



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

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ABSTRACT Chronic pulmonary aspergillosis (CPA) is an uncommon and problematic pulmonary disease, complicating many other respiratory disorders, thought to affect ~240000 people in Europe. The most common form of CPA is chronic cavitary pulmonary aspergillosis (CCPA), which untreated may progress to chronic fibrosing pulmonary aspergillosis. Less common manifestations include: *Aspergillus* nodule and single aspergilloma. All these entities are found in non-immunocompromised patients with prior or current lung disease. Subacute invasive pulmonary aspergillosis (formerly called chronic necrotising pulmonary aspergillosis) is a more rapidly progressive infection (<3 months) usually found in moderately immunocompromised patients, which should be managed as invasive aspergillosis. Few clinical guidelines have been previously proposed for either diagnosis or management of CPA. A group of experts convened to develop clinical, radiological and microbiological guidelines. The diagnosis of CPA requires a combination of characteristics: one or more cavities with or without a fungal ball present or nodules on thoracic imaging, direct evidence of *Aspergillus* infection (microscopy or culture from biopsy) or an immunological response to *Aspergillus* spp. and exclusion of alternative diagnoses, all present for at least 3 months. *Aspergillus* antibody (precipitins) is elevated in over 90% of patients. Surgical excision of simple aspergilloma is recommended, if technically possible, and preferably *via* video-assisted thoracic surgery technique. Long-term oral antifungal therapy is recommended for CCPA to improve overall health status and respiratory symptoms, arrest haemoptysis and prevent progression. Careful monitoring of azole serum concentrations, drug interactions and possible toxicities is recommended. Haemoptysis may be controlled with tranexamic acid and bronchial artery embolisation, rarely surgical resection, and may be a sign of therapeutic failure and/or antifungal resistance. Patients with single *Aspergillus* nodules only need antifungal therapy if not fully resected, but if multiple they may benefit from antifungal treatment, and require careful follow-up.



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Introduction

Chronic pulmonary aspergillosis (CPA) was first recognised as a fatal condition in 1842 in Edinburgh, UK [1], and the first recorded patient treated with amphotericin received the drug in 1957, because of CPA complicating tuberculosis (TB) [2]. The first radiological description of aspergilloma was in France, in 1938, and was described as a “mega-mycetome intra-bronchiectasique” [3]. The middle of the 20th century saw many clinical descriptions of aspergilloma. Aspergillosis was first “classified” in 1959, with the terms “mycetoma” used, whereas now this refers to a subcutaneous fungal infection [4]. In the 1960s *Aspergillus* antibody detection was discovered in London, UK [5] and became adopted as a means of confirming the aetiology of fungal balls seen on chest radiographs and tomography. The terms semi-invasive pulmonary aspergillosis [6] and chronic necrotising pulmonary aspergillosis [7] were introduced in the early 1980s. Advances in thoracic surgery, during this era, produced cures from aspergilloma in some patients with single lesions and recognition that outcomes were often poor in those with multicavity disease, termed complex aspergilloma [8, 9]. Very few patients are described in the literature as being treated with amphotericin B [10], and early open trials of itraconazole, without standardised response criteria, showed partial clinical benefits without radiological change [11]. Subsequently criteria for the diagnosis and categorisation of patients were proposed in 2003 [10], and later refinements to the criteria and classification of the disease were proposed [12, 13]. Several prospective treatment studies were undertaken [14–16]. The global burden of CPA following pulmonary TB (prevalence of 1.74 million), complicating allergic bronchopulmonary aspergillosis (ABPA) (CPA prevalence of 411,000) and sarcoidosis (CPA prevalence of 72,000) have been estimated [17–19], showing the extent of the problem internationally.

The number of CPA patients improved the understanding and tools needed for diagnosis, clear evidence of antifungal responses in many patients led to both the European Society for Clinical Microbiology and Infectious Diseases (ESCMID), in cooperation with European Confederation of Medical Mycology, and the European Respiratory Society (ERS), to support the development of clinical guidelines for diagnosis and management. Detailed recommendations regarding the management of aspergilloma were published by the Infectious Diseases Society of America in 2000 [20], and updated in 2008 [21]: Single aspergilloma was best managed with surgical resection ((strength of recommendation (SOR) B and quality of evidence (QoE) III)) and chronic cavitary pulmonary aspergillosis (CCPA), with long-term medical therapy using either itraconazole or voriconazole (SoR B, QoE III). Otherwise no other clinical guidelines for CPA have been published.

