# Chronic pulmonary aspergillosis: rationale and clinical guidelines for diagnosis and management

David W. Denning[1], Jacques Cadranel[2], Catherine Beigelman-Aubry[3], Florence Ader[4,5], Arunaloke Chakrabarti[6], Stijn Blot[7,8], Andrew J. Ullmann[9], George Dimopoulos[10] and Christoph Lange[11–14] on behalf of the European Society for Clinical Microbiology and Infectious Diseases and European Respiratory Society

**Affiliations**: [1]The National Aspergillosis Centre, University Hospital of South Manchester, The University of Manchester and the Manchester Academic Health Science Centre, Manchester, UK. [2]Service de Pneumologie, AP-HP, Hôpital Tenon and Sorbonne Université, UPMC Univ Paris 06, Paris, France. [3]Dept of Diagnostic and Interventional Radiology, University Hospital CHUV, Lausanne, Switzerland. [4]Dept of Infectious Diseases, Hospices Civils de Lyon, Lyon, France. [5]Centre International de Recherche en Infectiologie (CIRI), INSERM U1111, CNRS UMR5308, Lyon, France. [6]ane14.5(t)t74Tc.19018.[(CN)-17.4(Un306.1(rsi.6(s)(o)15.4([y)y]38(a)U)17.)-1.8Gh464(ane14.5(t)tU

## Introduction

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## Methods

A ESCMID F I S G (EFISG) (F. A , C. B , A , A. C , D. D A.J. ) ERS (S. B , J. C , G. D , C. L ). D 2014. C E C C M I D M 2014, C ESCMID ERS.

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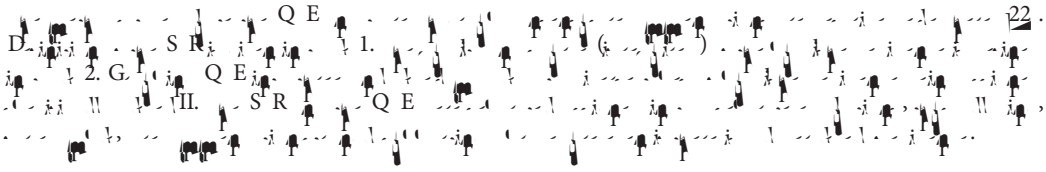
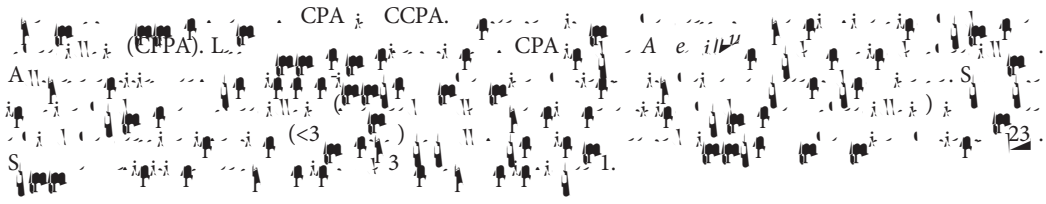


### *Consensus definitions of CPA*



*Aspergilloma*

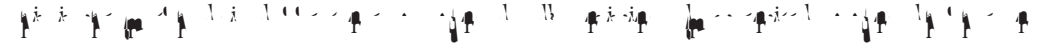


TABLE 3 Diagnostic criteria for different management of chronic pulmonary aspergillosis (CPA)

| Term | Definition |
|---|---|
| **Simple aspergilloma** | Single pulmonary cavity containing a fungal ball, with serological or microbiological evidence implicating *Aspergillus* spp. in a non-immunocompromised patient with minor or no symptoms and no radiological progression over at least 3 months of observation. |
| **CCPA** | One or more pulmonary cavities (with either a thin or /thick wall) possibly containing one or more aspergillomas or irregular intraluminal material, with serological or microbiological evidence implicating *Aspergillus* spp. with significant pulmonary and/or systemic symptoms and overt radiological progression (new cavities, increasing pericavitary infiltrates or increasing fibrosis) over at least 3 months of observation. |
| **CFPA** | Severe fibrotic destruction of at least two lobes of lung complicating CCPA leading to a major loss of lung function. Severe fibrotic destruction of one lobe with a cavity is simply referred to as CCPA affecting that lobe. Usually the fibrosis is manifest as consolidation, but large cavities with surrounding fibrosis may be seen. |
| ***Aspergillus* nodule** | One or more nodules which may or may not cavitate are an unusual form of CPA. They may mimic tuberculoma, carcinoma of the lung, coccidioidomycosis and other diagnoses and can only be definitively diagnosed on histology. Tissue invasion is not demonstrated, although necrosis is frequent. |
| **SAIA** | Invasive aspergillosis, usually in mildly immunocompromised patients, occurring over 1–3 months, with variable radiological features including cavitation, nodules, progressive consolidation with "abscess formation". Biopsy shows |

