ERS/ESCMID Clinical Practice Guidelines: chronic pulmonary aspergillosis

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Aspergillus Guideline:
Chronic Pulmonary Aspergillosis

Joint ESCMID and ERS guidelines

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Chronic Pulmonary Aspergillosis - subsets

Simple/single Aspergilloma

*Aspergillus* nodule(s)

Chronic Cavitary Pulmonary Aspergillosis / Complex Aspergilloma (CCPA)

Chronic Fibrosing Pulmonary Aspergillosis (CFPA)

Subacute invasive (SIA)/Semi-Invasive / Chronic Necrotizing Pulmonary Aspergillosis (CNPA)

**Note** – fungal balls (aspergilloma) may be seen in any of these conditions, except *Aspergillus* nodule
Different patterns of CPA

Aspergillus nodule

Simple aspergilloma

Chronic cavitary pulmonary aspergillosis

Chronic fibrosing pulmonary aspergillosis
Single (simple) aspergilloma

Figure 2 Simple aspergilloma which developed within a post-tuberculous cicatricial atelectasis of the left upper lobe with saccular bronchiectasis. Surgical resection by VATS was done because of recurrent hemoptysis and a requirement for anticoagulant therapy.

Courtesy Dr Beigelman, Lausanne, Switzerland
Figure 13 - Nodule of the right upper lobe with irregular and slightly spiculated borders that was surgically resected and proven to be an *Aspergillus* nodule.
Figure 6 – Aspergillus nodules of variable size and borders and fungus ball filling a cavity with a wall of variable thickness in a patient with preexisting bronchiectasis and cicatricial atelectasis of the middle lobe. Successive axial views with lung windows.
Patients may have 1, 2 or more nodules. Cough and dyspnoea are common, 30% weight loss, occasional haemoptysis. 57% had positive IgG antibody.
Figure 3 - Chronic cavitary pulmonary aspergillosis showing marked progression. Chest X-rays prior to 2007 (1990’s) showed ‘upper lobe fibrosis’, without a firm diagnosis. A large cavity with pleural thickening on the left. In 2012, bilateral large cavities with pleural thickening and atelectasis of both upper lobes, with some pleural thickening.

Neither cavity contains a visible fungal ball.
Chronic cavitary pulmonary aspergillosis
Pleural thickening and early aspergilloma formation

Figure 10 - Cavity with irregular edge and aspergilloma presenting as a coarse and irregular network in a patient with a previous left upper lobe resection. Note apical pleural thickening.
# Radiological diagnosis of CPA

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Features of cavitation, fungal ball, pleural thickening and/or upper lobe fibrosis</td>
<td>Raise suspicion of CPA for physicians</td>
<td>Radiological report must mention possible CPA</td>
<td>A</td>
<td>II</td>
<td>Roberts, 1987; Kim, 2000; Franquet, 2001; Denning, 2003; Greene, 2005; Kobashi, 2006; Godet, 2014</td>
<td>CPA is often missed for years and patients mismanaged. Microbiological testing required for confirmation High quality CT with vessel visualisation</td>
</tr>
</tbody>
</table>
Figure 4 - Chronic cavitary pulmonary aspergillosis (CCPA). Multiple cavities with a fungus ball lying within the largest one. The wall of the cavities cannot be distinguished from the thickened pleura nor the neighboring alveolar consolidation.

The extra pleural fat is hyperattenuated (yellow arrows).
Dilated oesophagus = yellow star.
Bilateral aspergillomas in CCPA - related to NTM infection

Courtesy Pr Khalil- Pr Cadranel, Tenon Hospital, France
Bilateral aspergillomas in CCPA - related to NTM infection

Figure 8 – CCPA in a smoker with previous infection to *Mycobacterium kansasii*, undernutrition and cirrhosis. Severe hemoptysis.

Typical bilateral fungus balls (stars) almost filling the cavities on the left side.
Irregular walls of the cavity on the right side.
Enhanced thickened pleura (yellow arrows).

Note hypertrophic systemic arteries (red arrows).

