**Summary**

CPA is a slowly destructive lung infection, with marked systemic features (weight loss, fatigue) and pulmonary features (productive cough, haemoptysis, breathlessness) almost indistinguishable from TB. CPA presents like 'smear negative TB'. It usually follows a pulmonary insult, especially TB, sarcoidosis, pneumothorax and emphysema/COPD). Most patients are not immunocompromised, although HIV infection may be present. Some patients have subtle immune defects including reduced natural killer, T helper and/or B cells and sometimes reduced gamma interferon or interleukin 12 production. Rates of progression vary, but worsening symptoms and lung destruction or fibrosis occur over many months or years. The key diagnostic features are cavitary lung lesions on radiology, sometimes containing a fungal ball (aspergilloma) and elevated serum *Aspergillus* antibody. A simple aspergilloma (<10% of cases) is best surgically removed. Antifungal therapy is effective at controlling symptoms and progression in about 60% of patients. Untreated mortality is 75-80% over 5 years, reduced to ~40% with long term antifungal therapy. Estimates suggest a prevalence of ~1.2M CPA cases after pulmonary TB, and probably ~3 million overall.

**Prevalence**

The prevalence of CPA is not known with confidence. In the late 1960s, one year after completion of anti-TB treatment in the UK, 25% of 544 patients with a residual cavity had *Aspergillus* antibodies and at least 14% CPA (aspergilloma) on chest Xray. On resurvey three years later, 34% of all patients had developed *Aspergillus* antibodies, >20% had CPA and 42% of these were coughing up blood. Overall 63% of patients with *Aspergillus* antibodies developed CPA with an aspergilloma within 3 years.

In Japan 20% of treated TB patients had antibodies to *Aspergillus*. Two surveys in India showed *Aspergillus* antibodies in 23% and 25% of patients with “chronic lung diseases”, 90% of whom had had prior TB. In Brazil 65% patients at a tertiary chest clinic with positive *Aspergillus* antibodies had an
aspergilloma. Most patients with ‘recurrent TB’ in Iran had *Aspergillus* antibody detectable. Based on this data and global modeling of TB, the global CPA prevalence was estimated at between 0.8 and 1.37 million, after tuberculosis (Table). It does not account for cases mis-diagnosed as TB initially or CPA complicating other underlying conditions.

Table. Relative frequency of pulmonary tuberculosis and CPA for countries with populations exceeding 50M (population 2005 and TB data 2007).

<table>
<thead>
<tr>
<th>Country</th>
<th>Population (2005)</th>
<th>Annual pulmonary TB cases, alive at 1 year</th>
<th>Estimated annual CPA caseload from TB</th>
<th>5 year estimated CPA prevalence from TB</th>
<th>5 year prevalence rate per 100,000 population</th>
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<tbody>
<tr>
<td>Global total</td>
<td>6,512,276,000</td>
<td>5,899,619</td>
<td>372,385</td>
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<td>1,853</td>
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<td>84</td>
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</table>

Since then, a cross-sectional study of TB patients in Nigeria, found both HIV positive and negative patients had CPA (8.7%), with the highest proportion (19%) in smear and GeneXpert negative, HIV negative patients. In Uganda, a 2 year prospective study in 285 patients who had had TB 2-7 years earlier, found CPA present in 14 (4.9%, 95% CI 2.8–7.9%). CPA was significantly more common in those with chest radiography cavitation (26% versus 0.8%; p<0.001), but possibly less frequent in HIV co-infected patients (3% versus 6.7%; p=0.177). The annual rate of new CPA development between surveys was 6.5% in those with chest radiography cavitation and 0.2% in those without (p<0.001). Series of CPA patients have been reported from China and Hong Kong, India, Korea, Japan, Cuba, France, Spain and UK in the years 2017-2019.
In countries with a high pulmonary TB incidence, TB is the dominant underlying disease accounting for up to 80% of cases. When pulmonary TB is less frequent, other pulmonary disorders are more important, notably COPD and non-tuberculcous mycobacterial infection, and prior TB was present in <20% of cases. Overall therefore, a provisional prevalence estimate of 3 million CPA patients was made.

Clinical presentation
Patients with chronic pulmonary aspergillosis present most commonly with weight loss, chronic productive cough, hemoptysis of variable severity, significant fatigue, and/or shortness of breath. Fever, night sweats and chest discomfort occur occasionally. The systemic symptoms of chronic cavitary pulmonary aspergillosis are an important point of distinction from a simple aspergilloma, in which these do not occur.

Radiology
Radiographic examination usually reveals one or more cavities, typically within the upper lobes, which may or may not contain fungus balls. Pleural thickening is common.

A simple aspergilloma is a fungus ball in a single pulmonary cavity with limited surrounding inflammation, pleural thickening, or fibrosis, and few symptoms. Chronic cavitary pulmonary aspergillosis usually begins as ill-defined regions of consolidation that progress to form clearly defined cavities. Cavities may contain fungus balls, debris, or fluid. There are often multiple cavities of different sizes. The interior of the cavity may show marked irregularity, representing fungal growth on the cavity wall. Cavities may be thick- or thin-walled. Pleural thickening is common but not universal. New cavity formation or expansion of one or more existing cavities over time is highly characteristic, and typically occurs over months in the absence of treatment.

