

Correspondence

Use of Commercial Interferon- γ Assays in Immunocompromised Patients for Tuberculosis Diagnosis

To the Editor:

We read with interest the recent article by Ferrara and colleagues (1) describing the routine use of QuantiFERON-TB Gold (QFTGold) (1, 4) for tuberculosis (TB) diagnosis. The authors report sensitivity of the tuberculin skin test (TST) as 33.3% and for QFT-Gold as 66.7%. The authors also report a high number of indeterminate results with the QFT-Gold test (23%) related, in particular, to the extent of immunosuppression in the patient groups. This paper (1) opens discussion on some important issues:

1. In a prospective study, we have evaluated the other new blood test for tuberculosis, T-SPOT.TB (Oxford-Immuneotec, Oxford, UK), against the TST. T-SPOT.TB enumerates individual activated TB-specific T cells using enzyme-linked immunospot (ELISPOT) methodology (3). A total of 500 patients who were referred to the Lombardia Centre for Tuberculosis Control as TB suspects or during routine contact tracing were enrolled.

2. The sensitivity of the TST found in those later confirmed with TB disease was 87.0% (40/46). This is much higher than the 33% sensitivity reported by Ferrara and colleagues, and more consistent with the usual reported sensitivity for the TST (6). Given the unusually low sensitivity found for the TST by Ferrara and coworkers, it would be useful for them to set out any underlying immunosuppression of these patients. In addition, as only 6 of the 11 reported subjects with TB disease were confirmed by culture, it would be useful for them to set out the basis of diagnosis for the remaining 5.

3. The sensitivity of the T-SPOT.TB test in our population was found to be 95.3%. This is significantly higher than that reported for the QFT-Gold test, and this difference in sensitivity appears to be a consistently emerging observation (2, 3, 5).

4. Comparison of numbers of indeterminate results between QFT-Gold and T-SPOT.TB is also illuminating. In our study, the tested population included a group of 138 immunocompromised hematology patients exposed to an infectious case during their chemotherapy and 32 patients immunosuppressed for other reasons (immunological diseases, cancer, HIV). In this (often severely) immunosuppressed subpopulation, the indeterminate rate for T-SPOT.TB was only 4.7%.

The authors conclude that commercial interferon- γ tests are suitable for routine diagnosis of TB infection, but the performance of the tests is negatively affected by patients' immunosuppression. We would caution the authors to the evident methodological and clinical differences between the two new blood tests for TB; our results would suggest that T-SPOT.TB performs successfully even in immunosuppressed patient groups.

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References

1. Ferrara G, Losi M, Meacci M, Meccugni B, Piro R, Roversi P, Bergamini BM, D'Amico R, Marchegiano P, Rumpianesi F, *et al.* Routine hospital use of a commercial whole blood interferon- γ assay for tuberculosis infection. *Am J Respir Crit Care Med* 2005;172:163–165.
2. Piana F, Codecasa LR, Cavallerio P, Orfeo N, Barbarano L, Morra E, Cirillo DM. Use of IFN- γ test in contact tracing in a haematology department for identifying nosocomial spreading of tuberculosis. Presented at 26th Annual Congress of the European Society of Mycobacteriology; June 26–29, 2005; Istanbul, Turkey. Abstract book, p. 59.
3. Lalvani A, Pathan AA, McShane H, Wilkinson RJ, Latif M, Conlon CP, Pasvol G, Hill AV. Rapid detection of *Mycobacterium tuberculosis* infection by enumeration of antigen-specific T cells. *Am J Respir Crit Care Med* 2001;163:824–828.
4. Pai M, Riley LW, Colford JM. Interferon- γ assays in the immunodiagnosis of tuberculosis: a systematic review. *Lancet Infect Dis* 2004;4:761–776.
5. Mori T, Sakatani M, Yamagishi F, Takashima T, Kawabe Y, Nagao K, Shigeto E, Harada N, Mitarai S, Okada M, *et al.* Specific detection of tuberculosis infection with an interferon- γ -based assay using new antigens. *Am J Respir Crit Care Med* 2004;170:59–64.
6. Huebner RE, Schein MF, Bass JB. The tuberculin skin test. *Clin Infect Dis* 1993;17:968–975.