*Chronic cavitary pulmonary aspergillosis*

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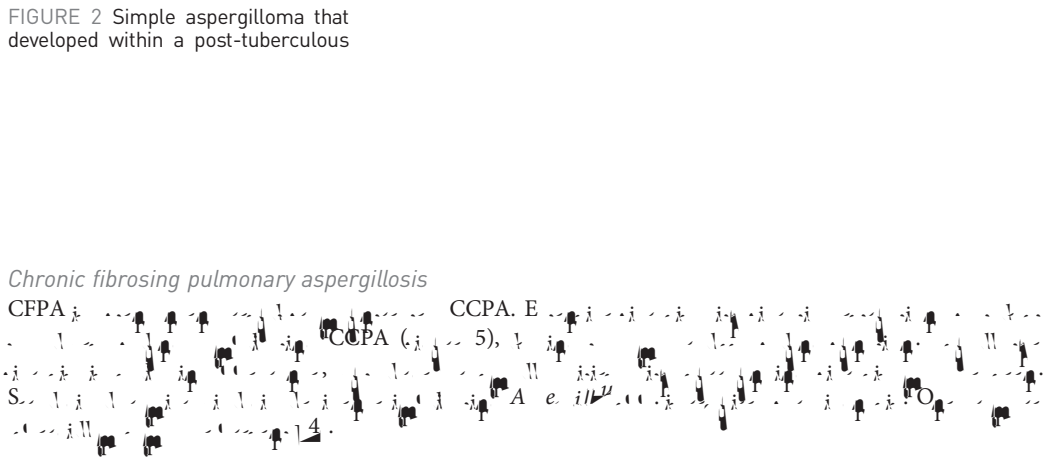

FIGURE 2 Simple aspergilloma that developed within a post-tuberculous

*Chronic fibrosing pulmonary aspergillosis*

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Aspergillus *nodule*

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*Subacute invasive aspergillosis*

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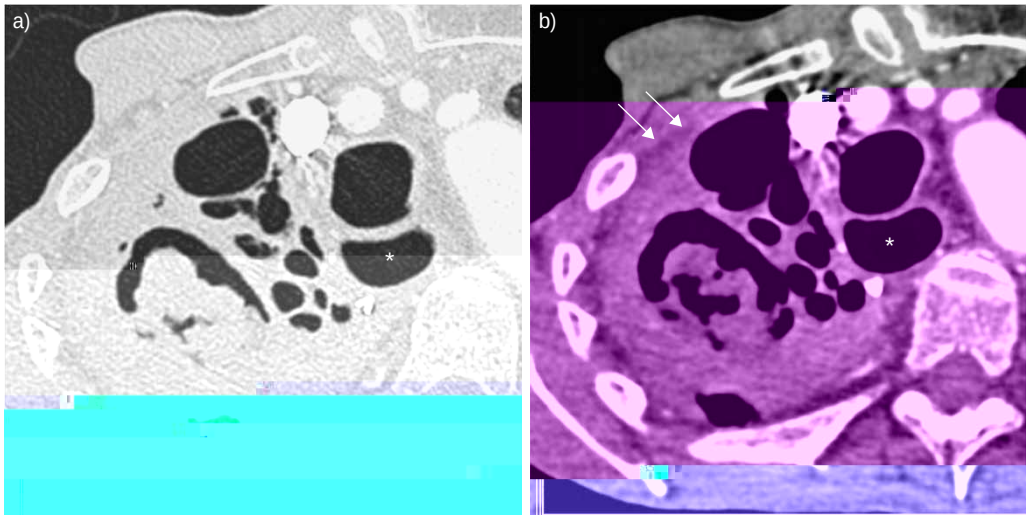


FIGURE 4 Imaging showing chronic cavitary pulmonary aspergillosis showing an axial view with a) lung and b) mediastinal windows at the level of the right upper lobe. Multiple cavities are visible with a fungus ball lying within the largest one. The wall of the cavities cannot be distinguished from the thickened pleura or the neighbouring alveolar consolidation. The extra pleural fat is hyperattenuated (white arrows). *: the dilated oesophagus should not be confused with a cavity.

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FIGURE 5 Imaging of chronic fibrosing pulmonary aspergillosis complicating chronic cavitary pulmonary aspergillosis, which followed tuberculosis, with mild chronic obstructive pulmonary disease. Complete opacification of the left hemi-thorax developed between February 1998, when a left upper lobe cavity with a fluid level was present, and May 1999. Multiple left lung autopsy percutaneous biopsies showed evidence of chronic inflammation, but no granulomas or fungal hyphae.


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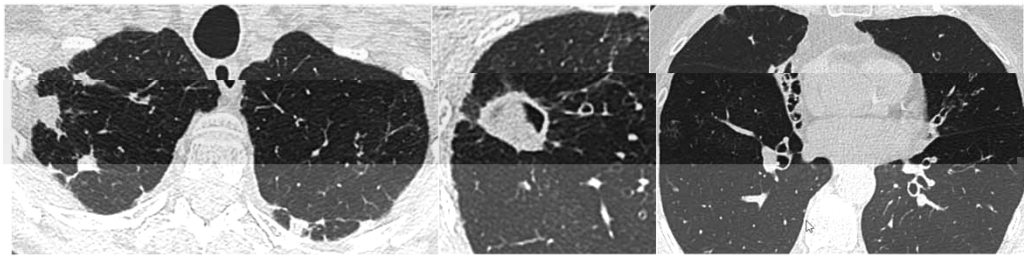

FIGURE 6 Successive axial views within the lung window showing *Aspergillus* nodules, of variable size and borders, and a fungus ball filling a cavity with a wall of variable thickness in a patient with pre-existing bronchiectasis and cicatricial atelectasis of the middle lobe.

