Diagnosis

Resistance mechanisms in *Mycobacterium tuberculosis*: 2008 update

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The history of tuberculosis (TB) changed dramatically after the introduction of anti-mycobacterial agents. Drug treatment is fundamental for controlling TB, promoting the cure of the patients and breaking the chain of transmission. Soon after the introduction of the first anti-mycobacterial drugs, drug resistant bacilli started to emerge, and currently there is an important increase in the incidence of TB with mono, multiple and extensively drug resistant strains. The natural drug resistance of *M. tuberculosis* has traditionally been attributed to the unusual cell envelope and active multidrug efflux pumps. This resistance is important because it decreases the numbers of drugs available to treatment and could promote the emergence of resistant strains with high level of resistance. Acquired drug resistance in *M. tuberculosis* is caused essentially by mutations in chromosomal genes. Although no single mutation has been found in *M. tuberculosis* to cause a MDR phenotype, recently was demonstrated that some specific mutations as *emb*B codon 306 and katG codon 315 could increase the fitness and promote the emergence of strains with future alteration in other genes related to high level of resistance to different drugs. Even though alterations in several genes had been related with resistance in *M. tuberculosis*, there are several resistant strains which do not present these classic mutations, suggesting the possibility of the other mechanisms of resistance. The knowledge about resistance is related with development of new drugs, new diagnostics methods and best control to TB-MDR expansion.

Scenes from the anti-mycobacterial drug wars

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While drug resistant strains of *M. tuberculosis* have become notorious, resistance of the atypical mycobacteria not only to antibiotics, but also to disinfectants, is an emerging problem.

The first new class of agents to be used against *M. tuberculosis* were the fluoroquinolones, but resistance to these drugs rapidly developed, repeating the experience of their use with other bacteria. The mechanisms of resistance to the fluoroquinolones in other bacteria are mutations in the gyrase and topo IV, increases in the activity of efflux pumps, and the presence of pentapeptide proteins on transmissible plasmids. The only documented mechanisms of FQ resistance in mycobacteria are gyrase mutations, mostly in gyrA, and occasionally in gyrB. While mycobacterial efflux pumps have been alleged to pump out the fluoroquinolones, none have yet been causally implicated in a resistant strain. Overexpression of the

pentapeptide MfpA causes resistance that is synergistic with gyrA mutations, but it is not known whether it plays a role in FQ resistant strains, and its normal function has yet to be defined.

Different atypical mycobacteria show a range of sensitivity to disinfectants, especially the quanternary ammonium compounds. Although these compounds are bacteriocidal against most other bacteria, and seem to be effective against mycobacteria in some lab tests, their use has been associated with mycobacterial infections after minor surgical procedures. One explanation may be that resistant bacteria are selected at high frequencies, through an unknown mechanism, and are then resistant to all compounds of this class.

Novel approaches for the diagnosis and drug resistance detection in *M. tuberculosis*

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Tuberculosis (TB) remains one of the major causes of global death from a single infectious agent. Of major concern for TB control is the emergence of drug resistance since the management of multidrug-resistant strains of *M. tuberculosis* is more difficult, leading to the use of second-line drugs that are less active, more expensive and more toxic for the patients. The recent description of 'extensively drug-resistant' (XDR) strains of *M. tuberculosis*, resistant to the main first- and second-line drugs stresses the need for new and improved methods for TB diagnosis and for the rapid detection of drug resistance. Continuous advances in molecular biology, a better understanding of the molecular basis of drug resistance and new approaches for the rapid detection of mycobacterial growth have provided new tools for the rapid detection of drug resistance and early diagnosis of the disease. This presentation will review the latest developments for TB diagnosis and drug resistance detection both by phenotypic and genotypic methods.

The main *Mycobacterium tuberculosis* lineages responsible for multidrug-resistant and extensively drug resistant tuberculosis in Argentina

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In the mid '90s, a few multidrug-resistant (MDR) *Mycobacterium tuberculosis* strains spread in Argentinean hospitals, mainly among AIDS patients. The most conspicuous was the so-called strain "M" of the Haarlem 2 lineage, which caused a prolonged epidemic in Buenos Aires City and suburbs. Other two strains contributed to a hospital outbreak in Rosario City, namely strain "Ra" and "Rb" of the LAM3 and T1 Tuscany lineages, respectively. Simultaneously, strain "O" of the LAM5 lineage was isolated from inmates in a penitentiary nearby Buenos Aires. Ten years later, lineages formerly associated to MDR TB transmission still prevail over other MDR TB strains circulating in our country. Furthermore, frequencies of *M. tuberculosis* lin-

eages responsible for new cases of MDRTB and extremely drug resistant (XDR) TB reported to the national surveillance system are different from frequencies of lineages observed in the pansusceptible *M. tuberculosis* population. In particular, H2 and LAM5 lineages are substantially overrepresented among MDR and XDR strains. In contrast, LAM3 and T1 Tuscany lineages show neither an increased frequency among MDR strains nor a leaning towards a drug resistance gain.

In conclusion, autochthonous strains of the H2 and LAM5 lineages, which are infrequent in our setting as susceptible strains, seem to posses a singular ability to build up drug resistance without impairing their ability to spread.