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Latent tuberculosis: which test in which situation?

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Summary

Detection of latent tuberculosis infection (LTBI) is a cost-effective procedure in patients at high risk of developing tuberculosis later and who could benefit from preventive treatment. The commonest situation where screening is indicated is the search for infected contacts of an index case with pulmonary tuberculosis. As a screening procedure the current tendency is to replace the time-honoured tuberculin skin test by one of the new blood tests measuring the release of interferon gamma by sensitised T lymphocytes after stimulation by specific peptides from *M. tuberculosis*. The main advantage of the new tests is the absence of interference with BCG and non-tuberculous mycobacteria, which confers high specificity on the test. This allows a more selective choice of persons for whom preventive treatment is indicated. Some controversial issues remain, such as sensitivity in children and immunocompromised subjects, the predictive value of the blood test and interpretation of possible changes in test results over time. The technical aspects required for performance of the tests must be considered.

Key words: tuberculosis; latent tuberculosis infection; tuberculin skin test; interferon-gamma assays; contact investigations

Résumé

La détection de l'infection tuberculeuse latente (ITBL) est rentable dans toutes les situations où les personnes infectées courent un risque élevé de développer ultérieurement une tuberculose et peuvent être bénéficier d'un traitement préventif. La situation la plus fréquente où un dépistage est indiqué est la recherche de contacts infectés dans l'entourage d'un patient atteint de tuberculose pulmonaire. Comme méthode de dépistage, on tend actuellement à remplacer le traditionnel test tuberculinique par un des nouveaux tests sanguins qui mesurent la libération d'Interféron Gamma par les lymphocytes sensibilisés au contact des antigènes spécifiques de *M. tuberculosis*. L'avantage principal des nouveaux tests est l'absence d'interférence avec la vaccination BCG et les mycobactéries non-tuberculeuses, qui confèrent ainsi aux tests une spécificité élevée. En conséquence, le choix des personnes chez lesquelles un traitement préventif est indiqué est beaucoup plus sélectif. Il reste cependant des controverses, telles que l'indication et l'interprétation des tests chez les enfants et les personnes immunodéprimées, la valeur prédictive des tests et l'interprétation des modifications possibles de la réponse au cours du temps. Les impératifs techniques inhérents aux tests doivent être respectés.

Introduction

Subjects in contact with patients with smear-positive pulmonary tuberculosis may be infected if the index case coughs up and expels mycobacteria into the air. Infected contacts will then develop a progressive immune response and some will also develop the disease after a variable length of time (from several days to several years depending on the immunological status). The risk of reactivation is estimated to be between 5 and 10% throughout life and depends on several factors, such as age, sex, size of the tuberculin reaction, immune status, diabetes, smoking, drug treatment and nutritional status [1–4]. The risk is higher in the 2 years following infection and decreases with time [5].

In all countries the first priority is rapid detection and treatment of patients with transmissible forms of tuberculosis. In regions with a high incidence of tuberculosis a search for contacts among the relatives of smear-positive cases may succeed

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in detecting a large number of secondary cases, but the search for infected contacts is less of a priority except among close relatives and small children, who may rapidly develop severe forms of the disease [6]. In countries with a low incidence of tuberculosis the search for infected contacts is also considered a priority [7]. Soon after the introduction of antibiotics active against tuberculosis (as early as 1959), trials were conducted which demonstrated that, if properly prescribed and taken, preventive treatment reduces the risk of future disease [8, 9] and is cost-effective [10]. In theory at least, if applied rigorously to infected individuals or to whole populations with a high rate of latent infection, this policy could be successful in lowering the incidence of tuberculosis in the future [11].

Screening for infected individuals may also be considered in other population groups with a risk of infection higher than the local average, such as prison inmates, exposed health-care workers or immigrants from high-incidence countries or regions.

As individuals with latent tuberculosis are by definition healthy and do not present radiological abnormalities (except, in some cases, a scar from an earlier primary infection), screening must rely on immunological markers of infection. For nearly a century screening relied on the tuberculin skin test (TST) but the recent introduction of T-cell interferon gamma release assays (TIGRA) has changed the approach to screening and the indications for preventive treatment [12–15].