### *Diagnosis*

*Diagnostic criteria*

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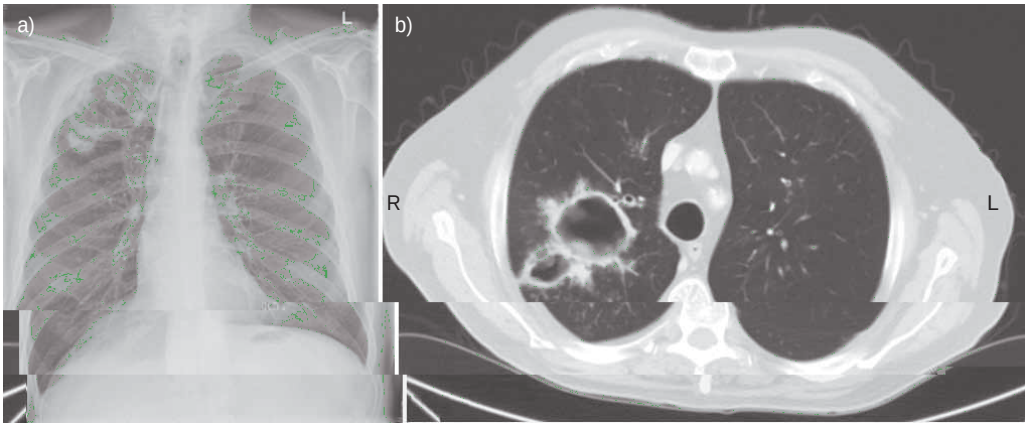


FIGURE 7 Subacute invasive aspergillosis in a patient with hepatocellular carcinoma being treated with the sorafenib (a multityrosine and Raf kinase inhibitor with some immunosuppressive features against T-cells). a) The chest radiograph shows a large irregular right upper-lobe cavitary lesion that developed with multiple symptoms over 6 weeks during treatment with sorafenib. The patient presented with unresectable hepatocellular carcinoma. b) The computed tomography scan shows a dual cavity with moderately thick walls, an external irregular edge and some material within the cavity on an almost normal lung background. L: left side; R: right side.


FIGURE 8 Chronic, cavitary pulmonary aspergillosis in a smoker with previous infection caused by *Mycobacterium kansasii*, poor nutrition and cirrhosis. The patient had had several episodes of severe haemoptysis treated by arterial embolisation with long-term treatment by voriconazole. a, b) Axial and c, d) coronal sections in mediastinal (b and d) and lung windows (a and c). Typical bilateral fungus balls (*) are seen almost filling the cavities on the left side. Of note are small air pockets within the fungus ball (c and d) on the left side and the irregular walls of the cavity on the right side (a) representing surface growth of *Aspergillus* on the interior cavity surface. The fungus balls appear hypoattenuated compared to enhanced thickened pleura (thick white arrows) and alveolar consolidation (arrow heads). Note the hypertrophic systemic arteries (thin white arrow). Figure reproduced from A. Khalil (Tenon Hospital, Paris, France; personal communication).

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*Contribution of histology, microscopy, culture and PCR on respiratory samples to the diagnosis of CPA*

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*Contribution of galactomannan antigen to the diagnosis of CPA*

[illegible] *A. fumigatus* [illegible] (GM) [illegible] (BAL). [illegible] 77.2% 77.0%, [illegible] ( [illegible] 0.4), [illegible] 66.7% 63.5%, [illegible] 0.7. [illegible] CPA 38. I[illegible] BAL GM- [illegible] 85.7% 76.3%, [illegible] >0.5 28. I[illegible] GM [illegible] 23% 39. BAL (S R B, Q E II) [illegible] GM (S R C Q E III). [illegible] CPA.