From the Authors:

Dr. Piana and colleagues comment on the low sensitivity of the tuberculin skin test (TST) in patients with active tuberculosis as reported in our study, which examined routine use of the new interferon- γ (IFN- γ) QuantiFERON-TB Gold (Cellestis Ltd., Carnegie, Victoria, Australia) test for the diagnosis of tuberculosis infection (1). They also compare the 33.3% rate of positive TST in our report with the 87.0% rate of positive TST that they observed among 46 patients with tuberculosis in an unpublished study. Further, they highlight the special characteristics of our inpatients with active disease. In fact, out of the 11 patients with tuberculosis, 4 had extrapulmonary or disseminated disease while three others had concomitant cancer or were taking immunosuppressive drugs; all these medical conditions are known to significantly reduce the rate of positive TST results (2, 3). Moreover, the low proportion of patients with positive microbiology results was also due to the significant fraction of cases with extrapulmonary localization or with concomitant immunosuppression.

Piana and colleagues also refer to the results of a contact tracing investigation among 138 immunosuppressed patients in a hematology unit, where they used the T-SPOT.TB test (Oxford Immuneotec Ltd.) to detect infected contacts (4). In that study, they identified 35 contacts who were positive with T-SPOT.TB and negative with the TST, thus suggesting a higher sensitivity of T-SPOT.TB. These results are consistent with recent reports on the use of T-SPOT.TB (5, 6), showing high sensitivity for the diagnosis of tuberculosis infection in immunosuppressed patients. This does not seem to be the case with the QuantiFERON-TB Gold test used in our study, as we observed a high proportion of indeterminate results, which were strongly associated with immunosuppression (1).

As discussed in our article, at the present time, only data from preselected cohorts of patients have been published for QuantiFERON-TB Gold. QuantiFERON-TB Gold (a whole blood test based on the ELISA technique) and T-SPOT.TB (using the ELISPOT technology on pre-separated blood cells) have some methodological differences (7). Only the ELISPOT test has been used in those patients in whom the TST is most often falsely negative, such as HIV-infected patients (6) and newborns (8). Data in these vulnerable groups are lacking for QuantiFERON-TB Gold, and direct comparative studies of both blood tests in parallel have not yet been published. Therefore, in our paper, we focus on the rate of indeterminate results of the QuantiFERON-TB Gold in patients routinely tested for tuberculosis infection in a hospital setting. We did not infer any conclusions regarding the other commercially available test.

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References

1. Ferrara G, Losi M, Meacci M, Meccugni B, Piro R, Roversi P, Bergamini BM, D'Amico R, Marchegiano P, Rumpianesi F, et al. Routine hospital use of a new commercial whole blood interferon- γ assay for the diagnosis of tuberculosis infection. *Am J Respir Crit Care Med* 2005;172:163–165.
2. American Thoracic Society; Centers for Disease Control and Prevention. Diagnostic standards and classification of tuberculosis in adults and children. *Am J Respir Crit Care Med* 2000;161:1376–1395.
3. Huebner RE, Schein MF, Bass JB Jr. The tuberculin skin test. *Clin Infect Dis* 1993;17:968–975.
4. Piana F, Codecasa LR, Cavallerio P, Orfeo N, Barbarano L, Morra E, Cirillo DM. Use of IFN- γ test in contact tracing in a haematology department for identifying nosocomial spreading of tuberculosis. Presented at 26th Annual Congress of the European Society of Mycobacteriology; June 26–29, 2005; Istanbul, Turkey. Abstract book, p. 59.
5. Richeldi L, Ewer K, Losi M, Hansell DM, Roversi P, Fabbri LM, Lalvani A. Early diagnosis of subclinical multidrug-resistant tuberculosis. *Ann Intern Med* 2004;140:709–713.
6. Liebeschuetz S, Bamber S, Ewer K, Deeks J, Pathan AA, Lalvani A. Diagnosis of tuberculosis in South African children with a T-cell-based assay: a prospective cohort study. *Lancet* 2004;364:2196–2203.
7. Pai M, Riley LW, Colford JM Jr. Interferon-gamma assays in the immunodiagnosis of tuberculosis: a systematic review. *Lancet Infect Dis* 2004;4:761–776.
8. Richeldi L, Ewer K, Losi M, Bergamini BM, Roversi P, Deeks J, Fabbri LM, Lalvani A. T cell-based tracking of multidrug resistant tuberculosis infection after brief exposure. *Am J Respir Crit Care Med* 2004;170:288–295.