Methods

An expert group from the ESCMID Fungal Infections Study Group (EFISG) (F. Ader, C. Beigelman-Aubry, A. Chakrabarti, D.W. Denning and A.J. Ullmann) and from the ERS (S. Blot, J. Cadranet, G. Dimopoulos and C. Lange) searched the published and grey literature. Documents and views were shared by email, teleconferences, and face-to-face meetings during 2014. Consensus on a disease definition, diagnosis, therapy and monitoring was reached, and different recommendations graded. The preliminary recommendations were presented at the European Congress on Clinical Microbiology and Infectious Diseases in May 2014, and further feedback was received. The guideline recommendations were finalised by group consensus and approved by the Councils of both ESCMID and ERS.

Literature searching for relevant scientific publications was performed through PubMed. Main keywords used were “chronic pulmonary aspergillosis”, “chronic cavitary pulmonary aspergillosis”, “chronic necrotising pulmonary aspergillosis”, and “aspergilloma”. No time frame was defined. The latest literature search was conducted in August 2014; however, throughout the writing of the guidelines new scientific data were incorporated if they added value. The literature searches were performed without restrictions in type of publications. Additional studies could be identified *via* reference lists. Furthermore we considered unpublished studies in conference abstracts, mainly identified *via* the *Aspergillus* website (www.aspergillus.org.uk), a worldwide comprehensive resource providing information about *Aspergillus*. This database is kept up-to-date through weekly literature searches. Papers of interest and importance are uploaded, omitting case reports, industrial applications of aspergillosis and some (repetitive) reviews. Abstracts from the major meetings are uploaded, although not all are captured. In principle no language restrictions were applied, but for articles in foreign languages at least an English abstract must have been available.

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TABLE 1 Strength of recommendation grades

Grade	Definition
A	ESCMID (EFISG), ECMM and ERS strongly support a recommendation for use
B	ESCMID (EFISG), ECMM and ERS moderately support a recommendation for use
C	ESCMID (EFISG), ECMM and ERS marginally support a recommendation for use
D	ESCMID (EFISG), ECMM and ERS support a recommendation against use

ESCMID: European Society for Clinical Microbiology and Infectious Diseases; EFISG: ESCMID Fungal Infections Study Group; ECMM: European Confederation of Medical Mycology; ERS: European Respiratory Society.

The methods to evaluate the QoE and to reach group consensus recommendations are described elsewhere [22]. Definition of the SoR is given in table 1. The quality and source (if required) of the published evidence is defined in table 2. Grouping QoE into three only levels may lead to diverse types of published evidence being assigned specifically a level II. The SoR and the QoE were separately assigned in two separate evaluations, thus allowing, for example, a recommendation strongly supporting a procedure even if there is a lower level of evidence.

Consensus definitions of CPA

The most common form of CPA is CCPA. Untreated it may progress to chronic fibrosing pulmonary aspergillosis (CFPA). Less common manifestations of CPA include *Aspergillus* nodule and single aspergilloma. All these entities are found in non-immunocompromised patients with prior or current lung disease. Subacute invasive pulmonary aspergillosis (formerly called chronic necrotising pulmonary aspergillosis) is a more rapidly progressive infection (<3 months) usually found in moderately immunocompromised patients [23]. Summary definitions are shown in table 3 and shown in figure 1.

Aspergilloma

This is the morphological appearance of a fungal ball, consisting almost entirely of fungal hyphae and extracellular matrix. It is the most characteristic imaging feature of CPA and usually visualised on computed tomography (CT) scanning of the thorax, in a pulmonary or pleural cavity or an ectatic bronchus. It may be found in all forms of CPA except *Aspergillus* nodule. Aspergilloma is a late manifestation of disease, formed by the collapse into a cavity of the fungal surface growth inside that cavity. It is exceptionally unusual for a fungal ball to be caused by any other fungus. The term “air crescent” has also been noted in invasive pulmonary aspergillosis (IPA), when the material seen in the cavity is infarcted lung containing *Aspergillus* (or another fungus). This latter entity is best referred to as a “mycotic lung sequestrum”, and is seen in immunocompromised patients. An aspergilloma is highly characteristic of CPA, but additional information is required to classify the disease and decide on therapy.

Single (simple) pulmonary aspergilloma

Single (simple) pulmonary aspergilloma is a single fungal ball in a single pulmonary cavity. There is no progression over months of observation and very few, if any pulmonary or systemic symptoms and serological or microbiological evidence implicating *Aspergillus* spp. (figure 2).

