GAFFI POLICY BRIEF

Chronic pulmonary aspergillosis: global misdiagnosis of TB-like fungal lung disease

Overview

About 1.4 million people are thought to die from tuberculosis (TB) each year, but only 45% of patients have their illness confirmed by a laboratory.

Those without lab confirmation are still treated as if they have TB, with minimal investigation for other conditions such as fungal disease.

Many of these patients deteriorate and die, with around 20% mortality in year 1, and 10% annually thereafter.

The most common fungal disease for which misdiagnosis of TB occurs is **chronic pulmonary aspergillosis (CPA)**. While high-income countries have access to fungal disease diagnostics, most low resource settings do not.

Recent research from India, Vietnam and Ghana found that 54-57% of patients who had completed their 6-month treatment course for TB – but then had new symptoms and a suspected relapse of TB – actually had CPA. By preventing this misdiagnosis, these unnecessary deaths can be avoided.

How many people have fungal lung disease?

The burden of CPA has been estimated using data from many countries. India has the highest number of TB patients in the world; in 2020, there were 2 million TB lung cases, of whom nearly 500,000 died. Probable numbers of cases of CPA in India alone, extrapolated from incidence data using multiple sources, are shown in the Table below.

Group (India)	CPA cases	Country of origin of data used for extrapolation
Misdiagnosed as TB initially	213,830	Nigeria, Indonesia, Pakistan
In 12 months after TB diagnosis, mimics TB relapse	149,770	Indonesia, Uganda
2-5 years after TB therapy	261,260	UK, Uganda, Korea, Brazil, USA
Annual deaths	143,480	10 countries

CPA contributes to a large number of deaths in India (and elsewhere). Diagnosis of CPA with antifungal therapy should significantly bring down deaths, which are currently attributed to TB.

Key diagnostic tests and treatment for fungal lung disease

Aspergillus antibody detection is critical for CPA diagnosis and listed as a WHO Essential Diagnostic[1]. One such *Aspergillus* antibody test takes only 30-minutes and is easy and

[1] WHO Selection and Use of Essential In Vitro Diagnostics 2021
www.who.int/publications/i/item/9789240019102

inexpensive. Several other high performance antibody tests are also commercially available, most costing under $10. Chest X-rays are also critical for diagnosis, and diagnostic accuracy is improved with CT scanning of the lungs. Fungal culture is important to aid diagnosis and to monitor for antifungal resistance.

Infrequently other airborne fungi cause similar clinical and X-ray patterns to CPA of infection (i.e. *Histoplasma*, *Coccidioides*, *Cryptococcus*, *Pneumocystis*).

Access to fungal disease diagnostics would allow all patients with CPA and other fungal lung conditions to be treated, supported by continuous educational programs for professional awareness and skills. The earlier the diagnosis is made, and therapy started, the better the patient's recovery, lowering the chance of chronic debility and death.

At least 60% of the patients treated with oral or intravenous antifungal drugs listed on the WHO's Essential Medicine List respond, with improved symptoms and X-ray changes.

European clinical guidelines for the diagnosis & management of CPA are published[2], and include diagnostic and treatment recommendations for low resource settings. A global response providing access to current diagnostics and therapies could conservatively save over 130,000 lives each year.

Does misdiagnosis of CPA actually matter?

In pre-chemotherapy era studies (1905-1970), 20% of patients died of TB over 10 years if the TB diagnosis was based solely on culture (i.e. negative smear). In contrast, 20% of undiagnosed and untreated CPA patients die in just 1 year.

Currently, the mortality of people with unconfirmed TB – but treated as if they have TB – is higher than in confirmed TB cases; this anomaly is most likely the result of an incorrect diagnosis. Misdiagnosis of CPA has a high impact on patients as well as on TB control strategies: CPA fatalities are currently included in TB mortality statistics.

In addition, anti-TB treatment is not harmless. Liver toxicity attributable to anti-TB drugs has been reported in 5%–28% of patients, with 1-3% being severe and some leading to death. Thus, CPA and TB-like fungal disease misdiagnosis leads to excessive anti-TB therapy, cost, patient toxicity and death.

International concern about antimicrobial resistance (AMR) mandates the use of appropriate therapy[3] only in people who actually have TB. Incorrect therapy leads to a lack of confidence in medical professionals and healthcare services.

GAFFI recommends:

1. Diagnosis and awareness improvements:
   - *Aspergillus* antibody and fungal culture testing be added to TB diagnostic guidelines. Countries include these tests in the standard care package for possible TB in diagnostic labs supporting lung disease and TB clinics.

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[2] GAFFI news August 2018: Is it TB or a fungal lung infection? New life saving guidelines released today. https://gaffi.org/is-it-tb-or-a-fungal-lung-infection-new-life-saving-guidelines-released-today/

[3] WHO Antimicrobial resistance. 2021. www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance

- Unconfirmed TB cases (clinically diagnosed and GeneXpert negative) and those who return with new symptoms after completion of anti-TB therapy be tested for fungal lung disease. This testing approach be embedded in TB algorithms.
- As imaging, preferably including CT scans, is an important adjunct for distinguishing fungal lung disease from TB, it should be available to all patients.

2. Access to treatment improvements:
   - Antifungal agents listed on the WHO Essential Medicines List are made more widely available to patients.
   - Oral treatment with itraconazole or voriconazole for at least 6 months is initial treatment for CPA and included in local guidelines. Intravenous antifungal therapy should be reserved for very ill patients, those with azole resistant strains, patients who fail or cannot tolerate oral therapy, and those with potentially severe drug interactions.
   - Itraconazole or voriconazole be closely monitoring for adverse events, as is done currently for anti-TB therapy.

How much will these recommendations cost?

1. The global cost of screening for CPA using an *Aspergillus* antibody test ($4-$10) and fungal culture ($5-10) would be ~$70 million annually.
2. Treatment with itraconazole for 6 months would cost ~$235 million at $4 daily.
3. Monitoring costs are similar to those for TB therapy.

What will the benefits of change bring?

First and foremost, this program would reduce mortality by ~50% of mis-diagnosed TB patients who have fungal lung disease. Conservative estimates of lives saved would be over 130,000 annually. Unnecessary anti-TB therapy would be avoided, with its negative consequences for patient health and its significant cost.

Further, patients with fungal lung disease are usually chronically unwell, and antifungal therapy improves quality of life, enabling many to go back to work or other care duties.

Finally, TB units would deliver higher quality care, providing better outcomes, with more rewarding work and better recognition for their contributions to health.

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