Adult Hospital and Ventilator-associated Pneumonia Guidelines: Eminence- rather than Evidence-based

To the Editor:

We read with interest the guidelines on the management of adult hospital and ventilator-associated pneumonia issued by the American Thoracic Society/Infectious Diseases Society of

America (ATS/IDSA) (1). However, we were disappointed by the subsection entitled “Modulation of colonization.” The guidelines confirm that the oropharynx is the major source of potential pathogens that cause lower airway infections, an observation made by Johanson more than 30 years ago (2). Eradication of aerobic gram-negative bacilli (AGNB) carriage with chlorhexidine mouthwashes is a new message. In the randomized controlled trial (RCT) of DeRiso and colleagues (3), potential pathogens were not identified, although it is well known that AGNB, in particular *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, are intrinsically resistant to chlorhexidine. A recent English RCT failed to confirm the DeRiso study (4).

We would like to make it quite clear that oropharyngeal decontamination on its own has never been shown to reduce mortality (5), and that the ATS/IDSA Guideline Committee is misleading the readers in mentioning the two individual RCTs of large sample size showing an absolute mortality reduction of 8% under the heading of oral decontamination. These two RCTs evaluated oral and gut decontamination using enteral and parenteral antimicrobials, which is quite different from only oropharyngeal decontamination. Those two RCTs were included in the most recent meta-analysis of 36 RCTs of selective decontamination of the digestive tract (SDD) showing a significant relative mortality reduction of 22% (odds ratio [OR], 0.78; 95% confidence interval [CI], 0.68–0.89) (6). Unfortunately, the committee did not mention this meta-analysis, while meta-analyses were commonly included in the guidelines for other maneuvers.

A proper resistance analysis should distinguish multiresistant AGNB, methicillin-resistant *Staphylococcus aureus* (MRSA), from vancomycin-resistant enterococci (VRE). In a Parisian intensive care unit (ICU) with high endemic levels of *Klebsiella pneumoniae* producing extended spectrum β -lactamase (ESBL), SDD cleared the resistant outbreak strain in a randomized design (7). Similarly, 5 years of SDD in an Innsbruck ICU rendered the unit free from multiresistant AGNB (8). In an observational study in a Manchester unit with endemicity of ESBL-producing *Klebsiella*, SDD given to all patients cleared the outbreak strain within 3 months (9). Therefore, SDD did not increase the AGNB resistance problem but solved the problem of endemicity of multiresistant AGNB.

Fair enough, SDD, by design, is not active against MRSA, and seven SDD RCTs undertaken in units with MRSA endemicity show a trend toward a higher MRSA infection rate (10–16). Under these circumstances, enteral vancomycin must be added to the classical polymyxin/tobramycin/amphotericin B (PTA) protocol (17). Two American RCTs evaluated PTA in an ICU setting with VRE endemicity, and reported the same carriage and infection rates in both groups (18, 19). Eight RCTs assessed SDD, including enteral vancomycin, and VRE problems did not emerge (17, 20–26). Three ecology studies demonstrated that the introduction of new potent antimicrobials, such as piperacillin/tazobactam, which disregard the ICU patient's normal flora, promoted VRE, while enteral vancomycin, given to treat *Clostridium difficile* in a VRE environment, did not promote VRE (27–29). Antimicrobial resistance, being a long-term issue, has been evaluated in eight SDD studies: bacterial resistance associated with SDD has not been a clinical problem (30–37). The recommendation of the ATS/IDSA Guideline Committee that routine SDD should be discouraged because of resistance is expert opinion and not supported by evidence.

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