NEW DIAGNOSTIC TOOLS IN CHILDHOOD TUBERCULOSIS

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Tuberculosis (TB) is one of the leading causes of disease and death worldwide. In many countries, TB control programs include efficient detection and treatment of latent infection (LTBI). Since infection in children is usually recent, prompt diagnosis and treatment of LTBI are essential. Accurate diagnosis of LTBI in contacts depends largely on tuberculin skin testing (TST). However, the TST is limited by a lack of specificity, especially in BCG vaccinated populations. The TST is also unable to distinguish recent infection from remote infection. Newly developed interferon-gamma release assays (IGRAs) have become commercially available to detect TB infection. One potential major advantage of IGRAs over the TST is to be unaffected by prior BCG. As a consequence, IGRAs are thought to be more specific than TST, at least in BCG-vaccinated populations. Furthermore, studies have shown a variable but generally high sensitivity of IGRAs (1). Although there is evidence for a greatest potential benefit of IGRAs in the diagnosis of TB infection in cases with difficult diagnosis, such as BCG-vaccinated children, adequate comparisons between TST and IGRAs in BCG-vaccinated children are limited.

Interpretation of the TST in BCG-vaccinated children is not entirely uncontroversial. However, a tuberculin reaction of 15 mm or more in diameter is generally considered to be a good criterion for identifying latent M. tuberculosis infection in vaccinated persons. This position came from both longitudinal and cross-sectional studies. In a longitudinal study, Chee et al examined the risk of TB disease in BCG-vaccinated children for the 4 years subsequent to TST reading at age 12. They found that a TST reading of 15 mm or more predicted the development of TB disease with a specificity of 98.2%, and a sensitivity of 27.1% (2). In a cross-sectional study, Menzies et al found that the percentage of
schoolchildren with TST reading of 15 mm or more varied from 1 to 3 % according to socio-economic status (3). Finally, a recent meta-analysis confirmed that patients who had received BCG vaccination were more likely to have a positive skin test, and that indurations larger than 15 mm were more likely to result from tuberculosis infection than from BCG vaccination (4). As a whole, specificity of 15 mm cutoff in BCG-vaccinated persons can be evaluated to 97-98%. Sensitivity of this 15 mm cutoff, estimated in patients with tuberculosis disease, ranged from 75% (5) to 83% (6). In a recent study, we demonstrated that TST cutoff of 15 mm or greater in BCG-vaccinated persons exposed to an idex TB case was significantly associated to many factors reflecting the degree of recent exposure, attesting the potential usefulness of this cutoff in identifying recent LTBI in BCG-vaccinated children (7).

Very few studies have compared IGRAs and TST reading in BCG vaccinated persons, with this cutoff of 15 mm. When done, specificities are very close. Johnson et al. assess the influence that BCG vaccination may have on the specificities of both ESAT-6 Quantiferon (QFT) and TST in a group of healthy young people who had not been exposed to M. tuberculosis (8). Five months after BCG immunization, only 1 of 54 students had a TST result of >=15 mm and none tested positive by QFT. Specificities were 98% and 100%, respectively. In a recent study in military personnel, no statistically significant difference in specificity between the QFT-G and TST was found using a 15-mm induration cutoff value (9). Values were 99.8% and 99.1%, respectively. It was also recently shown that overall agreement between IGRAs and TST increased with increasing cutoffs for TST (10). Furthermore, discrepancies between IGRAs and TST results may also be due to IGRAs, rather than to TST. A possible lack of sensitivity of IFN-gamma assays in detecting individuals with TST of 15 mm or greater, despite negative bacillus Calmette-Guérin vaccination status, was recently demonstrated (11).
A recent consensus statement of a Wolfheze workshop organised by KNCV/EuroTB proposed that a combination of TST followed by IGRAs should be an optimal approach for contact tracing in incidents where there is a known index or source case (1). In BCG-vaccinated children exposed to an index case, this approach would appear particularly useful for TST results between 10 and 15 mm. In this size range of induration, IGRAs demonstrated a much higher specificity than TST. Performing IGRAs on the day of TST administration or on the day of TST reading did not affect the result of the test (12). However, a boosting of IGRA responses has been observed several weeks after a TST. It was shown that 15% of QuantiFERON-TB Gold (QFT-G) turned positive one month after a first negative QFT-G and a first TST <15 mm, in low-risk students aged 20-29 years (13). Consequently, and similarly to TST, a positive IGRA result from a follow-up test performed after an initial evaluation including a TST is not synonymous of recent infection, but would also represent boosting of sensitivity.

TST positive results in contact investigation are also significantly associated with age, suggesting that positive TST responses may be largely related to remote infection (7, 11). It was suggested that IGRAs may provide more quantitative and dynamic measurement of cellular immune response than the TST, which would be important for serial testing studies (14). However, the failure to differentiate recent infection from background LTBI appears not specific to TST, but is also likely shared by IGRAs. Indeed, in situations with high community exposure to M. tuberculosis, ELISPOTs, whole-blood assays and TSTs are each positive in a majority of healthy adult controls (15, 16).

In conclusion, IGRAs offer an alternative to TST for the diagnosis of LTBI in children, but discordances between TST and IGRAs are observed, and remain largely unexplained as a result of the lack of a gold standard for LTBI. Consequently, adequate strategy of testing for latent infection in the context of a contact tracing programme remains unclear. To improve the
efficiency of contact investigations, different strategies for different patient groups, stratified according to their risk factors for infection, may be considered.

References

