Summary
CPA is a slowly destructive lung infection, with marked systemic features (weight loss, fatigue) and pulmonary features (productive cough, haemoptysis, breathless) almost indistinguishable from TB. It occurs after a pulmonary insult, usually TB, sarcoidosis, pneumothorax, emphysema), probably with some subtle immune defects, not well defined. Rates of progression vary, but worsening symptoms and lung destruction or fibrosis occur over many months of years. The key diagnostic features are cavitary lung lesions on radiology, sometimes containing a fungal ball (aspergilloma), and Aspergillus antibodies. A simple aspergilloma (<10% of cases) is best surgically removed. Antifungal therapy is very effective at controlling symptoms and progression in about 60% of those with more extensive disease. Mortality is 20-30% in the first 3 months after presentation (Korea, Japan), and about 10% annually thereafter. Estimates suggest a prevalence of ~1.2M CPA cases after pulmonary TB.

Prevalence
The prevalence is not known. 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 1,2.

In Japan 20% of treated TB patients had antibodies to Aspergillus 3. Two surveys in India showed Aspergillus antibodies in 23% and 25% of patients with “chronic lung diseases”, 90% of which had prior TB 4,5. In Brazil 65% patients at a tertiary chest clinic with positive Aspergillus antibodies had an aspergilloma 6.

Based on this data and global modeling of TB, the global prevalence was estimated at between 0.8 and 1.37 million 7. The burden in HIV positive patients is not known, but dually infected cases do occur.
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>
</tr>
</thead>
<tbody>
<tr>
<td>Global total</td>
<td>6,512,276,000</td>
<td>5,899,619</td>
<td>372,385</td>
<td>1,173,881</td>
<td>18.0</td>
</tr>
<tr>
<td>China</td>
<td>1,312,253,000</td>
<td>1,052,925</td>
<td>67,387</td>
<td>212,427</td>
<td>16.2</td>
</tr>
<tr>
<td>India</td>
<td>1,130,618,000</td>
<td>1,297,047</td>
<td>83,011</td>
<td>261,679</td>
<td>23.1</td>
</tr>
<tr>
<td>United States</td>
<td>302,741,000</td>
<td>8,907</td>
<td>588</td>
<td>1,853</td>
<td>0.6</td>
</tr>
<tr>
<td>Indonesia</td>
<td>219,210,000</td>
<td>420,853</td>
<td>26,935</td>
<td>84,907</td>
<td>38.7</td>
</tr>
<tr>
<td>Brazil</td>
<td>186,075,000</td>
<td>70,789</td>
<td>5,663</td>
<td>17,852</td>
<td>9.6</td>
</tr>
<tr>
<td>Pakistan</td>
<td>165,816,000</td>
<td>204,955</td>
<td>13,117</td>
<td>41,350</td>
<td>24.9</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>153,122,000</td>
<td>243,361</td>
<td>15,575</td>
<td>49,098</td>
<td>32.1</td>
</tr>
<tr>
<td>Russia</td>
<td>143,470,000</td>
<td>116,234</td>
<td>7,439</td>
<td>23,450</td>
<td>16.3</td>
</tr>
<tr>
<td>Nigeria</td>
<td>140,879,000</td>
<td>299,297</td>
<td>19,155</td>
<td>60,383</td>
<td>42.9</td>
</tr>
<tr>
<td>Japan</td>
<td>127,449,000</td>
<td>17,724</td>
<td>1,134</td>
<td>3,576</td>
<td>2.8</td>
</tr>
<tr>
<td>Mexico</td>
<td>105,330,000</td>
<td>15,326</td>
<td>981</td>
<td>3,092</td>
<td>2.9</td>
</tr>
<tr>
<td>Philippines</td>
<td>85,496,000</td>
<td>216,228</td>
<td>13,839</td>
<td>43,624</td>
<td>51.0</td>
</tr>
<tr>
<td>Vietnam</td>
<td>84,074,000</td>
<td>97,497</td>
<td>3412</td>
<td>10,757</td>
<td>12.8</td>
</tr>
<tr>
<td>Germany</td>
<td>82,409,000</td>
<td>3,339</td>
<td>100</td>
<td>316</td>
<td>0.4</td>
</tr>
<tr>
<td>Egypt</td>
<td>77,154,000</td>
<td>9,266</td>
<td>593</td>
<td>1,869</td>
<td>2.4</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>74,661,000</td>
<td>124,710</td>
<td>7,981</td>
<td>25,160</td>
<td>33.7</td>
</tr>
<tr>
<td>Turkey</td>
<td>71,169,000</td>
<td>11,042</td>
<td>707</td>
<td>2,228</td>
<td>3.1</td>
</tr>
<tr>
<td>Iran</td>
<td>70,765,000</td>
<td>9278</td>
<td>594</td>
<td>1,872</td>
<td>2.6</td>
</tr>
<tr>
<td>Thailand</td>
<td>65,946,000</td>
<td>64,566</td>
<td>4,132</td>
<td>13,026</td>
<td>19.8</td>
</tr>
<tr>
<td>France</td>
<td>61,013,000</td>
<td>5,517</td>
<td>166</td>
<td>522</td>
<td>0.9</td>
</tr>
<tr>
<td>UK</td>
<td>60,261,000</td>
<td>4,189</td>
<td>118</td>
<td>370</td>
<td>0.6</td>
</tr>
<tr>
<td>Congo (DR)</td>
<td>59,077,000</td>
<td>125,538</td>
<td>8,034</td>
<td>25,327</td>
<td>42.9</td>
</tr>
<tr>
<td>Italy</td>
<td>58,645,000</td>
<td>2,807</td>
<td>84</td>
<td>265</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Clinical presentation
Patients with chronic pulmonary aspergillosis present most commonly with weight loss, chronic productive cough, hemoptysis of variable severity, fatigue, and/or shortness of breath. Fever and night sweats 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.