The blood tests measure the release of interferon gamma by T lymphocytes after stimulation with antigens from *M. tuberculosis*, like the tuberculin skin test, but the antigens used are specific peptides from *M. tbc* instead of a mixture of antigens, most of which are common to all mycobacteria, including *M. bovis BCG* [16]. The antigens used in commercial forms of the tests are encoded in the region of difference (RD1) of the *M. tuberculosis* genome, which is deleted in all *M. bovis BCG* strains and absent in the vast majority of non-tuberculous mycobacteria.

Compared with the tuberculin skin tests, the TIGRAs have several characteristics that make them appear better adapted to screening for latent infection: they are much more *specific* than TST because they are not influenced by prior vaccination with BCG and by contact with most non-tuberculous mycobacteria (the exception being *M. kansasii*, *M. szulgai* and *M. marinum*) [16–18] and they can be repeated without any *booster effect*.

In clinical practice TIGRAs, like TST, are essentially used to diagnose latent tuberculous infections (LTBI). The problem is that there is no gold standard for the diagnosis of LTBI (and there cannot be such a standard). Most investigators, however, agree that positive TIGRAs would occur almost exclusively in subjects who have encountered *M. tuberculosis*, ie subjects who actually have either LTBI or active tuberculosis. The consensus is therefore that positive TIGRAs should never be considered false positive, although the cutoffs for positivity of the commercial tests may need to be adjusted to optimise their accuracy [19]. As regards sensitivity, on the other hand, data from TIGRAs obtained in patients with active tuberculosis can be used as a surrogate for LTBI because a gold standard for active tuberculosis does exist (positive culture for *M. tuberculosis* together with a compatible clinical situation). Here it appears that there are some false negative TIGRAs, but fewer than false negative TST [20, 21]. Thus TIGRAs may prove positive where TST is negative, particularly in situations such as severe viral or drug-induced immunosuppression [22, 23].

In a study among 590 HIV-positive patients the test performed satisfactorily in all subjects with CD4 cell counts over 100 [24]. Among patients on haemodialysis, and among patients who were immunocompromised for reasons other than HIV, the blood test also performed better than the TST [25, 26].

In children the use of TIGRAs has produced controversial results. In one Australian study a high rate of indeterminate test results was observed among children exposed to tuberculosis but not among children with documented tuberculosis [27]. In another study conducted in Nigeria the blood tests correlated better than the TST with intensity of exposure [28]. In Gambia, TST showed high specificity among exposed children and a good correlation with ESAT-6/CFP-10 Elispot [29]. The reason for these discrepancies is not clear but may be related to the tuberculin used, the cutoff considered for positivity or the background prevalence of infection with non-tuberculous mycobacteria. A study performed in Germany has confirmed that the blood tests allow a distinction between infection with *M. tbc* and with non-tuberculous mycobacteria in children in a low-prevalence country [30]. Individual observations suggest that the blood tests may convert to positive before the TST [31].

In spite of their high specificity, the TIGRAs do not allow a distinction between latent infection and disease (the same applies to TST), and hence their use for the diagnosis of tuberculosis remains controversial [32–34]. As a potential indicator of disease the tests are probably useful only in populations where the prevalence of LTBI is low, as in children from low-incidence countries [35].

The TIGRAs correlate better than the TST with the intensity of contact with the index case, in children [28] and in adults [36–38].

In contrast to the TST, the TIGRAs can be repeated without any booster effect. The possible influence of a TST performed before blood sampling is controversial, some studies having demonstrated no influence [39, 40] while others observed a possible effect [41].

Comparison between TST and TIGRAs

As the TIGRAs are more specific than the TST, the number of contacts with a positive blood test in a contact investigation is lower than the number of persons with a positive TST, particularly if the proportion of BCG-vaccinated individuals is high [18]. But even in populations with no prior BCG vaccination the number of individuals found to be positive is lower, probably due to the exclusion of false positivity associated with sensitisation with non-tuberculous mycobacteria [19, 42], although a true difference in sensitivity between both tests is also possible. As there is no gold standard for latent infection (except the later development of disease), the true sensitivity of the blood tests cannot yet be assessed. In individuals where the sensitivity of the TST is low, the TIGRAs may be positive even if the TST is negative [22]. The main similarities and differences between TST and TIGRAs are reported in table 1.