TABLE 2 Quality of evidence (QoE) levels and source of evidence

QoE	Definition
I	Evidence from at least one properly designed randomised, controlled trial; with the primary objective of the study aligned with the recommendation being made.
II	Evidence from at least one well-designed clinical trial, without randomisation; from cohort or case-controlled analytic studies (preferably from more than one centre); from multiple time series; or from dramatic results of uncontrolled experiments.
r	Meta-analysis or systematic review of randomised control trial
t	Transferred evidence <i>i.e.</i> results from different patient cohorts, or similar immune-status situation
h	Comparator group: historical control
u	Uncontrolled trials
a	Published abstract presented at an international symposium or meeting
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees.

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 <i>Aspergillus</i> 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 <i>Aspergillus</i> 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 hyphae in invading lung tissue and microbiological investigations reflect those in invasive aspergillosis, notably positive <i>Aspergillus</i> galactomannan antigen in blood (or respiratory fluids).

CCPA: Chronic cavitory pulmonary aspergillosis; CFPA: chronic fibrosing pulmonary aspergillosis; SAIA: subacute invasive aspergillosis/chronic necrotising/semi-invasive

Chronic cavitory pulmonary aspergillosis

CCPA, formerly called complex aspergilloma, usually shows multiple cavities, which may or may not contain an aspergilloma (figures 3 and 4), in association with pulmonary and systemic symptoms and raised inflammatory markers, over at least 3 months of observation [10]. Untreated, over years, these cavities enlarge and coalesce, developing pericavitary infiltrates or perforating into the pleura, and an aspergilloma may appear or disappear. Thus serological or microbiological evidence implicating *Aspergillus* spp. is required for diagnosis.

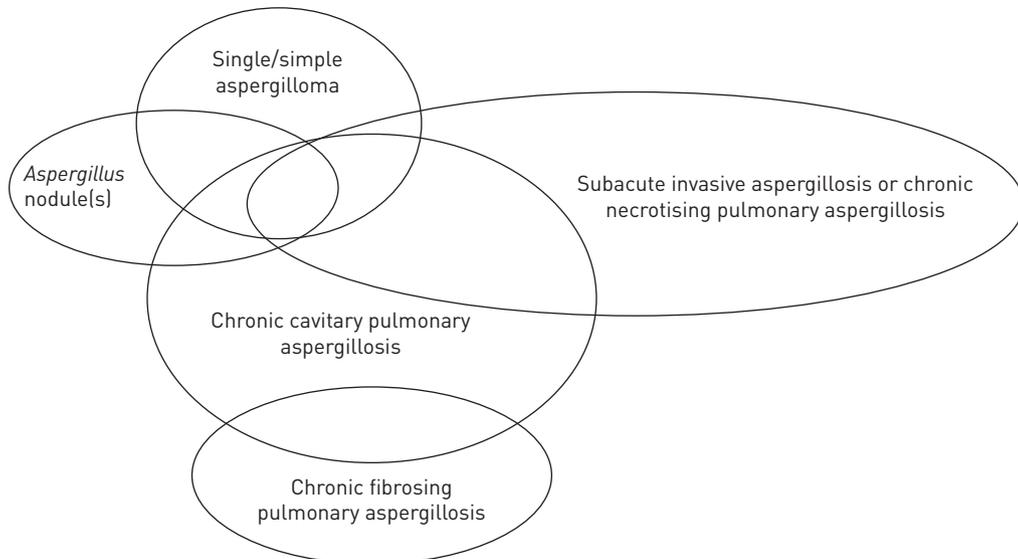


FIGURE 1 A schematic to illustrate the different forms of chronic pulmonary aspergillosis, in particular the overlap that is often seen.



FIGURE 2 Simple aspergilloma that developed within a post-tuberculous cicatricial atelectasis of the left upper lobe with saccular bronchiectasis. Surgical resection by video-assisted thoracic surgery was performed because of recurrent haemoptysis and a requirement for anticoagulant therapy.

Chronic fibrosing pulmonary aspergillosis

CFPA is often an end result from untreated CCPA. Extensive fibrosis with fibrotic destruction of at least two lobes of lung complicating CCPA (figure 5), leading to a major loss of lung function. Usually the fibrosis is solid in appearance, but large or small cavities with surrounding fibrosis may be seen. Serological or microbiological evidence implicating *Aspergillus* spp. is required for diagnosis. One or more aspergillomas may be present [4].