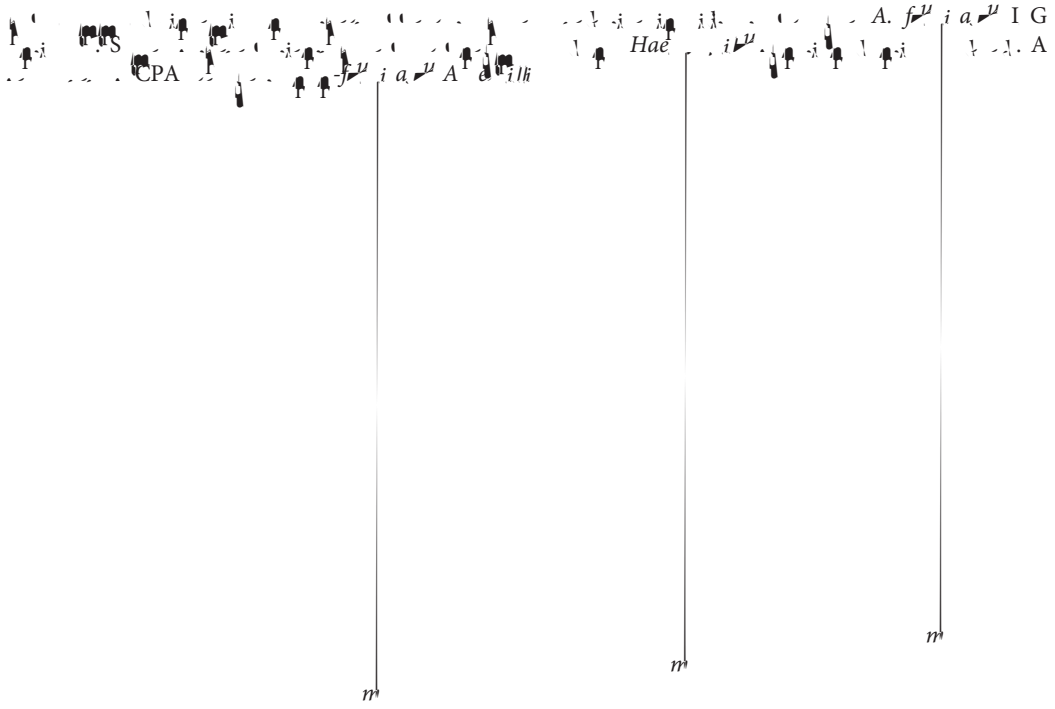
*Antibody diagnosis of CPA*

D[illegible] *A. fumigatus* [illegible] CPA (. [illegible] 6). [illegible] *A. fumigatus* [illegible] 100%. [illegible] 29. N[illegible] *A. fumigatus* [illegible] 5, 29, 42, 43, 45–47, 52–54. [illegible] *A. fumigatus* I G[illegible] CPA 42–44. I[illegible] C[illegible] *Histoplasma Coccidioides* [illegible] E[illegible] A[illegible] *A. fumigatus* IgG [illegible] (S R A Q E II). F[illegible] I[illegible] *A. fumigatus* IE[illegible] (S R B Q E II), [illegible] 10, 51, [illegible] IG (S R A Q E II) [illegible] ( [illegible] PCR, *A. fumigatus* [illegible] / [illegible] etc). [illegible] *A. fumigatus* IG [illegible] *A. fumigatus* [illegible] O[illegible] CPA [illegible]

TABLE 4 Key tests on respiratory samples for patients with cavitary or nodular pulmonary infiltrate in non-immunocompromised patients

| Test | Strength of recommendation | Quality of evidence |
|---|---|---|
| **Direct microscopy for hyphae** [#] | A | II |
| **Fungal culture (sputum or BAL)** [¶] | A | III |
| **Histology** | A | II |
| **Fungal culture (transthoracic aspiration)** | B | II |
| ***Aspergillus* PCR (respiratory secretion)** [+] | C | II |
| **Bacterial culture (sputum or BAL)** | C | IIt |

BAL: bronchoalveolar lavage. [#]: positive microscopy is a strong indicator of infection; [¶]: bacterial culture plates are less sensitive than fungal culture plates; [+]: PCR more sensitive than culture.



Imaging findings

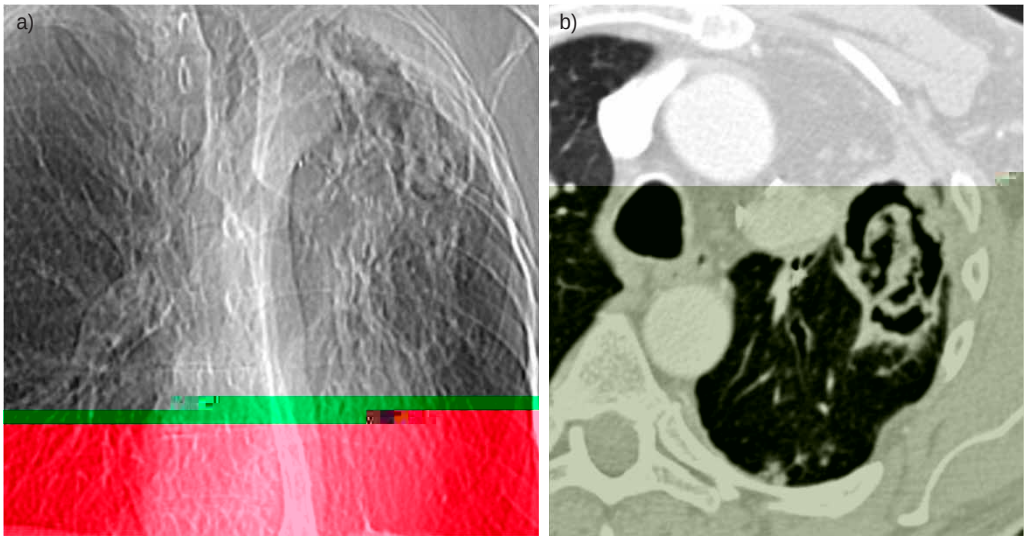
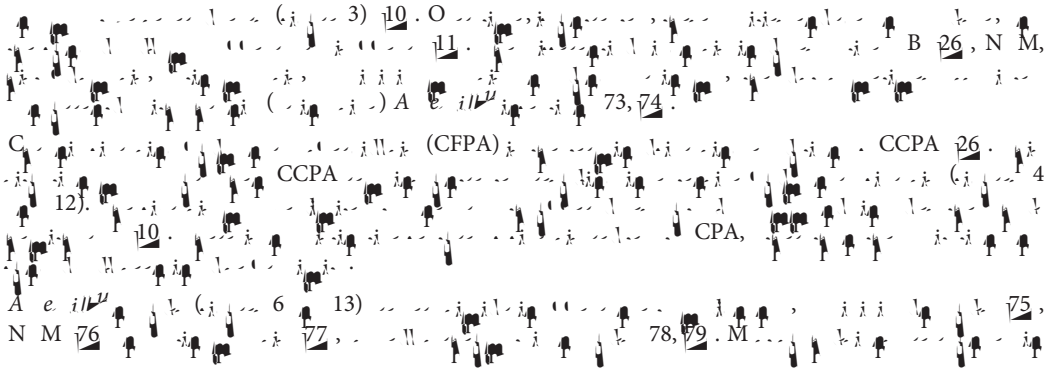



