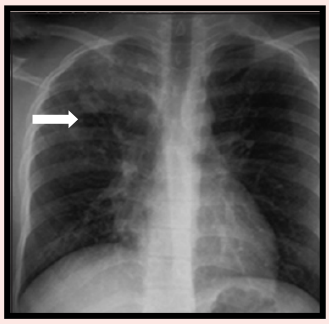
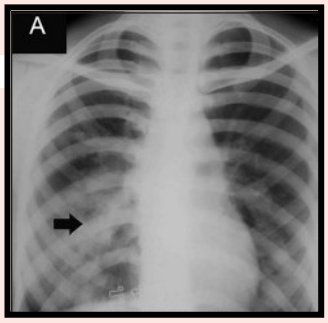
आई सी एम आर – राष्ट्रीय प्रजनन स्वास्थ्य अनुसंधान संस्थान, मुंबई
ICMR - National Institute for Research in Reproductive Health, Mumbai

POLICY BRIEF
February 2020

Reducing TB Burden
Screening Aspergillosis in ATT Non-responders





Pulmonary TB Aspergillosis Diagnostic Dilemma - Similar Clinical Symptoms and Chest X-ray Images from Patients of Pulmonary TB and Aspergillosis. [Adapted from Bhalla et al., 2015 [1] and Agarwal et al, 2011 [2]

Whom is this Policy Brief for?

- National TB-Comorbidity Coordination Committee and National Technical Working Group on TB – Comorbidities, Central TB Division, Ministry of Health and Family Welfare, Govt. of India
- Department of Health Research
- Epidemiology and Communicable Diseases, Division of Indian Council of Medical Research
- National TB Institutes and TB Hospitals
- Pulmonologists

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Executive Summary

- A total of 4.03 lakh TB patients do not show clinical improvement upon ATT (includes new cases, MDR, XDR) and are called **ATT non-responders.**
- ATT non-responders are potent agents of disease spread and a huge financial burden .
- According to WHO reports and Indian studies, **more than one third of these ATT non-responders have Aspergillosis a** lung infection caused by the fungus *Aspergillus* fumigatus.
- Aspergillosis shows clinical manifestations similar to that of pulmonary tuberculosis and may lead to misdiagnosis.
- Patients with co-existing tuberculosis and aspergillosis require therapy with both ATT and antifungal drugs to show clinical improvement.

Our study found the following gap:

- **Current RNTCP guidelines for diagnosis and treatment do not mention screening ATT non - responders for aspergillosis.**

This policy brief is aimed at addressing the above mentioned gap based on the results of our pilot study wherein, a total of 188 out of 500 (37.6%) suspected pulmonary TB (PTB) cases were positive for aspergillosis by indigenously developed AfuPEPLISA test. The result echoed previous Indian and global findings including from WHO.

Based on these findings, it is recommended to include the following in the RNTCP guidelines-

- **Screening of ATT non-responders for aspergillosis.**
- **A specific therapeutic strategy including Anti-Tubercular Therapy and Anti-Fungal Therapy for the patients with co-existing aspergillosis and TB.**

Background

- With 2.79 million cases of TB, India is the country with the highest burden of TB (3, 4).
- The success rate of the treatment among microbiologically new TB patients (Category I) is above 85% (3, 4). Among previously treated microbiologically confirmed TB patients (Category II), the success rate is at 70% (3, 4).
- The remaining 15% and 30% respectively from treatment categories I & II, and category IV (MDR-TB) and category V (XDR-TB) form a subset **'ATT non-responders'**.
- **ATT non-responders** are those patients who do not respond to anti-tubercular therapy (ATT) in the desired manner despite the mycobacteria showing sensitivity to the given drugs (5).
- **ATT non-responders** in India includes 1.73 lakhs of new TB patients (Cat I), 80,000 of previously treated TB patients (Cat II) and 1.5 lakh Drug resistant TB cases (MDR-Cat IV and XDR-Cat V) (3, 4).
- **ATT non-responders** show higher morbidity and mortality, besides being potent agents of disease spread.