Aspergillus nodule

One or more nodules (<3 cm), which do not usually cavitate, are an unusual form of CPA (figure 6). They may mimic carcinoma of the lung, metastases, cryptococcal nodule, coccidioidomycosis or other rare pathogens and can only be definitively diagnosed on histology. Nodules in patients with rheumatoid arthritis may be pure rheumatoid nodules or contain *Aspergillus*. Tissue invasion is not demonstrated, although necrosis is frequent. Sometimes lesions larger than 3 cm in diameter are seen and may have a necrotic centre. These are not well described in the literature and are best described as “mass lesions caused by *Aspergillus* spp.”.

Subacute invasive aspergillosis

Subacute invasive aspergillosis (SAIA) was previously termed chronic necrotising or semi-invasive pulmonary aspergillosis. SAIA occurs in mildly immunocompromised or very debilitated patients and has

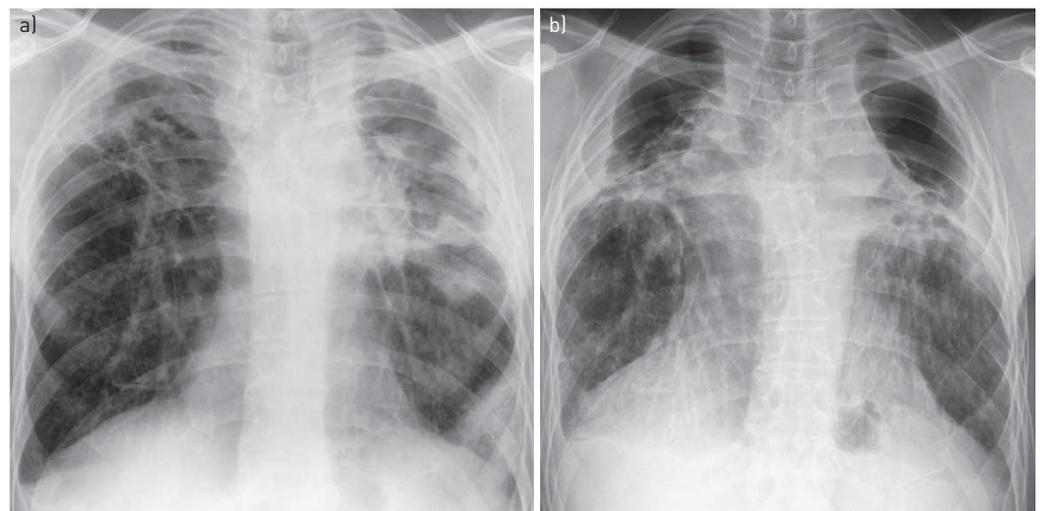


FIGURE 3 Chronic cavitary pulmonary aspergillosis showing marked progression between a) 2007 and b) 2012. Chest radiographs prior to 2007 (i.e. 1990s) showed “upper lobe fibrosis”, without a firm diagnosis. A large cavity with pleural thickening is visible on the left in both images, with additional small cavities inferiorly in 2012, and contraction of the left upper lobe. The right side shows interval development of a large cavity, with some pleural thickening. Neither cavity contains a fungal ball.