FIGURE 9 Cavity with irregular edge and aspergilloma presenting as a coarse and irregular network in a patient with a previous left upper-lobe resection. Note the apical pleural thickening bordering the cavity well seen on the topogram of the a) computed tomography scan. b) Axial view with lung window at the level of the left upper lobe.



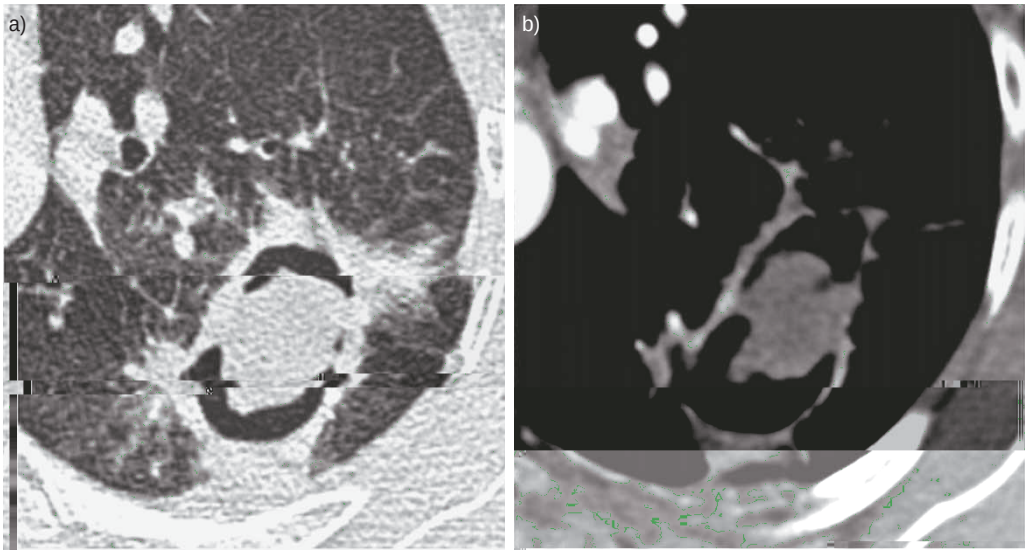



FIGURE 10 Aspergilloma in chronic, cavitary pulmonary aspergillosis. Axial view with a) lung and b) mediastinal windows. The fungus ball appears as a left upper lobe solid oval mass partially surrounded by a crescent of air, the "air-crescent" sign (a), within a thick-walled and slightly irregular cavity. Note in this case the nondependent location of the aspergilloma and the typical absence of enhancement after contrast media administration in (b).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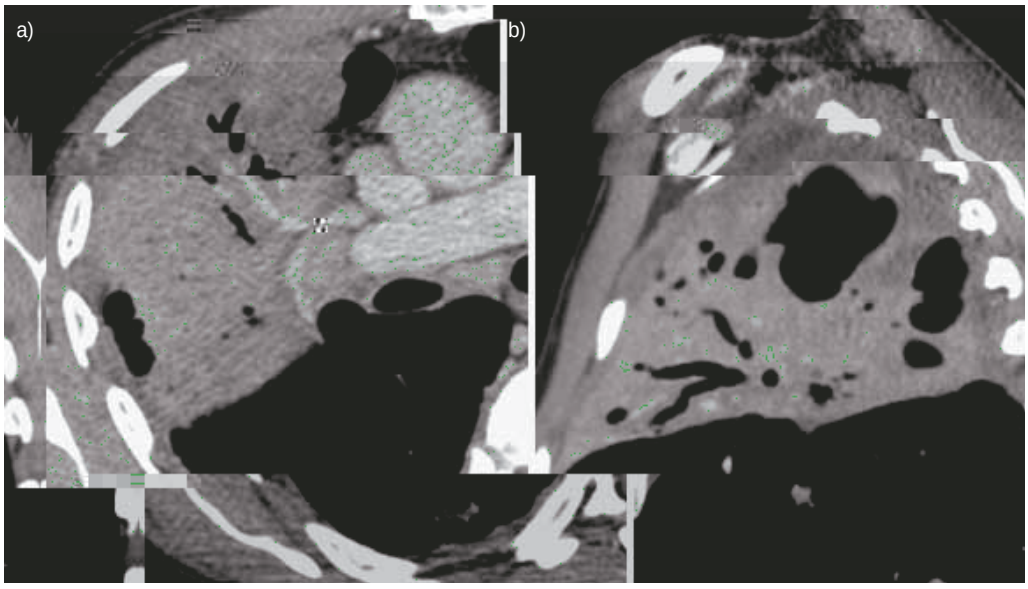


FIGURE 11 Chronic cavitary pulmonary aspergillosis of the right upper lobe. a) Axial view and b) sagittal reformat in mediastinal window show cavitary alveolar consolidation delimited inferiorly by fissures. Note the dense extrapleural fat.