*Courtesy Pr Khalil- Pr Cadranel, Tenon Hospital, France*
Consolidation with cavitation

Figure 11 - Chronic cavitary pulmonary aspergillosis of the right upper lobe. Mediastinal window shows cavitary alveolar consolidation delimited inferiorly by fissures. Note the dense extrapleural fat.
Large nodules is a rare manifestation of CPA

Figure 14 - Chronic pulmonary aspergillosis presenting as bilateral upper lobe lung masses. Partly necrotic and cavitary on the left.
Progression of CCPA to chronic fibrosing pulmonary aspergillosis

1992
1994 on no Rx
1997 still on no Rx
Chronic pulmonary aspergillosis caused by *A. calidouustus* with rapid progression to CFPA

November 2008

December 2008
Subacute invasive/chronic necrotising aspergillosis

Figure 7 - Subacute invasive aspergillosis complicating hepatocellular carcinoma being treated with sorafenib. Cavitary lesion developed with multiple symptoms over 6 weeks. He presented with unresectable hepatocellular carcinoma. Note the almost normal lung background.
Clinical phenotypes of chronic *Aspergillus* spp. diseases

- **Single/simple aspergilloma**
- **Aspergillus nodule(s)**
- **Chronic cavitary pulmonary aspergillosis (CCPA)**
- **Chronic fibrosing pulmonary aspergillosis (CFPA)**
- **Subacute Invasive aspergillosis (SAIA) or chronic necrotizing pulmonary aspergillosis (CNPA)**
### Underlying diseases in patients with CPA (%)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Smith</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classical tuberculosis</td>
<td>17</td>
<td>31-81</td>
</tr>
<tr>
<td>Atypical tuberculosis</td>
<td>16</td>
<td>?</td>
</tr>
<tr>
<td>ABPA</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>COPD/emphysema</td>
<td>33</td>
<td>42-56</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>17</td>
<td>12-17</td>
</tr>
<tr>
<td>Lung cancer survivor</td>
<td>10</td>
<td>?</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>22</td>
<td>9-12</td>
</tr>
<tr>
<td>Sarcoidosis (stage II/III)</td>
<td>7</td>
<td>12-17</td>
</tr>
<tr>
<td>Thoracic surgery</td>
<td>14</td>
<td>8-11</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Asthma / SAFS</td>
<td>12</td>
<td>6-12</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>4</td>
<td>2-11</td>
</tr>
<tr>
<td>None</td>
<td>1</td>
<td>15</td>
</tr>
</tbody>
</table>
Chronic Pulmonary Aspergillosis – Diagnostic criteria

Required:
1. Characteristic CT appearance of a fungus ball in a pulmonary or pleural cavity, or dilated bronchus,
AND
2. Any direct or indirect microbiological evidence of *Aspergillus* infection (see below).
Chronic Pulmonary Aspergillosis – Diagnostic criteria

Required:
1.1 Characteristic CT appearance of a fungus ball in a pulmonary or pleural cavity, or dilated bronchus,
AND
1.2 Any direct or indirect microbiological evidence of *Aspergillus* infection (see below).
OR

Required:
2.1 Radiological features consistent with chronic pulmonary aspergillosis (including cavity(ies), pleural thickening, extensive fibrosis or nodule)
AND
2.2 Clinical or radiological evidence of at least 3 months disease (sometimes inferred)
[Note shorter durations of disease may be seen in SIA/CNPA, which becomes CPA because of its chronicity],
AND
2.3 Histological or microbiological or immunologic evidence of *Aspergillus* infection (e.g. histological evidence of *Aspergillus*-like hyphae in lung biopsy or *Aspergillus* culture from a percutaneous cavity aspiration; strongly positive BAL antigen; positive IgG antibody/precipitins). Respiratory tract culture or PCR positive for *Aspergillus* is supportive.
Chronic Pulmonary Aspergillosis – Diagnostic criteria

Required:
1.1 Characteristic CT appearance of a fungus ball in a pulmonary or pleural cavity, or dilated bronchus, AND
1.2 Any direct or indirect microbiological evidence of *Aspergillus* infection (see below). OR

Required:
2.1 Radiological features consistent with chronic pulmonary aspergillosis (including cavity(ies), pleural thickening, extensive fibrosis or nodule) AND
2.2 Clinical or radiological evidence of at least 3 months disease (sometimes inferred) [Note shorter durations of disease may be seen in SIA/CNPA, which becomes CPA because of its chronicity], AND
2.3 Histological or microbiological or immunologic evidence of *Aspergillus* infection (e.g. histological evidence of *Aspergillus*-like hyphae in lung biopsy or *Aspergillus* culture from a percutaneous cavity aspiration; strongly positive BAL antigen; positive IgG antibody/precipitins). Respiratory tract culture or PCR positive for *Aspergillus* is supportive.