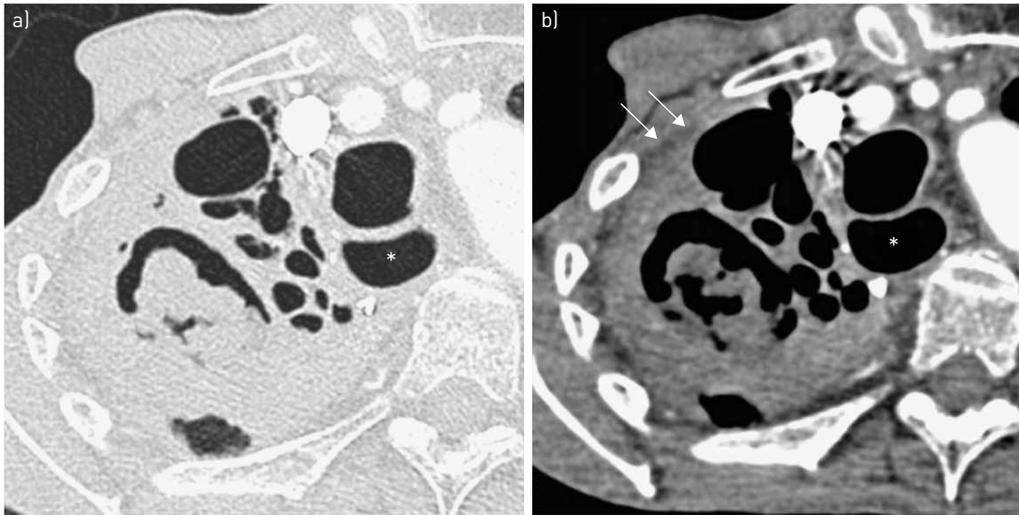


FIGURE 4 Imaging showing chronic cavitary pulmonary aspergillosis showing an axial view with a) lung and b) mediastinal windows at the level of the right upper lobe. Multiple cavities are visible with a fungus ball lying within the largest one. The wall of the cavities cannot be distinguished from the 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.

similar clinical and radiological features to CCPA (figures 7 and 8) but is more rapid in progression [7]. SAIA typically occurs in patients with diabetes mellitus, malnutrition, alcoholism, advanced age, prolonged corticosteroid administration or other modest immunocompromising agents, chronic obstructive lung disease, connective tissue disorders, radiation therapy, non-tuberculous mycobacterial (NTM) infection or HIV infection [24–27]. Patients are more likely to have detectable *Aspergillus* antigen in blood [28], and will show hyphae invading lung parenchyma, if a biopsy is done.



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.

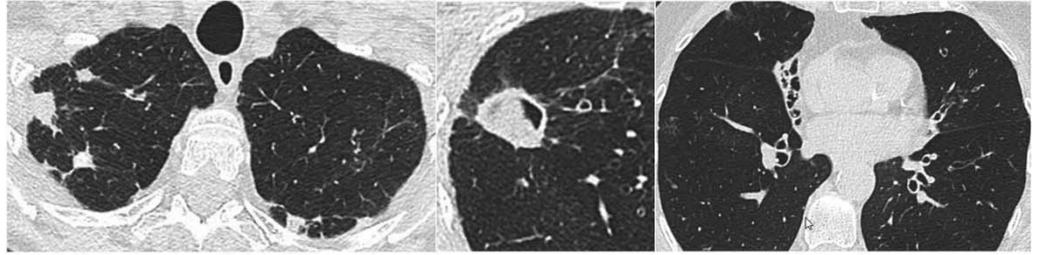


FIGURE 6 Successive axial views within the lung window showing *Aspergillus* nodules, of variable size and borders, and a fungus ball filling a cavity with a wall of variable thickness in a patient with pre-existing bronchiectasis and cicatricial atelectasis of the middle lobe.

Diagnosis

Diagnostic criteria

The diagnosis of CPA requires a combination of characteristics: a consistent appearance in thoracic imaging (preferably by CT), direct evidence of *Aspergillus* infection or an immunological response to *Aspergillus* spp. and exclusion of some alternative diagnoses (see section below). In addition, by convention the disease will have been present for at least 3 months, even if that duration is inferred and based on symptoms or progressive radiological abnormality. Patients are usually not immunocompromised by HIV-infection, cancer chemotherapy or immunosuppressive therapy. A few patients have some level of immunosuppression and, arbitrarily, we recommend a cut-off of 10 mg prednisolone daily (or equivalent) for clinical management. Intermittent higher levels of immunosuppression may accelerate progression of CPA, if not controlled with antifungal therapy.

If a fungal ball is observed, then confirmation that *Aspergillus* is responsible requires only an *Aspergillus* IgG or precipitins test to be positive, which it will be in >90% of cases. If antibody testing is not positive then other evidence of *Aspergillus* infection is required. Patients may have both CPA and other infections that occur concurrently.

In patients with one or more cavities consistent with CPA then any of the following can be used to confirm the diagnosis, if other diagnoses have been excluded (refer to paragraph below): *Aspergillus* IgG or precipitins positive, strongly positive *Aspergillus* antigen or DNA in respiratory fluids, percutaneous or excision biopsy showing fungal hyphae on microscopy or growing *Aspergillus* spp. from a cavity. If hyphae are seen to be invading lung parenchyma, the diagnosis is acute or subacute invasive aspergillosis. Respiratory samples showing hyphae consistent with *Aspergillus* and/or growing *Aspergillus* spp. and/or with a positive *Aspergillus* PCR assay support the diagnosis, but are not enough alone for a confirmed diagnosis of CPA as numerous other conditions can yield *Aspergillus* in the airways.