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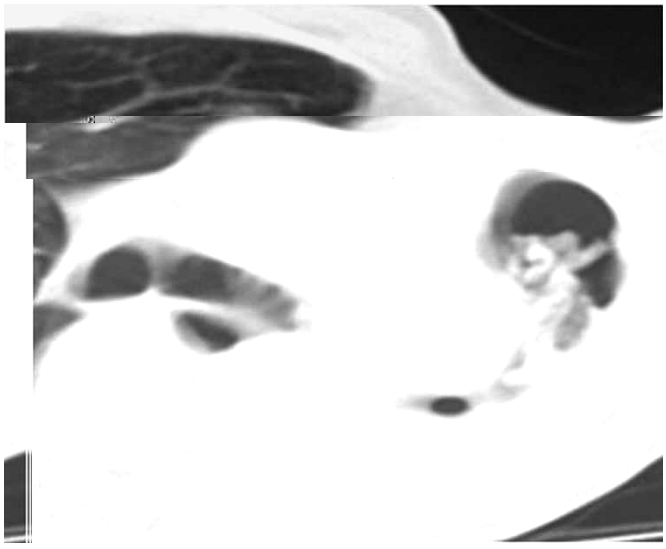

FIGURE 12 Chronic fibrosing aspergillosis with atelectasis and fibrosis of the whole left lung, secondary to untreated chronic cavitary pulmonary aspergillosis. The cavity contains strands of *Aspergillus*.

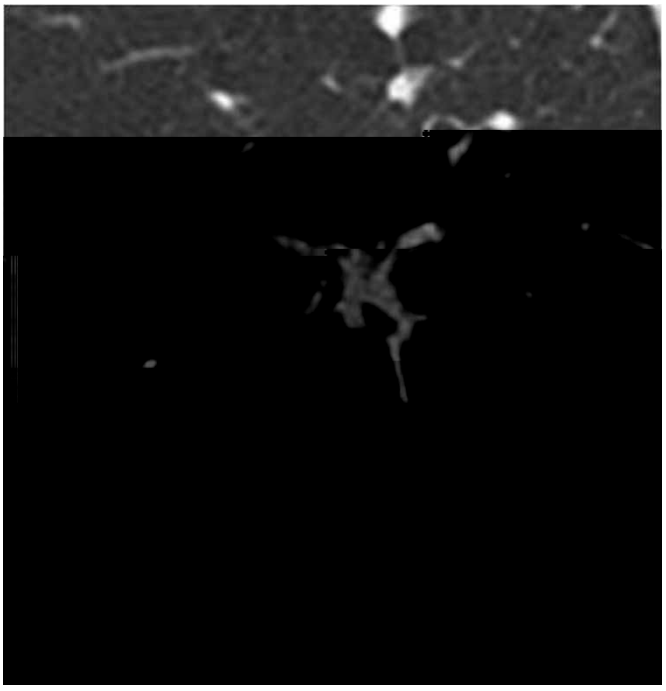

FIGURE 13 Axial view of lung window at the level of the right upper lobe. Nodule of the right, upper lobe, with irregular and slightly spiculated borders that was surgically resected and proven to be an *Aspergillus* nodule.

***Treatment and follow-up***

*Oral triazole therapy of CPA*

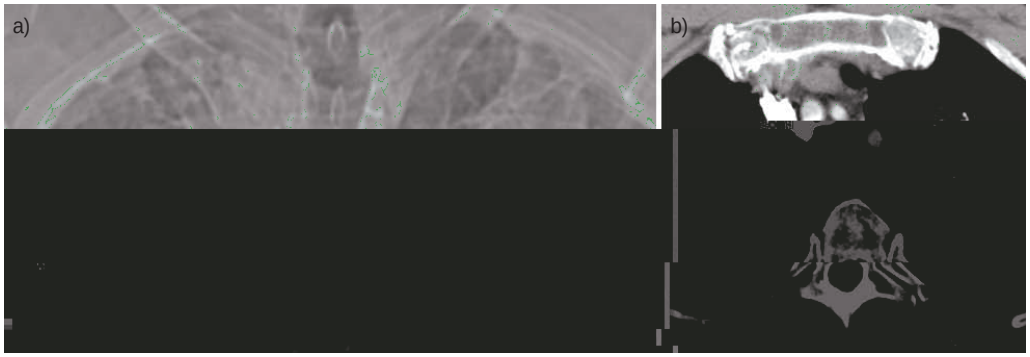


FIGURE 14 Chronic pulmonary aspergillosis presenting as bilateral upper lobes lung masses partly necrotic and cavitary on the left. a) Topogram of the chest computed tomography. b) Axial view in mediastinal window with contrast media administration.



