Multidrug-resistant tuberculosis emergence: a renewed challenge

Emergência de tuberculose resistente: renovado desafio

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The global increase in the incidence of tuberculosis (TB), observed since the beginning of the 1990s, reached its peak in 2004 and was followed by a slow decline, which was associated with the cure of 85% of the cases reported in the countries that adopted the directly observed treatment, short-course strategy, proposed in 1993. However, the epidemiological markers were different in regions where the HIV burden is heavy, or where foci of multidrug-resistant TB (MDR-TB) or extensively drug-resistant TB (XDR-TB) were identified.[1] According to the World Health Organization (WHO), there was a 65% increase in the number of cases of MDR-TB from 2000 to 2007. In 2005, the rates of primary and acquired MDR-TB were, respectively, 2.9% (range, 2.2-3.6%) and 15.3% (range, 9.6-21.1%). There were approximately 500,000 cases, only 30,000 (8.5%) of which were diagnosed, a low proportion having access to appropriate treatment.

Unfortunately, due to the lack of laboratories that can perform routine cultures and sensitivity tests, there is a lack of data regarding MDR-TB and XDR-TB in the group of 22 countries responsible for 80% of the worldwide TB burden, Brazil ranking 19th among those countries. A recent systematic review of 32 studies reported no association between HIV infection status and the prevalence of MDR-TB.[2] However, in South Africa (where there is adequate laboratory infrastructure), the proportion of HIV infection in the general population is high (over 20%) and the proportion of cure achieved with anti-TB treatment is low, there was an increase in MDR-TB, as well as numerous outbreaks of XDR-TB, principally in hospitals and prisons that did not adopt the TB infection control measures proposed by the WHO in 1999.[3] In a cohort analysis conducted in 6 countries and involving over 100 cases of MDR-TB occurring in 2008, cure rates ranged from 20% to 80%.[4] In a recent systematic review and meta-analysis, the cure rate was 62% (range, 58-67%).[5]

Principally in HIV-infected children and adults, MDR-TB is associated with a high mortality rate. In addition, recent reports have demonstrated that, contrary to what has been the case since the 1950s, some resistant strains of *Mycobacterium tuberculosis* can be more virulent than others.[6] According to mathematical models, the incidence of MDR-TB will decrease only when 75% of the MDR-TB cases are detected and when 80% of such cases respond favorably to treatment. In this context, in order to achieve the goals of the Stop TB partnership (a partnership hosted by the WHO and established in 2001) and the WHO Global Plan to Stop TB, proposed in 2006 with the objective of eradicating the disease by 2050, the international community began to give high priority to the following approaches to controlling MDR-TB and XDR-TB: a) access to "quick and effective" diagnosis; b) development of new drugs to treat active disease and infection; and c) new approaches to controlling infection in institutional and household contacts. Individuals with HIV infection or comorbidities are at a higher risk of harboring resistant strains of *M. tuberculosis*, as are those with resistant TB contacts, as well as homeless individuals and patients treated in hospitals/emergency rooms, jails or prisons that do not adopt effective measures to control infection.

In order to diagnose resistant TB, the WHO recommended, in June of 2008, the use of molecular tests and, in November of 2009, the use of colorimetric tests; however, the WHO emphasizes that, before such technologies are incorporated into the clinical routine, cost-effectiveness and cost-benefit studies should be conducted and that the impact of those tests on the health care system in which they are to be used should be evaluated.[7] Since studies investigating the effectiveness of the treatment of latent infection caused by resistant TB are scarce, the approach to institutional or household MDR-TB contacts has not been prioritized. In a recent survey conducted in 25 countries, it was reported that the guidelines of 10 countries (40%) required the evaluation of contact with MDR-TB, and that drugs potentially active against MDR-TB were employed in only 2 countries (8%).[8]

With the increase in MDR-TB and XDR-TB, the use of preventive treatment of individuals at risk of harboring such strains has become strategic, since it will reduce morbidity and mortality, as well as the costs to the health care system. The recent identification of new

drugs that are effective in treating MDR-TB (the diarylquinoline TMC207 and the nitroimidazopyran PA-824) brings a positive outlook for the control of MDR-TB and XDR-TB.[9,10] Data for 2007 show that, in Brazil, drug sensitivity tests were performed in only 2,780 (30.7%) of the 9,048 patients at risk of harboring resistant strains of *M. tuberculosis* (cases of treatment failure, recurrence or retreatment due to noncompliance). Only 372 cases of MDR-TB were reported. Of those, 7.8% were HIV-infected patients, and 14% died.

