The value of biological markers with focus on ADA and IFN-γ for diagnosis of tuberculosis

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Introduction

• Tuberculosis (TB) is a major cause of morbidity and mortality.
• The global incidence of TB is increasing by 0.4% per annum.
• Our tools for diagnosis and prevention are inadequate to contain the epidemic.
Tuberculous pleurisy

• The Diagnosis of TB pleural effusion, which requires the isolation of *M. tb* from the pleural fluid or pleural biopsy specimens or the demonstration of caseating granulomas on histological examination of biopsy, is still difficult.

• 10-35% culture

• 20-81% molecular tests

• 86% histological and microbiological
Tuberculous pleurisy

- Pleural effusion results from an immune reaction to *M. tuberculosis* antigens, then, the diagnostic potential of soluble markers of immune activation can be considered.

- Adenosine deaminase (ADA), a purine degrading enzyme implicated in mononuclear phagocyte maturation, and IFN-γ, a T-cell derived cytokine that plays a pivotal role in granulomatous inflammation, have been reported to accumulate in the pleural fluid of TB patients and to predict TB pleurisy with high sensitivity and specificity.
Test Condition

- Highest Yolden index ($ Sensitivity + specificity - 1 $)
- TP, FP, TN, FN
- Groups:
  - Exudative effusion
  - Malignant effusion
  - Paraneumonic effusion
Sensitivity and specificity of ADA

Sensitivity

Specificity

ADA

(46) (47) (48) (49) (50) (51) (52) (53) (54) (55) (56) (57) (58) (59) (60) (61) (62) (63) (64) (65) (66) (67) (68) (69) (70) (71) (72) (73)
Sensitivity, specificity and the threshold value for ADA

- Sensitivity: 92% (56%-100%)
- Specificity: 89% (55%-100%)
- Threshold value: 42 IU/L (10-70)
Q-value for ADA

Q-value: 93% (weighted 88%)

Increasing sensitivity to 100% decreases specificity to approximately 90%
TB discriminating with malignant and paraneumonic effusions

Q-value for discriminating TB from Malignant effusion: 95.2%

Q-value for discriminating TB from paraneumonic effusion: 96%
IFN-γ-based tests

Early secretary antigenic target-6 (ESAT-6)

Culture filtrate protein-10 (CFP-10)
Sensitivity and specificity of IFN-γ
Sensitivity, specificity and the threshold value for IFN-γ

• Sensitivity: 87% (57%-100%)

• Specificity: 97% (90%-100%)

• Threshold value: 4.9 IU/L (0.8-13)
Q-value for IFN-γ

Q-value: 96.4% (weighted 95.2%)

Increasing sensitivity to 100% decreases specificity to approximately 95%
TB discriminating with malignant and paraneumonic effusions

Q-value for discriminating TB from Malignant effusion: 96%

Q-value for discriminating TB from paraneumonic effusion: 94.2%
Pre-and Post-test probability

Pre-test probability

Post-test probability

IFN-γ, 96.4%

ADA, 93%

Pre-test probability

Post-test probability

ADA, 93%

IFN-γ, 96.4%
Tuberculous meningitis (TBM)

- TBM is one of the most harmful infectious diseases, and accounts for 1% of all forms of TB.
- About 30% of TBM patients die despite anti-tuberculosis chemotherapy, and early treatment is essential for satisfactory improvement.
- The diagnosis of TBM is difficult due to the low sensitivity of AFB and defining the growth of *Mycobacterium tuberculosis bacilli* is time consuming.
- A quick, non-invasive test to confirm TBM would therefore be helpful.
Diagnostic value of ADA in TBM

Sensitivity: 50-100% (79%)
Diagnostic value of ADA in TBM

Specificity: 63-99% (91%)
Q-value for ADA

Q-value: 85%
Latent tuberculosis infection (LTBI)

- In many high-income countries, the diagnosis and treatment of latent tuberculosis infection (LTBI) are an integral part of tuberculosis (TB) control and plans (hopes) for elimination.
- Limitation in LTBI Diagnosis
  - TST (lack of enough specificity) due to BCG vaccination.
  - The TST cannot discriminate the 90% of persons with LTBI who will never develop active TB from the 10% who will.
Latent tuberculosis infection (LTBI)

- IGRAs offer important potential advantages over the TST.
- They are unaffected by prior BCG vaccination, hence are more specific, and are *ex vivo* tests, *thus* reducing the potential risk of adverse events and of boosting.
- requiring only a single patient visit.
- The only gold standard for LTBI is the later development of active TB.
Latent tuberculosis infection (LTBI)

- TST is sensitive.
- IGRA is specific.

- It is suggested that at first do TST and if TST is positive, confirm it with IGRA.
Thank you for your attention