry Hines Blvd, University of Texas Southwestern Medical Center, Dallas, TX, 75390, USA. E-mail: Shashi.kant@utsouthwestern.edu

Received: Dec 20 2012 | Accepted after revision: Jan 14 2013

Conflict of interest: None declared.

References

1 Migliori GB, Sotgiu G, Gandhi NR, *et al.* Drug resistance beyond extensively drug-resistant tuberculosis: individual patient data meta-analysis. *Eur Respir J* 2013; 42: 169–179.
2 Gumbo T. New susceptibility breakpoints for first-line antituberculosis drugs based on antimicrobial pharmacokinetic/pharmacodynamic science and population pharmacokinetic variability. *Antimicrob Agents Chemother* 2010; 54: 1484–1491.
3 World Health Organization. Drug-resistant tuberculosis. Frequently asked questions. www.who.int/tb/challenges/mdr/tdrfaqs/en/ Date last accessed: December 17, 2012. Date last updated: January 24, 2012.

4 Udwadia Z, Vendoti D. Totally drug-resistant tuberculosis (TDR-TB) in India: every dark cloud has a silver lining. *J Epidemiol Community Health* 2013; **67**: 471–472.
5 Srivastava S, Pasipanodya JG, Meek C, *et al.* Multidrug-resistant tuberculosis not due to noncompliance but to between-patient pharmacokinetic variability. *J Infect Dis* 2011; 204: 1951–1959.

Eur Respir J 2013; 42: 291–292 | DOI: 10.1183/09031936.00205212 | Copyright ©ERS 2013

From the authors:

We wish to thank S. Srivastava and colleagues for their correspondence in response to our article [1], which raised three major issues deserving further discussion.

First, the importance of considering totally drug-resistant (TDR) tuberculosis (TB) (a term that the World Health Organization no longer recommends the use of, in favour of the term: resistance beyond extensively drug-resistant (XDR)-TB) cases as being curable [1].

No case is incurable by definition; we need to re-enforce the message that, although difficult-to-treat, XDR-TB cases can have concrete chances of winning their battle against the disease. This message is even more convincing now that we have much improved diagnostic tools *e.g.* GenXpert [2] and new drugs, *e.g.* delamanid, bedaquiline and PA-824 [3, 4].

Secondly, we fully agree that the present evidence on the extent of drug susceptibility testing, as of today, still provides suboptimal predictions for the *in vivo* effect of second-line anti-TB drugs and further research is needed. In addition, the real impact of the cocktail of anti-TB drugs prescribed on an individual basis is not fully clear. It is difficult, in fact, to attribute cause and effect to each specific drug and the design of prospective clinical trials is also difficult when dealing with XDR-TB and other complicated multidrug-resistant cases.

Thirdly, in our opinion S. Srivastava and colleagues are right to suggest that therapeutic drug monitoring represents the future for improving the quality of second-line anti-TB drugs prescription.

Any contribution in this direction will represent a significant step forward in improving patient management, optimising doses, minimising adverse events and, consequently, maximising the drugs' effect.

@ERSpublications
Totally drug-resistant TB, drug susceptibility testing and therapeutic drug monitoring
http://ow.ly/ksmfx

Giovanni Sotgiu[1], Antonio Spanevello[2,3] and Giovanni Battista Migliori[3]

[1]Epidemiology and Medical Statistics Unit, Dept of Biomedical Sciences, University of Sassari-Research, Medical Education and Professional Development Unit, AOU, Sassari, [2]Università degli Studi dell'Insubria, Varese, and [3]World Health Organization Collaborating Centre for Tuberculosis and Lung Diseases, Fondazione S. Maugeri, Care and Research Institute, Tradate, Italy.

Correspondence: G. B. Migliori, S. Maugeri Foundation, Via Roncaccio 16, Tradate, Varese, 21049, Italy. Email: giovannibattista.migliori@fsm.it

Received: Feb 15 2013 | Accepted: Feb 15 2013

Conflict of interest: None declared.

References

1 Migliori GB, Sotgiu G, Gandhi NR, *et al.* Drug resistance beyond extensively drug-resistant tuberculosis: individual patient data meta-analysis. *Eur Respir J* 2013; 42: 169–179.
2 Weyer K, Mirzayev F, Migliori GB, *et al.* Rapid molecular TB diagnosis: evidence, policy making and global implementation of Xpert MTB/RIF. *Eur Respir J* 2013; 42: 252–271.
3 Diel R, Loddenkemper R, Zellweger JP, *et al.* Old ideas to innovate TB control: preventive treatment to achieve elimination. *Eur Respir J* 2013 [In press DOI: 10.1183/09031936.00205512].
4 Skripconoka V, Danilovits M, Pehme L, *et al.* Delamanid improves outcomes and reduces mortality for multidrug-resistant tuberculosis. *Eur Respir J* 2013; 41: 1393–1400.

Eur Respir J 2013; 42: 292 | DOI: 10.1183/09031936.00028913 | Copyright ©ERS 2013