Aspergillosis is a lung infection caused by inhalation of airborne spores of a fungus, *Aspergillus fumigatus*. Patients with aspergillosis also present with high fever, persistent cough and weight loss similar to that of pulmonary TB. Important to note that radiological (X-ray) findings are similar for pulmonary TB and Aspergillosis (Please see figure on the cover page).

The following evidences highlight the co-existence of aspergillosis and tuberculosis in India and globally.

- 81% of 113 patients of aspergillosis in India received anti-TB therapy (6).
- One-third of aspergillosis cases in India are being initially misdiagnosed as TB (7).
- Sunita and Mahendra, 2008, detected *Aspergillus* in 46% TB patients (8).
- Sivasankari et al., 2014, detected *Aspergillus* in 30.7% TB patients (9).

- Denning et al., 2011, estimated that annually at least 3.7 lakhs patients in the world develop Chronic Pulmonary Aspergillosis following Pulmonary Tuberculosis (10).
- Fifty-five (44.3%) cases of relapse of pulmonary tuberculosis in a study from Iran were positive for serum -specific IgG against *Aspergillus* (11).
- Case reports that TB or MDR TB patients have concomitant aspergillosis (12-14)

Aim/ Objective:

This policy brief is aimed at inclusion of a screening program for aspergillosis in ATT non-responders and as pecific treatment guideline with a combination of ATT and Anti-Fungal Therapy (AFT) for the patients with co-existing aspergillosis and TB in the RNTCP guidelines

The pilot scale screening program consisted of development and validation of affordable AfuPEPLISA kits and evaluation of *Aspergillus* specific antibodies in sera of tuberculosis patients (15, 16).

AfuPEPLISA immunodiagnostic kits (indirect ELISA) with high sensitivity (For IgG assay 93%, For IgE assay 86%), specificity (For IgG assay 100% and IgE assay 92%), stability (for three years), reproducibility (less than 10% inter-plate and intra-plate error) and cost effectiveness (less than Rs 200 per sample inclusive of cost of manpower and reagents) were used to screen serum samples of a total of 500 suspected pulmonary TB cases (RBIPMT, Delhi).

A total of 188 (37.6%) suspected pulmonary TB (PTB) cases were positive for Specific IgE and IgG antibodies against *A. fumigatus* by AfuPEPLISA IgG and AfuPEPLISA IgE assay (Figure 1). A total of 56 (11%) were smear negative for TB and positive by AfuPEPLISA.

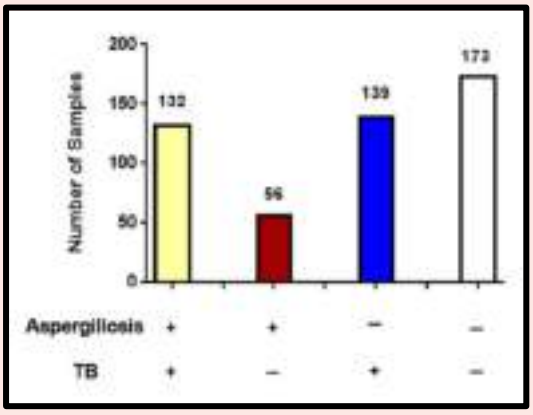

Figure 1. AfuPEPLISA kit with its reagents. Analysis of suspected cases of pulmonary tuberculosis screened for aspergillosis by AfuPEPLISA

Gap Analysis

- **Currently used RNTCP guidelines do not mention screening of ATT non-responders for aspergillosis and a specific treatment with a combination of ATT and Anti-Fungal Therapy (AFT) for the patients with co-existing aspergillosis and TB.**

Policy Recommendations

Short-term:

1. A scale-up study screening ATT non-responders for aspergillosis in TB referral hospitals under RNTCP program (Testing cost per sample using the in-house developed AfuPEPLISA assay is approximately Rs. 200 inclusive of manufacture and testing costs).
2. A specific therapeutic strategy including Anti- Tubercular Therapy (ATT) and Anti - Fungal Therapy (AFT) to be advised for the patients with co-existing aspergillosis and TB.

Long-term:

1. Based on the outcomes of scale-up study, inclusion of screening of aspergillosis in ATT non - responders in the RNTCP guidelines.
2. Establishment of aspergillosis testing facilities at district hospitals (approximate cost 5-7 lakhs for the equipments needed).

Key References

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