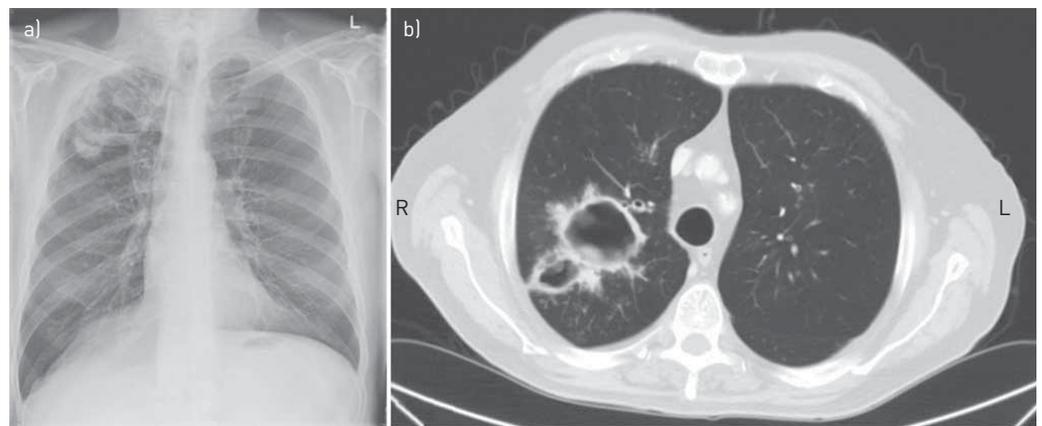


FIGURE 7 Subacute invasive aspergillosis in a patient with hepatocellular carcinoma being treated with the sorafenib [a multityrosine and Raf kinase inhibitor with some immunosuppressive features against T-cells]. a) The chest radiograph shows a large irregular right upper-lobe cavitory lesion that developed 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.

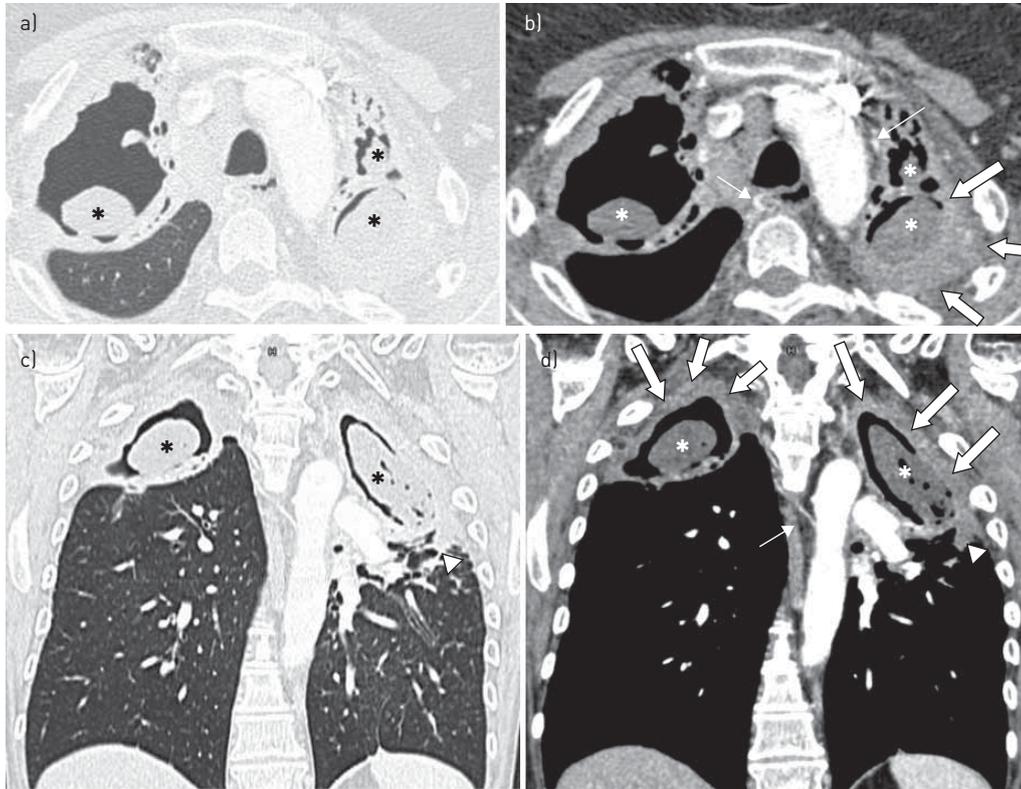


FIGURE 8 Chronic, cavitary pulmonary aspergillosis in a smoker with previous infection caused by *Mycobacterium kansasii*, poor nutrition and cirrhosis. The patient had had several episodes of severe haemoptysis treated by arterial embolisation with long-term treatment by voriconazole. a, b) Axial and 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).