Required:
Exclusion of histoplasmosis, coccidioidomycosis and paracoccidioidomycosis in endemic areas or those with pertinent travel history; actinomycosis. Active bacterial infection, including mycobacterial infection and/or malignancy may occur concurrently. Mycobacterial infections or malignancy may mimic CPA.
## Strength of Recommendation – Definition

<table>
<thead>
<tr>
<th>Grade of Recommendation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade A</td>
<td>ESCMID (EFISG) and ECMM <strong>strongly</strong> support a recommendation for use</td>
</tr>
<tr>
<td>Grade B</td>
<td>ESCMID (EFISG) and ECMM <strong>moderately</strong> support a recommendation for use</td>
</tr>
<tr>
<td>Grade C</td>
<td>ESCMID (EFISG) and ECMM <strong>marginally</strong> support a recommendation for use</td>
</tr>
<tr>
<td>Grade D</td>
<td>ESCMID (EFISG) and ECMM support a recommendation <strong>against</strong> use</td>
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## Quality of Evidence – Level Definition

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level I</strong></td>
<td>Evidence from at least 1 properly designed randomized, controlled trial</td>
</tr>
<tr>
<td><strong>Level II</strong></td>
<td>Evidence from at least 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from &gt;1 centre); from multiple time series; or from dramatic results of uncontrolled experiments</td>
</tr>
<tr>
<td><strong>Level III</strong></td>
<td>Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees</td>
</tr>
</tbody>
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## Added Index – Definition

<table>
<thead>
<tr>
<th>Added Index</th>
<th>Source of Level II Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>r</td>
<td>Meta-analysis or systematic review of RCT</td>
</tr>
<tr>
<td>t</td>
<td>Transferred evidence i.e. results from different patients‘ cohorts, or similar immune-status situation</td>
</tr>
<tr>
<td>h</td>
<td>Comparator group: historical control</td>
</tr>
<tr>
<td>u</td>
<td>Uncontrolled trials</td>
</tr>
<tr>
<td>a</td>
<td>For published abstract presented at an international symposium or meeting</td>
</tr>
</tbody>
</table>

Respiratory specimen diagnosis of CPA

<table>
<thead>
<tr>
<th>Test</th>
<th>Strength of Recommendation</th>
<th>Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct microscopy for hyphae&lt;sup&gt;a&lt;/sup&gt;</td>
<td>A</td>
<td>II</td>
</tr>
<tr>
<td>Fungal culture (sputum or BAL)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>A</td>
<td>III</td>
</tr>
<tr>
<td>Histology</td>
<td>A</td>
<td>II</td>
</tr>
<tr>
<td>Fungal culture (transparietal aspiration)</td>
<td>B</td>
<td>II</td>
</tr>
<tr>
<td><em>Aspergillus</em> PCR (respiratory secretion)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>C</td>
<td>II</td>
</tr>
<tr>
<td>Bacterial culture (sputum or BAL)</td>
<td>C</td>
<td>II&lt;sup&gt;lt&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
Molecular detection of *Aspergillus* spp. in sputum

<table>
<thead>
<tr>
<th>Laboratory result</th>
<th>CPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culture positive for <em>A. fumigatus</em></td>
<td>7/42 (16.7%)</td>
</tr>
<tr>
<td>qPCR positive for <em>Aspergillus</em> spp</td>
<td>30/42 (71.4%)</td>
</tr>
</tbody>
</table>
Aspergillus IgG in blood
Key diagnostic test

Falling levels is good, but takes months or years
# Aspergillus antibody diagnosis of CPA

<table>
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<tr>
<th>Population</th>
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<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cavitary or nodular pulmonary infiltrate in non-immunocompromised patients</td>
<td>Diagnosis or exclusion of CPA</td>
<td>Aspergillus IgG antibody</td>
<td>A</td>
<td>II</td>
<td>Guitard, 2012; Baxter, 2012; Van Toorenenbergen, 2012</td>
<td>IgG and precipitins test standardisation incomplete</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aspergillus IgM antibody</td>
<td>D</td>
<td>III</td>
<td>Brouwer, 1988; Schonheyder, 1987; Nimomiya, 1990;</td>
<td>Sensitivity for Aspergillus nodule uncertain</td>
</tr>
<tr>
<td>In context of asthma/ABPA/CF</td>
<td></td>
<td>Aspergillus IgA antibody</td>
<td>D</td>
<td>III</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aspergillus IgE antibody</td>
<td>B</td>
<td>II</td>
<td>Denning, 2003; Agarwal, 2012</td>
<td></td>
</tr>
</tbody>
</table>
Aspergillus IgG serology