The degree of positivity of the blood tests tends to decrease during and after preventive or curative treatment, but seldom reverts to negative. This may indicate that the bacterial load and antigenic stimulation have decreased [43, 44], but it seems premature to conclude that the TIGRAs can be used to predict the success or failure of antituberculous treatment [45]. An intriguing observation is the spontaneous reversion to negative of positive test results among contacts tested repeatedly but not treated preventively [46, 47]. This phenomenon is also observed with TST, though more rarely, and may reflect a decrease in the amount of circulating antigens from *M. tbc* and a consequent decrease in the stimulation of T lymphocytes. Whether this indicates that the mycobacteria have entered a stage of dormancy or have been eradicated spontaneously remains unclear [48].

The main interest of the TST is that it allows a crude but reliable evaluation of the risk of contacts with a positive test result developing tuberculosis in the future [1]. Predicting this is more difficult with the TIGRAs as there are no long-term follow-up studies comparing the risk of tuberculosis in populations with positive or negative test results [49]. The only study published up to now concerns a small group of 24 contacts who did not receive preventive therapy and where the contacts with a positive interferon-gamma test had approximately twice the risk of developing tuberculosis within the next 2 years compared to subjects with a positive tuberculin skin test [50]. Considering the fact that approximately half of the positive TST are false positive, at least in populations with a high BCG vaccination coverage, this is not surprising, but confirmation is expected in large populations. Clearly, the answer to this question would represent an important advance in our understanding of the mechanism of latent tuberculosis infection and its control [51].

Indeterminate test results

Although the test results are usually given as positive or negative, some of them cannot be interpreted and must be considered indeterminate. The most common reason for such results is the fact that the positive mitogen control fails to react, indicating the absence of stimulable lymphocytes. This may be due to pre-analytic errors (freezing of the blood sample during transportation) or real absence of living lymphocytes. An indeterminate result may be an indication of an immune defect and should arouse clinical suspicion. Some factors, such as very young or very old age, immune deficiencies and use of oral steroids, may be associated with a higher rate of indeterminate results [52, 53]. Indeterminate test results should not be confused with false negative results which may be observed in some rare patients with active tuberculosis.

Table 1

Main similarities and differences between tuberculin skin tests (TST) and T-cell Interferon-Gamma Assays (QuantiFERON-TB Gold = QFT and T-SPOT.*TB*)

	TST	QFT	T-SPOT.TB
Influenced by prior BCG vaccination	Yes	No	No
Influenced by non-tuberculous mycobacteria	Yes	No (with exceptions)	No (with exceptions)
Booster effect if repeated	Possible	No	No
False positive results	Possible	No evidence	No evidence
False negative results	Possible	Possible	Possible
Correlation with exposure intensity	Partial	Yes	Yes
Antigens used	PPD RT23	ESAT-6, CFP-10	ESAT-6, CFP-10
Technique	In vivo skin test	ELISA	ELISPOT
Results given in	mm of induration	IFN-γ units	Spot-forming units

Technical aspects

Two commercial tests are currently available on the European market, the QuantiFERON-TB Gold (and its modified version QuantiFERON-TB in Tube), relying on Elisa technology, and the T-SPOT-*TB* test, relying on Elispot technology. They are more costly than tuberculin skin tests. In Switzerland both commercial tests are included in the official List of Analyses and are refunded by health insurance.

In Elisa technology the concentration of interferon gamma released by lymphocytes after incubation with specific *M. tbc* antigens is measured directly in the whole blood. In Elispot technology the number of lymphocytes releasing interferon gamma is counted visually after standardisation of the number of lymphocytes in each incubation well.

Both tests must be performed in laboratories with adequate equipment and trained staff, and the pre-analytic requirements must be carefully observed, particularly the delay between sampling and analysis (not more than 8 hours) and the need to transport the samples at room temperature (freezing or exposure to cold may inhibit the lymphocytes) [53].

Both commercial tests rely on a similar principle but differ in their operational characteristics. In comparative studies they appear to give similar results among healthy adults, but they may differ in children and immunocompromised patients and the results may be discordant. A detailed comparison of the operational characteristics and performance of the tests is outside the scope of this paper and has been addressed in several publications [22, 55–57].