SAIA should be diagnosed according to established definitions of invasive aspergillosis in immunocompromised patients (or highly debilitated patients), with a slower course than acute invasive aspergillosis (1–3 months), and commonly with both detectable *Aspergillus* antibody and antigen in the serum. Histological confirmation derives from seeing hyphae invading lung parenchyma.

Depending on geographical location and travel history there are three fungal conditions that are similar in presentation: chronic cavitary pulmonary histoplasmosis, paracoccidioidomycosis and coccidioidomycosis. Antibody/antigen detection and respiratory cultures will usually allow for the distinction to be made.

Mycobacterial infection is the usual differential diagnosis for CPA and either pulmonary TB or NTM infection may precede, follow or occasionally occur contemporaneously with CPA. Pulmonary samples for smear, mycobacterial nucleic acid amplification and culture are important components of the differential work up of possible CPA. Diagnosing a mycobacterial infection does not exclude CPA. Other differential diagnoses include necrotising lung cancer, pulmonary infarction, vasculitides and rheumatoid nodule.

Persistent cavities in the lung, as found in CPA, may be infected with conventional bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and anaerobic bacteria. Almost all require treatment, but do not negate a diagnosis of CPA.

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

The presence of *Aspergillus fumigatus* in sputum is not diagnostic because of the ubiquitous nature of the fungus and the different pathologies attributable to the fungus. However, the presence of *A. fumigatus* in a bronchoscopic specimen is far more common in infection compared to colonisation [29] and is consistent with infection, including CPA. Microscopy of sputum or bronchoscopy specimens often reveals fungi, but has not been systematically studied (SoR A and QoE III) (table 4). Culture-positive rates in published series are 56–81% (SoR A and QoE II) [10, 30, 31]. Respiratory samples cultured on media specific for fungi have a

higher yield than bacterial culture plates [32]. Culture of multiple samples increases yield in those with allergic bronchopulmonary aspergillosis [33, 34], which is probably true for all forms of pulmonary aspergillosis. Routine-processing procedures for isolating filamentous fungi from respiratory sputum samples underestimate *Aspergillus* airway infection; sputum plugs separated from saliva and inoculation of aliquots of ~150 mg directly onto potato dextrose agar increases the yield [35]. Culture from higher volume, undiluted respiratory specimens has a much higher yield for *Aspergillus* than the UK Health Protection Agency standard culture method [36]. Positive cultures during antifungal therapy are consistent with azole resistance [37].

Molecular detection methods, such as PCR, are more sensitive than culture (SoR C and QoE II) [17]. Often the signal strength is strong, which is more consistent with infection and indicates a high fungal load. Strong PCR signals detected during antifungal therapy is most consistent with antifungal resistance and direct detection of key resistance mutations is technically possible [17].

Biopsy or resection of lesions allows definitive distinction between subacute invasive aspergillosis and CCPA and better definition of the tissue response to *Aspergillus* infection (SoR B and QoE II) (table 5). Septate hyphae may be found in a resected cavity, sometimes filling and obliterating it, with a chronic inflammatory reaction. Occasionally a granuloma is found and there may be fibrosis surrounding or mixed with an inflammatory infiltrate. In contrast, histology in SAIA shows hyphae present in lung parenchyma, with an acute inflammatory or necrotic tissue response [10, 12, 29, 40, 41].

Contribution of galactomannan antigen to the diagnosis of CPA

The sensitivity and specificity of galactomannan *Aspergillus* antigen (GM) assay in bronchoalveolar lavage (BAL) fluid specimens was 77.2% and 77.0%, respectively (with a cut-off level of 0.4), and in serum was 66.7% and 63.5%, respectively, with serum at a cut-off level of 0.7 for the diagnosis of CPA [38]. In another study the BAL GM-antigen detection test had a sensitivity and specificity of 85.7% and 76.3%, respectively, with a cut-off level of >0.5 [28]. In a recent study, the sensitivity of serum GM was only 23% [39]. Thus BAL (SoR B, QoE II) and not serum GM (SoR C and QoE III) should be used in diagnosis of CPA.