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TABLE 9 Duration of therapy for chronic pulmonary aspergillosis (CPA)

| Population | Intention | Intervention | SoR | QoE | Ref. | Comment |
|---|---|---|---|---|---|---|
| **CPA patients on antifungal therapy** | Control of infection, arrest of pulmonary fibrosis, prevention of haemoptysis, improved quality of life | 6 months of antifungal therapy | B | II | [15, 30, 31, 59, 83, 89, 96] | Optimal duration of therapy in CPA is unknown, indefinite suppressive therapy may be appropriate in selected patients |
| | | Long-term antifungal therapy, depending on status and drug tolerance | C | III | [15, 30, 89, 59] | |
| **SAIA/CNPA** | Cure | 6 months | B | II | [15, 30] | Longer durations may be necessary in those with continuing immunosuppression |

SoR: strength of recommendation; QoE: quality of evidence; SAIA: subacute invasive aspergillosis; CNPA: chronic necrotising pulmonary aspergillosis.

65% 32% 103 B CPA 10, 51.

### *Local cavity therapy for CPA*

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### *Follow-up*

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TABLE 10 Intravenous alternatives for the treatment of chronic pulmonary aspergillosis (CPA)

| Population | Intention | Intervention | SoR | QoE | Ref. |
|---|---|---|---|---|---|
| **CPA patients with progressive disease, who fail, are intolerant of or have triazole resistance** | Control of infection | Micafungin 150 mg·day$^{-1}$ | B | II | [16, 90, 97, 98–100] |
| | | Amphotericin B deoxycholate 0.7–1.0 mg·kg$^{-1}$·day$^{-1}$ | C | III | [10] |
| | | Liposomal AmB 3 mg·kg$^{-1}$·day$^{-1}$ | B | IIa | [101] |
| | | Caspofungin 50–70 mg·day$^{-1}$ | C | IIa | [96, 102] |

SoR: strength of recommendation; QoE: quality of evidence.


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*Corticosteroid therapy and CPA*

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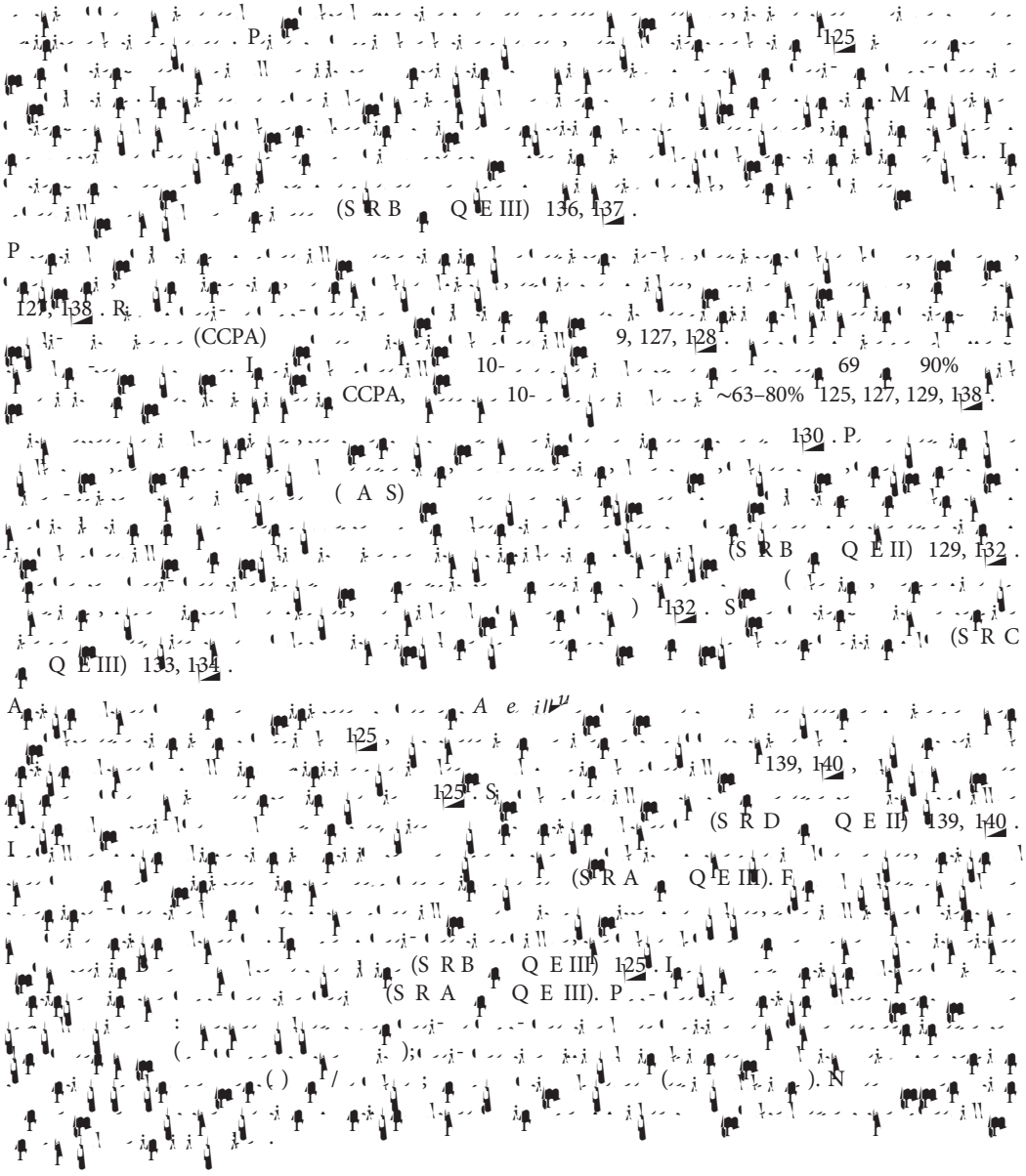