A simple aspergilloma is a fungus ball in a single pulmonary cavity with limited surrounding inflammation, pleural thickening, or fibrosis. 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. It is most common for the cavities to be thin-walled and to lack associated pleural thickening, although both thick cavity walls and pleural thickening occur in some cases. 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.

Chronic fibrosing pulmonary aspergillosis (late stage of disease) is 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 \(^8,9,10\). Raised inflammatory markers are common, Cultures are positive for *Aspergillus* spp. (usually *A. fumigatus*) in \(\sim 25\%\) of patients. *Aspergillus* PCR is more often positive (\(\sim 80\%\)) \(^11\).

**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 over 5 years and subsequently died. In contrast other patients have remained well on treatment for 20+ years.

![Radiographs showing progressive changes in CPA](image)

**Management**
Simple aspergilloma should be resected, usually requiring a lobectomy. Survival rates after such surgery is excellent all over the world, if patients are carefully selected \(^12,13,14\). About 5\% of patients immediately suitable for surgery. Recurrence does occur. 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 \(^8,15,16\). 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.

![Graph showing response rates]

Similar response rates are seen with IV amphotericin B (short term), IV micafungin (short term), IV caspofungin (short term), oral voriconazole and oral posaconazole. Therapy needs to be long term. Drug interactions are problematic, especially rifampicin, anticonvulsants and some ARVs. Itraconazole 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).

**Japanese mortality data**

**Korean mortality data**

**Morbidity impact**
The impact of CPA on quality of life is probably best 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).
Key questions and observations:

- Prevalence data are modeled on UK cases with pulmonary cavities after TB treatment, before modern TB chemotherapy was introduced. Does it still pertain now?
- The radiological abnormalities were based on chest X-rays, not scans, and on the presence of an aspergilloma (present in ~25% of CPA cases only).
- What is the frequency of CPA in TB patients without cavities following therapy (modeling assumption was 2%)?
- What is the impact of HIV infection on prevalence, and diagnosis? Is CPA controllable with reversal of immunosuppression with ARVs?
- How many smear negative TB cases don’t have TB but have CPA?
- Is there a common genetic predisposition to TB and CPA (our current data does not suggest this, but is not yet genome-wide).
- In Africa, Aspergillus antibody tests are not yet available almost everywhere, yet is simple technology, which could be further improved.
- A new lateral flow *Aspergillus* antigen device may be useful for direct detection of *Aspergillus* on sputum, which would greatly alter diagnostic perspectives for the better.
- In the UK, Japan, France and India antifungal therapy is partially successful (~60%). No experience in Africa.
- Progression rates vary and some patients need really aggressive therapy, others are stable for long periods. Distinguishing them is not possible currently.

References


David Denning
April 2013