

Advance in the diagnosis of pulmonary tuberculosis in children?

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The study was conducted in a health reference center in New Delhi, India with 50 children with suspected pulmonary tuberculosis (TB) who underwent: clinical evaluation, chest X-ray, tuberculin test, secretions culture (sputum, induced sputum (IS) and gastric lavage (GL) and GeneXpert-Rif TB test (molecular test based on PCR real-time).

The authors included in the study 2-month to 12-year old patients who had clinical signs or symptoms suggestive of TB: fever or cough for more than 2 weeks, loss or no weight gain and a history of contact with people with TB. Inpatients or outpatients were admitted. On two successive days, spontaneous sputum and then LG were collected from children able to expectorate. LG and then IS were collected from children unable to expectorate. The specimens were taken immediately to the laboratory. In addition, in selected cases, transthoracic-fine needle aspiration and bronchoalveolar lavage were performed. Sputum smear microscopy was performed by Ziehl–Neelsen stain and culture by MGIT method. Xpert was performed according to the manufacturer's instructions and the result was achieved in the laboratory after 1h and 45 min.

Based on clinico-radiological data, smear and tuberculin test patients were classified into TB and non-TB. This analysis, which excluded the result of culture and Xpert, allowed classifying patients with TB into: confirmed (smear positive) or probable TB (cases without smear positive but with clinic-radiological data consistent with pulmonary TB). Statistical analysis included sensitivity, specificity measures, positive predictive value and negative predictive value.

The diagnosis of TB was established in 23 patients (mean age 63.9 months old).

Sputum was positive in 7 (TB confirmed) and negative in 43. After clinico-radiological analysis, 27 patients were considered non-TB and 16 probable TB. In these cases, Xpert was positive in 10/16 and culture in 6 of them. Xpert was not positive (detectable) among the 27 non TB. Among 34 cases of Xpert negative, there was 1 culture positive.

Xpert was positive in 16 (69.5%) patients, and 12 (52.17%) patients were culture positive, out of 23 patients with TB. The other patients were diagnosed in clinico-radiological tests.

The analysis of Xpert showed: sensitivity 91.6% (IC 95% 59.7-99.5) and specificity 86.8% (IC 95% 71.1-95.05). VPP = 68.75% and VPN = 97.05%.

The authors comment on the high sensitivity of Xpert, higher than the values found in the meta-analysis of Detjen¹ and reiterate its high specificity. They also emphasize the high sensitivity of Xpert in relation to culture in the group of smear-negative patients, despite the use of MGIT, considered more sensitive than the traditional Loewestein Jensen. In this study, Xpert was superior to culture and the authors consider it a point of care in the diagnosis of TB in children.

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The study has the merit of being one of the few that evaluates Xpert in children along with other conventional diagnostic methods used in hospitals. Xpert test has been used in different researches with children, the results of which were not always consistent, but overall allow us to conclude the following: Xpert is about two times more sensitive than smear microscopy of sputum or gastric lavage in children with bacterial TB. Bacterial TB is a form of the disease in which the presence of acid-fast bacilli (sputum smear or culture) can be identified. This makes sense, as Xpert is a molecular method using real-time PCR and it is capable of detecting fragments of bacillus' DNA. Thus, bacillary fragments would likely to be identified in patients who have advanced TB disease, hence Xpert positive. On the other hand, childhood TB can be divided into two categories: children (<10 years old) and adolescents (≥ 10 years old). The reason for this difference is the fact that the disease in adolescents is often diagnosable by sputum smear microscopy. That is, bacterial TB. Most adolescents are bacilliferous tuberculous patient. However, most children are not. As a factor and confused issue, the articles that evaluated Xpert in childhood consider TB in children the disease among patients under 14 years old. Thus, much of Xpert positive described in these articles is the result of adolescents and children included in the same case. That is, patients with bacterial TB along the microbiologically negative patients.

In this study, the authors partly found themselves in this ambiguous situation. The age range of the patients goes up to 12 years old. It is not known, however, if the successful outcome was due to Xpert positive among adolescents. In any case, the positive result of the test was superior to culture, different than other authors have reported^{2,3,4} Shing et al, in their article, even consider Xpert as a point-of-care testing (that is, state-of-the-art test) for the diagnosis of TB in childhood, in view of its high sensitivity and specificity. One cannot, however, fail to mention that the authors were engaged in processing the collected specimens of their patients as soon as possible so that the method was developed in full. These details are also not clear in other articles and allow reflection on the optimal research conditions obtained in this study, in a reference center, and almost never achieved in routine health care of endemic TB areas. Moreover, one should take into account that the sample of TB patients was small. Small numbers can bring some difficulties in interpretation.

Bringing the reflections on this study to Brazil, we noted that the country makes available Xpert (called in Brazil the rapid molecular MTB test) in the Public Health System since 2014 in various cities of Brazil. Private laboratories also have the method, although its cost is high. Following the guidance of the World Health Organization (WHO), TRM-TB in Brazil is the test of choice for initial diagnostic investigation of adults and adolescents with suspected TB. The test, being automated, allows the result - at the laboratory level - in about two hours and, moreover, offers the possibility to identify patients with rifampicin-resistant TB. This resistance is a multidrug-resistant TB marker (MDR-TB). Therefore, it offers great advantage on the prognosis of some patients who require special treatment schemes.

The Ministry of Health does not recommend MDR-TB in children under the age of 10, because most of them are not bacilliferous TB patients. The diagnosis is done then by indirect methods (clinical and radiological finds, tuberculin test, epidemiological data) (5). However, adolescents with suspected TB can benefit from TRM-TB because most of the cases come along with bacterial TB. Based on the encouraging results of this study, despite the caveats discussed, one should consider developing an investigation under routine conditions and in reference centers of TRM-TB in children in our setting. The rapid arrival of specimens to the laboratory and the prompt release of the test results seem challenges we still have to overcome. The future may show that maybe this is indeed a point of care in TP in childhood.

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