TABLE 11 Indications for and types of surgery for chronic pulmonary aspergillosis

| Population | Intention | Intervention | SoR | QoE | Ref. | Comment |
|---|---|---|---|---|---|---|
| **Single/simple aspergilloma** | Cure and prevention of life-threatening haemoptysis | Lobectomy or any other segmental resection | A | II | [9, 21, 124–130, 131] | Risk/benefit assessment required. Patients should be seen in centres with experience of aspergillosis surgery. |
| | | VATS | B | II | [129, 132] | May require conversion to thoracotomy. |
| **CCPA refractory to medical management (including multi-azole resistance) with antifungal treatment and/or life-threatening haemoptysis** | Improved control of disease, possibly cure | Careful risk assessment, followed by lobectomy or pneumectomy | A | II | [125, 127] | Prior embolisation as a temporising procedure. |
| | | Thoracoplasty with simultaneous cavernostomy and muscle transposition flap | C/D | III | [133, 134] | Highly experienced surgical team required. |

SoR: strength of recommendation; QoE: quality of evidence; CCPA: chronic cavitary pulmonary aspergillosis; VATS: video-assisted thoracic surgery.



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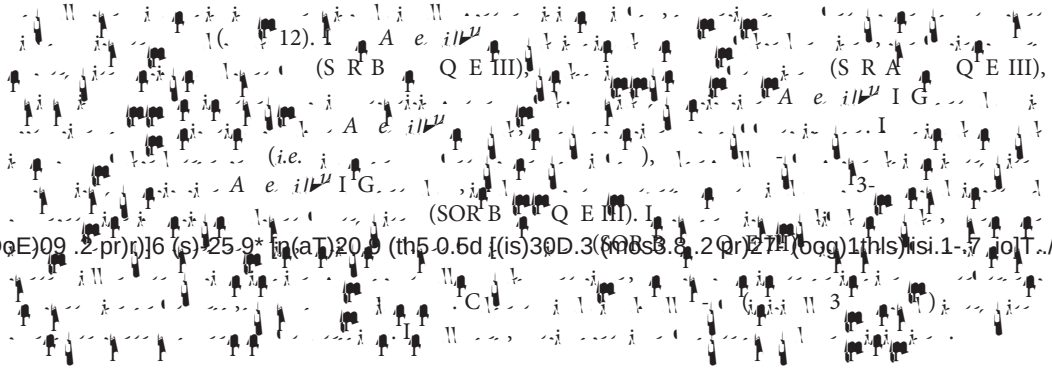

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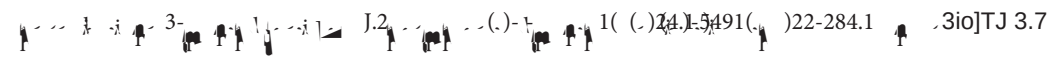
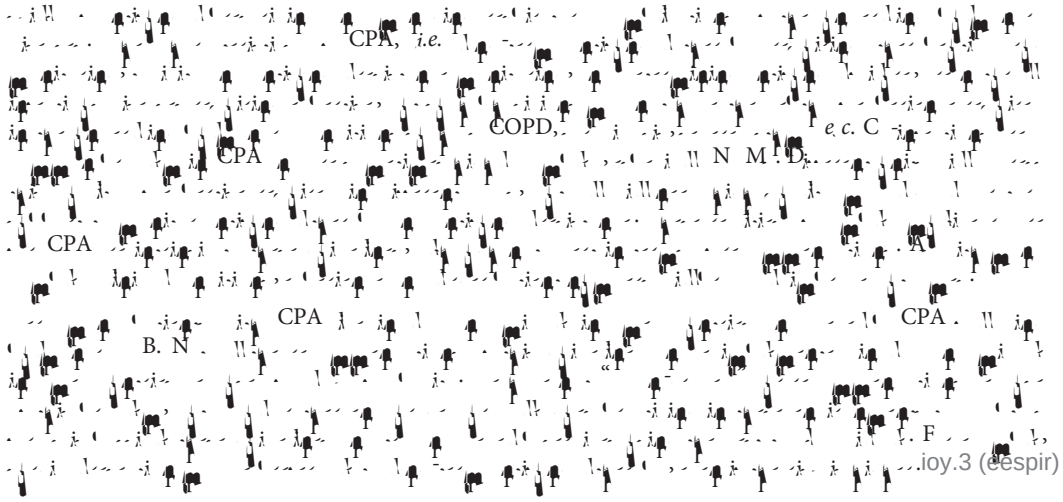
## Discussion

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