The analysis of the preliminary data collected in the II National Survey on Anti-TB Drug Resistance, a survey of 4,421 patients treated in 7 states (Rio de Janeiro, Rio Grande do Sul, Bahia, Federal District of Brasília, Santa Catarina, Minas Gerais and São Paulo), revealed primary and acquired isoniazid resistance rates of 6.0% (range, 5.2-6.8%) and 15.3% (range, 12.6-18.0%), respectively. For rifampicin, the rates were, respectively, 1.5% (range, 1.2-2.0%) and 8.0% (range, 6.1-10.4%). The primary and acquired MDR-TB rates were, respectively, 1.4% (range, 1.0-1.8%) and 7.5% (range, 5.7-9.9%).[1]* A comparison between these data and those reported in a study published in the current issue of our journal—a study of anti-TB drug resistance conducted by Marques et al.[11] and involving 783 samples collected in the state of Mato Grosso do Sul over a period of 7 years—reveals a lower proportion of primary isoniazid resistance (a rate of 2.9%; range, 2.3-3.5%) and a similarity in relation to the proportion of primary multidrug resistance (1.6%). However, acquired multidrug resistance was greater (20.3%), although it decreased over the study period (from 40% to 12%).

In view of this, the elevated levels of acquired MDR-TB described in the study conducted in Mato Grosso do Sul (which involved the entire health care system) and in the II National Survey on Anti-TB Drug Resistance indicate the need for urgent measures in Brazilian TB control programs that prioritize the early detection of MDR-TB, either by means of effective measures to control infection in hospitals/emergency rooms and prisons or by implementing phenotyping or molecular tests in local and referral laboratories, as well as by means of studies that evaluate the efficacy and effectiveness of new therapeutic regimens for active and latent MDR-TB.

[1] Data provided by Dr. José Ueleres Braga (Professor Hélio Fraga Referral Center-Oswaldo Cruz Foundation)

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References

1. World Health Organization [homepage on the Internet]. Geneva: World Health Organization, 2009 [cited 2010 Jan 01]. Global tuberculosis control: a short update to the 2009 report. Available from: http://www.who.int/tb/publications/global_report/2009/update/en/index.html
2. Suchindran S, Brouwer ES, Van Rie A. Is HIV infection a risk factor for multi-drug resistant tuberculosis? A systematic review. PLoS One. 2009;4(5):e5561.
3. Gandhi NR, Shah NS, Andrews JR, Vella V, Moll AP, Scott M, et al. HIV coinfection in multidrug- and extensively drug-resistant tuberculosis results in high early mortality. Am J Respir Crit Care Med. 2010;181(1):80-6.
4. World Health Organization [homepage on the Internet]. Geneva: World Health Organization/International Union Against Tuberculosis and Lung Disease, 2008 [cited 2010 Jan 01]. Anti-tuberculosis drug resistance in the world. Fourth global report [Adobe Acrobat document, 142p.]. Available from: www.who.int/tb/publications/2008/drs_report4_26feb08.pdf
5. Orenstein EW, Basu S, Shah NS, Andrews JR, Friedland GH, Moll AP, et al. Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis. Lancet Infect Dis. 2009;9(3):153-61.
6. Luciani F, Sisson SA, Jiang H, Francis AR, Tanaka MM. The epidemiological fitness cost of drug resistance in Mycobacterium tuberculosis. Proc Natl Acad Sci U S A. 2009;106(34):14711-5.
7. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde, Programa Nacional de Controle da Tuberculose. Recomendações para o Controle da Tuberculose no Brasil. Brasília: Ministério da Saúde; 2010.
8. Cain KP, Nelson LJ, Cegielski JP. Global policies and practices for managing persons exposed to multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2010;14(3):269-74.
9. Diacon AH, Pym A, Grobusch M, Patientia R, Rustomjee R, Page-Shipp L, et al. The diarylquinoline TMC207 for multidrug-resistant tuberculosis. N Engl J Med. 2009;360(23):2397-405.
10. Dalcomo MP, Andrade MK, Picon PD. Tuberculose multirresistente no Brasil: histórico e medidas de controle. Rev Saúde Publica. 2007;41(Suppl 1):34-42.
11. Marques M, Cunha EA, Ruffino-Netto A, Andrade, SM. Drug resistance profile of Mycobacterium tuberculosis in the state of Mato Grosso do Sul, Brazil, 2000-2006. J Bras Pneumol. 2010:36(2)224-231.