Comparison of 4 commercial assays using 250 patients with CPA in Manchester and normal controls from Uganda

<table>
<thead>
<tr>
<th>Siemens</th>
<th>Serion ELISA</th>
<th>Omega ELISA</th>
<th>Dynamiker ELISA</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.99</td>
<td>0.972</td>
<td>0.902</td>
<td>0.918</td>
</tr>
</tbody>
</table>

Area under ROC curve results
Frequency of Aspergillus antibodies after TB

- UK 1970 – 34%
- Japan 1989 – 20%
- India 2001 – 27%
- Brazil 1988 – 21%

## Antigen diagnosis of CPA

<table>
<thead>
<tr>
<th>Population</th>
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<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cavitary or nodular pulmonary infiltrate in non-immunocompromised patients</td>
<td>Diagnosis or exclusion of CPA</td>
<td>Antigen (BAL)</td>
<td>B</td>
<td>II</td>
<td>Izumikawa, 2012</td>
<td>Antigen studied in BAL and serum, but not sputum.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Antigen (serum)</td>
<td>C</td>
<td>II</td>
<td>Izumikawa, 2012; Kono, 2013; Shin, 2014</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Antigen (sputum)</td>
<td>No data</td>
<td>II</td>
<td>Shin, 2014</td>
<td></td>
</tr>
</tbody>
</table>
Prognosis

CPA + subacute IA
Korea (1995-2007)

75% mortality

CPA
Japan (2001-9)

80% mortality

Nam Int J Infect Dis 2010;14:e479; Ohba et al, Resp Med 2012; 106:724
Oral triazole therapy for CPA

<table>
<thead>
<tr>
<th>Antifungal agent and dose</th>
<th>Strength of Recommendation</th>
<th>Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itraconazole 200 mg bid, adjust with TDM</td>
<td>A</td>
<td>II</td>
</tr>
<tr>
<td>Voriconazole&lt;sup&gt;a&lt;/sup&gt; 150-200 mg bid, adjust with TDM</td>
<td>A</td>
<td>II</td>
</tr>
<tr>
<td>Posaconazole 400 mg bid (liquid); 300mg od (tablets)</td>
<td>B</td>
<td>II</td>
</tr>
</tbody>
</table>

<sup>a</sup> Lower doses advised in those over 70 years, low weight, significant liver disease and those of NE Asian descent who may be slow metabolisers

TDM = therapeutic drug monitoring
Impact of oral itraconazole therapy for chronic pulmonary aspergillosis after TB over 6 months

## Duration of antifungal therapy for CPA

<table>
<thead>
<tr>
<th>Population</th>
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<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPA patients on antifungal therapy</td>
<td>Control of infection, arrest of pulmonary fibrosis, prevention of haemoptysis, improved quality of life.</td>
<td>6 mo antifungal therapy</td>
<td>B</td>
<td>II</td>
<td>Agarwal, 2013; Yoshida, 2012; Nam, 2010; Felton, 2010; Camuset, 2007; Jain, 2006; Cadranel, 2012</td>
<td>Optimal duration of therapy in CPA is unknown, indefinite suppressive therapy may be appropriate in selected patients</td>
</tr>
<tr>
<td>Subacute IA/CNPA</td>
<td>Cure</td>
<td>6 mo</td>
<td>B</td>
<td>II</td>
<td>Camuset, 2007; Cadranel, 2012</td>
<td></td>
</tr>
</tbody>
</table>
Chronic pulmonary aspergillosis - response to itraconazole after 6 months therapy and follow up

Standard care
6 mo 12 mo
29% 7%
71% 64%

Oral itraconazole
6 mo 12 mo
35% 24%
41% 24%
23% 53%

Improved
Stable
Deterioration

Natural history with no therapy over 12 months
30% relapse off therapy in 6 months

Chronic cavitary pulmonary aspergillosis

Patient RW
June 2002

Stable, asymptomatic, normal inflammatory markers, just detectable Aspergillus precipitins