Some patients get Aspergillus nodules – which may be single or multiple, and occasionally cavitate. Some are asymptomatic, others are associated with many pulmonary symptoms and haemoptysis.
Chronic fibrosing pulmonary aspergillosis, otherwise known as ‘destroyed lung’ is a late stage of disease and characterized by the same radiographic findings that occur with chronic cavitary pulmonary aspergillosis in combination with significant fibrosis.

**Diagnosis**
The key test for CPA is a positive *Aspergillus* antibody test (precipitins) in serum. The best tests have >90% sensitivity and an 85% specificity. An affordable new lateral flow device with excellent performance characteristics has recently been commercialized. Raised inflammatory markers (CRP, plasma viscosity or ESR) are seen in about 50% of patients. *Aspergillus* antigen is sometimes detectable in serum, but usually in bronchoalveolar lavage, and in sputum, but the cut-off is much higher. Cultures are positive for *Aspergillus* spp. (usually *A. fumigatus*) in ~25% of patients. *Aspergillus* PCR is more often positive (~80%) and for low resource settings an algorithm is now available for diagnosis.

Many patients have some degree of impaired immunity. Low T helper, B cell and/or natural killer cells are frequent. Low pneumococcal and *Haemophilus* antibodies are frequent and usually partially responsive to conjugate vaccine. Poor production of gamma interferon or interleukin 12 (which is required to produce gamma interferon) is common in the more complex patients. Multiple genetic variants are also described.

**Typical untreated example**
An example of a Gujerati woman who had had TB and developed CPA was diagnosed in 1992. Without treatment, she lost the function of her whole left lung (chronic fibrosing pulmonary aspergillosis) over 5 years and subsequently died. In contrast other patients have remained well on treatment for 20+ years.

Management
Simple aspergilloma should be resected, usually requiring a lobectomy. Survival rates after such surgery is excellent, if patients are carefully selected. About 5% of patients with CPA are immediately suitable for resection surgery. Recurrence does occur in >25% of cases. Surgery in patients with multicavity disease who are
systemically unwell, has a considerable mortality and morbidity, and is rarely curative.

Antifungal therapy with oral itraconazole is about 60-70% effective in improving or stabilising symptoms and arresting progression. Response and deterioration rates documented in an RCT comparing oral itraconazole (400mg daily) with standard care over 6 months, followed by 6 months of follow up is shown in the figure below. Of those on standard care, 61% deteriorated at 6 months and 71% at 12 months. In contrast, 76% of patients improved or stabilized on itraconazole. Discontinuation of itraconazole lead to a 30% relapse rate 6 months later. Voriconazole therapy is probably slightly superior in terms of later deterioration and a reduced rate of azole resistance emergence, especially in those with large fungal balls.

Response can be assessed by symptom reduction, weight gain, reduced fatigue, falling inflammatory markers and Aspergillus IgG antibody titre, and reduction in pleural thickening on CT scanning or chest radiograph.

![Graph showing response rates](image)

Similar response rates are seen with IV amphotericin B (short term), IV micafungin (short term), IV caspofungin (short term), oral voriconazole, oral posaconazole and oral isavuconazole. Therapy needs to be long term (> 6 months). Drug interactions are problematic, especially rifampicin, anticonvulsants, some antiretroviral agents and cardiac drugs. Itraconazole and pan-azole resistance in A. fumigatus occurs in some patients, and this is difficult to treat.

Outcome
Recent series indicate a steep mortality shortly after presentation, with stabilization over time, probably because of antifungal therapy and a less severe phenotype (slower progressors). Continuous antifungal therapy with emergence of resistance probably prolongs survival.
Japanese mortality data

Korean mortality data

Morbidity impact
The impact of CPA on quality of life is can be measured with the St George's Respiratory Score which ranges from 1 (excellent health) to 100 (extremely ill). The spread of scores is shown in this prospectively collected data from a large cohort of UK patients (n=88). Responders get good improvements in their quality of life.

Key questions and observations:
- CPA is a global disease but prevalence data show some variability in frequency, depending in part on local pulmonary TB incidence and probably COPD prevalence. More prevalence studies are required.
- The impact of HIV infection on prevalence and diagnosis is not well studied.
- Substantial numbers of smear negative TB cases don't have TB but have CPA, but this is not yet well assessed.
- Dual mycobacterial (TB and NTM) infections are difficult to manage and need more study and new non-interacting antifungal agents.
- A new lateral flow assay for Aspergillus IgG antibody is now available and could transform diagnosis.
- Oral antifungal therapy is partially successful (~60%), but azole resistance is an issue.
- Progression rates vary and some patients need really aggressive therapy, others are stable for long periods.
References