Indications

Screening for LTBI is not an end in itself but should have therapeutic implications and contribute to evaluation of the risk of developing tuberculosis. The main indications for screening for tuberculosis infection are:

1. Screening for latent tuberculosis infection (LTBI) among TB contacts.
2. Screening for LTBI before immunosuppressive therapy (recommended) or in immunosuppressed patients (debatable).
3. Regular screening among exposed persons (health-care workers).
4. Screening of immigrants from high incidence countries (controversial).

Screening for LTBI among contacts

Considering the high specificity of the blood tests, two strategies for screening for latent tuberculosis infection may be considered: one strategy proposes to replace the tuberculin skin test entirely by the TIGRAs, at any rate in immunocompetent adults, assuming that the sensitivity of both tests is similar [58, 59]. The advantage of this strategy is that one single test is needed and therefore one single visit for screening. The disadvantage is an increase in overall costs, as the vast majority of tests will be negative. Another strategy proposes to perform a tuberculin skin test first, in order to exclude all contacts who are not infected, and then to test only the contacts with a positive TST to separate the true positives from the false positives. This strategy is less costly [60], but involves two visits (one to perform the TST and one to read the test and perform the blood test if the TST is positive) [61, 62]. Moreover, it requires the health care staff to be still able to perform and correctly read the TST. In population groups where the probability of immunosuppression is high or the risk of not presenting for the reading of the TST is high, immediate performance of the blood test may be preferable. On the other hand, according to a model developed by a Canadian group, in populations with a low prevalence of latent TB infection or a strong likelihood of false-positive TST due to prior BCG vaccination, sequential testing (TST with confirmation of positive test results by TIGRA) may be more cost-effective [13]. The same model concludes that in population groups where the prevalence of true positive TST is high (as in non-vaccinated children), the sequential strategy is less cost-effective than a strategy of single testing.

In healthy children not vaccinated with BCG, and living in regions where the prevalence of infections with non-tuberculous mycobacteria is low, the TST still appears to be a satisfactory screening test since it correlates fairly well with the future risk of tuberculosis [4, 63, 64]. Also, blood sampling in small children may fail in a large proportion of cases [27].

Screening before immunosuppressive therapy

Immunosuppressive therapy, particularly with anti-TNF, may increase the risk of reactivating tuberculosis in patients with latent tuberculosis infection [65–67]. Screening for LTBI before the introduction of immunosuppressive therapy and adequate preventive treatment is therefore justified. Since the TST may frequently be negative in patients already receiving drugs with immunosuppressive properties, the use of TIGRAs for screening is currently recommended [59].

Screening among exposed health-care workers

Health-care workers (HCW) may be exposed to tuberculosis more frequently than the local population, particularly in settings where tuberculosis is frequent among hospitalised patients [68] or if there are undiagnosed cases of tuberculosis in the hospital [69]. Hence regular monitoring of exposed staff is frequently recommended, but the use of TST is controversial because a large proportion of workers have received prior BCG vaccination and may present a false-positive reaction [70]. The use of a more specific screening method, avoiding the influence of BCG vaccination and the possible booster effect observed in serial testing with TST, is therefore welcome [71]. Serial testing of HCW with TIGRAs has been performed but the results may be confused by the fact that some HCW appear to revert after an apparent conversion, and thus the indications for preventive therapy may not be clear [72].

Screening immigrants from countries with a high incidence of tuberculosis

The use of TIGRAs for the screening of large population groups with a high rate of infection, such as migrants from countries with a high incidence of tuberculosis, has been considered but is not performed on a large scale. A recent analysis has concluded that such a screening procedure is cost-effective only in groups with a high risk of disease and in confirming a positive TST with a blood test [13].

Conclusions

a) The specificity of the blood tests narrows the indications for preventive therapy [73]. No preventive chemotherapy should therefore be prescribed without confirmation of infection by a blood test, except in children. This strategy reduces the number of persons needed to treat to avoid a future case of tuberculosis from 50 (using TST as a definition of infection) to 18 [74].
b) Due to technical constraints, the use of TIGRAs is currently restricted to the situations where they offer better specificity and cost-effectiveness than tuberculin skin tests.
c) There are still many open questions regarding the operational characteristics of the new TIGRA tests. Clarification of their predictive value and use in specific population groups (children, immunosuppressed patients) and changes in the performance, procedures or cost of the tests may enlarge their indication in the future.

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