Itraconazole stopped after 5 years

www.aspergillus.org.uk
Chronic cavitary pulmonary aspergillosis - relapse

Patient RW
January 2003

Marked change, with new cough, weight loss, ↑CRP/ESR and ↑Aspergillus precipitins

Itraconazole restarted
Chronic cavitary pulmonary aspergillosis - an example of radiographic failure

Patient SS
April 2004

Patient SS
July 2004, despite receiving itraconazole for 3 months
### Alternative intravenous therapy for CPA

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
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<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPA patients with progressive disease, who fail, are intolerant of triazoles or have triazole resistance</td>
<td>Control of infection</td>
<td>Micafungin 150mg/d</td>
<td>B</td>
<td>II</td>
<td>Kohno, 2011; Kohno, EJC MID 2013; Saito, 2009; Kohno, 2011; Kohno, 2004; Izumikawa, 2007; Yasuda, 2009; Nam, 2009</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amphotericin B deoxycholate 0.7-1.0mg/kg/d</td>
<td>C</td>
<td>III</td>
<td>Denning, 2003</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Liposomal AmB 3mg/kg/d</td>
<td>B</td>
<td>IIa</td>
<td>Newton, 2014</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Caspofungin 50-70mg/d</td>
<td>C</td>
<td>IIa</td>
<td>Kier, 2014; Kohno 2013</td>
<td></td>
</tr>
</tbody>
</table>
## Local cavity therapy for CPA

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPA with aspergilloma, unwilling or unable to take oral therapy, multi-azole resistance and inoperable</td>
<td>Control of infection</td>
<td>Instillation of amphotericin B deoxycholate into cavity</td>
<td>C</td>
<td>II</td>
<td>Giron, 1998; Kravitz, 2013</td>
<td>Experimental</td>
</tr>
</tbody>
</table>
### Follow up of Aspergillus nodule and after resection surgery

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspergillus nodule not treated with antifungal therapy</td>
<td>To identify progression early and/or carcinoma of lung if multiple lesions</td>
<td>3-6 mos clinical follow up with (low dose) imaging, inflammatory markers and Aspergillus IgG/precipitins</td>
<td>A</td>
<td>III</td>
<td>Farid, 2013; Muldoon, 2014</td>
<td>Not necessary if entire single nodule resected</td>
</tr>
<tr>
<td>Post-lobectomy/pneumonectomy</td>
<td>To detect recurrence early</td>
<td>3-6 mos then 6 monthly for 3 years with inflammatory markers and Aspergillus IgG/precipitins</td>
<td>A</td>
<td>III</td>
<td>Farid, 2013.</td>
<td>No predictors of recurrence yet described. Full re-evaluation if consistent increase in Aspergillus IgG titres.</td>
</tr>
</tbody>
</table>
CPA guidelines

- Evidence base strong for radiology and Aspergillus antibody
- Strong experiential evidence for resection of single aspergillomas – caution in multi-cavity disease
- Evidence base weak on treatment, although 3 RCTs done
- Basic pathogenesis not well understood
- Natural history of Aspergillus nodule not well documented
- Immune deficits common - long term therapy generally recommended.
- Azole resistance now a major problem
The Aspergillus Website

The Aspergillus Website is a worldwide comprehensive resource providing detailed information about the fungus Aspergillus and the illnesses it can cause. It is called aspergillus. This site is free to use and provides an encyclopedic resource on the fungus and its diseases.

It has an annual membership fee and some online courses are paid for.

What is Aspergillus?

Aspergillus is a fungus whose spores are present in the air we breathe, but does not normally cause illness. In those people with a weakened immune system, damaged lungs or with allergies, Aspergillus can cause disease.

Common Aspergillus infections include invasive aspergillosis, ARIA, CPA and aspergillosis. Click on images to learn more.

New section on drug interactions which you can search very quickly.

+ app for iPhones and Android (search antifungal interaction)

691 interactions were rated as minor, 919 moderate and 381 severe, = 2216 recorded interactions.

Sources of high numbers of Aspergillus spores include air conditioning units, composting and damp or flood damaged housing & hospital building projects.

www.aspergillus.org.uk

17 years

Over 1M pages read monthly in >125 countries

Supported by the Fungal Infection Trust – 20 year anniversary in 2011
7th ADVANCES AGAINST ASPERGILLOSIS

3 - 5 March 2016
Manchester Central Convention Complex
Manchester
United Kingdom

www.AAA2016.org