



COMMENT

Pyrazinamide susceptibility testing in all isolates of the *Mycobacterium tuberculosis* complex – a critical analysis[☆]

Testes de sensibilidade à pirazinamida em todos os isolados do complexo *Mycobacterium tuberculosis* – uma análise crítica

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In 1950 the World Health Organization (WHO) recognition of the public health threat caused by bovine tuberculosis led governments to implement control measures; these included the pasteurization of milk, rigorous inspection of carcasses in slaughterhouses, the culling of cattle with positive tuberculin tests and prohibiting animals from leaving infected farms. By these measures bovine tuberculosis was controlled or even eradicated. The tuberculosis due to *Mycobacterium bovis* (*M. bovis*) is now, therefore, an occupational zoonosis, with the risk groups coming from rural communities, farmers and handlers of cattle, workers of the meat industry, veterinarians and zoological garden workers.^{1,2}

Nowadays human infection by *M. bovis* is considered rare in developed countries, accounting for about 1% of all human tuberculosis cases.^{3–7} The laboratory identification of *Mycobacterium tuberculosis* complex (MTC) provides the clinical diagnosis of tuberculosis. The species *M. tuberculosis* and *M. bovis*, among others, belong to this complex. Although genotypically very similar, *M. bovis* is less easily transmitted between humans and is intrinsically resistant to pyrazinamide.^{4,8,9}

Based on this characteristic, the Direção Geral de Saúde (General Directorate of Health, DGS) has recently published Guideline 13/2010, in which it recommends performing drug susceptibility testing (DST) on all first-line anti-tuberculosis

drugs (differentiating isoniazid, rifampicin, streptomycin, ethambutol and pyrazinamide) in all isolates of *M. tuberculosis* complex and further subspecies differentiation when a pyrazinamide resistance isolate is found.¹⁰ It should be noted that the article 9/DT from DGS about first-line DST, in place since the year 2000, does not list the drugs.¹¹

This antibiotic, in the context of laboratory diagnosis, is not in the batch of anti-tuberculosis drugs to be first-line tested, although it is commonly used in first-line therapeutic regimens.¹² Testing it requires a different laboratory methodology from other DST, since this drug is only active in an acid environment. In a number of laboratories this test is performed whenever resistance to at least one of the remaining first-line drugs occurs.

The latest international recommendations, from the WHO and from the European Centre for Disease Prevention and Control (ECDC), do not include this drug in the group of the anti-tuberculosis drugs to be routinely tested. Both organizations refer to the low reproducibility and consequently unreliable results. WHO has emphasized also the expense.^{12,13}

The unit cost of these tests was calculated based on the selling prices to Administração Regional de Saúde do Norte (Northern Regional Health Administration) of a reagents kit required for DST implementation through a liquid culture system (BACTEC MGIT 960, Becton and Dickinson, Maryland, USA). The pyrazinamide susceptibility test costs around €45, almost three times as much as the other first-line DST. For a total cost evaluation of a test one would need to add the extra time spent, as well as costs of other reagents and laboratory material such as: suspension mediums, ethyl alcohol, bidistilled water, micropipette tips, syringes, needles, etc.

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The DGS Guidance, at a national level, will lead to thousands of pyrazinamide susceptibility tests per year, with an increased outflow of hundreds of thousands of Euros, which poses the question whether this can be really justified.

The arguments against, in addition to the international guidelines, also include the fact that studies that have been carried out have shown that the screening of *M. bovis*, based on pyrazinamide monoresistance, has a low positive predictive value, as well as others that have revealed the existence of *M. bovis* strains with other anti-tuberculosis resistance patterns.^{14,15}

Guideline 13/2010 from DGS is based on the significant increase in bovine tuberculosis; however, it is also clear that, nowadays, the *M. bovis* infection in human beings is, in practice, restricted to the risk groups. It would be very good if we could count on new prevention strategies, such as better communication between veterinary and human health working groups, to identify patients who are most susceptible to the disease. The pyrazinamide susceptibility test could then be performed on isolates from samples of these specific users and its cost/benefit ratio improved.

Conflicts of interest

The author has no conflicts of interest to declare.

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