Antibody diagnosis of CPA

Detection of *Aspergillus* antibodies is a key diagnostic feature of CPA (table 6). The presence of anti-*Aspergillus* antibodies differentiates between infected and colonised patients with a positive predictive value of 100% for detecting infection [29]. Numerous commercial assays are available, in addition to some in-house serology methods, usually *Aspergillus* precipitins detection by immunodiffusion or counter-immunoelectrophoresis [5, 29, 42, 43, 45–47, 52–54]. The three articles comparing different serological assays for *Aspergillus* IgG serology do not allow a definitive conclusion about comparative diagnostic performance for CPA [42–44]. It is likely that significant differences in sensitivity, specificity and coefficient of variation exist, and need to be explored with well characterised patient cohorts. Cross-reactivity with other fungi, such as *Histoplasma* or *Coccidioides* spp. may affect some tests, but is poorly studied and fortunately of limited concern in Europe.

All patients suspected of having chronic or subacute invasive aspergillosis should be tested for *A. fumigatus* IgG antibody or precipitins (SoR A and QoE II). False negative results do occur. If the clinical suspicion is high, *Aspergillus fumigatus* IgE test (SoR B and QoE II), especially in asthmatic and cystic fibrosis patients [10, 51], and an alternative IgG (SoR A and QoE II) test should be performed, with consideration given to other means of achieving the diagnosis (sputum culture and PCR, *Aspergillus* antigen, percutaneous biopsy/aspiration etc.). The performance of *A. fumigatus* IgG testing for possible *Aspergillus* nodules is not elucidated in the literature. Occasional patients with CPA have

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
<i>Aspergillus</i> PCR (respiratory secretion) [*]	C	II
Bacterial culture (sputum or BAL)	C	III

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.

TABLE 5 Contribution of antigen to the diagnosis of chronic pulmonary aspergillosis (CPA)

Population	Intention	Intervention	SoR	QoE	Ref.	Comment
Cavitary or nodular pulmonary infiltrate in non-immunocompromised patients	Diagnosis of exclusion of CPA	Antigen BAL	B	II	[38]	Antigen studied in BAL and serum, but not in sputum
		Antigen (serum) Antigen (sputum)	C No data	II	[28, 38, 39]	

SoR: strength of recommendation; QoE: quality of evidence; BAL: bronchoalveolar lavage.

hypogammaglobinaemia and others appear to have a selective inability to produce *A. fumigatus* IgG antibody. Some of these patients have poor pneumococcal and *Haemophilus* functional antibody levels. A few cases of CPA are due to non-*fumigatus* *Aspergilli*, and similar presentations may be seen with chronic cavitary pulmonary histoplasmosis, coccidioidomycosis and *Scedosporium* spp. Data are few on the value, if any, of measuring *A. fumigatus* IgA [49, 50] or IgM antibodies [48] and are, therefore, not recommended (SoR D and QoE III).

The antibody titre bears little relationship to the extent or severity of disease, although very high antibody titres are more common in those with aspergilloma [5]. Antibody titres generally slowly fall with successful therapy, but rarely become undetectable, unless continuous therapy has been given for years. A sharply rising antibody titre is usually a sign of therapeutic failure or relapse, but should be repeated before initiating a change in therapy in case of laboratory error.

Radiological diagnosis and follow-up of CPA

Technical aspects

Chest radiographs remain the first imaging modality for the suspicion and diagnosis of CPA (table 7). CT of the thorax offers much additional value, as it provides better definition and location of imaging abnormalities as well as their distribution and extent. Intravenous contrast administration (CT-angiography) is required at least for the baseline CT scan, prior to therapy. CT angiography may also be useful to evaluate new haemoptysis, and in case of possible failure of therapy (SoR B and QoE II). Use of average intensity projection post-processing of a CT could, helpfully, create slabs of variable thickness akin to a chest radiograph appearance.

Positron emission tomography (PET) doesn't appear to be useful, aspergillosis being one cause of a positive PET scan not attributable to malignancy (SoR D and QoE III) [57, 60]. An isometabolic halo pattern and an isometabolic nodule pattern on 2-fluoro-2-deoxy-D-glucose (F-FDG) PET/CT have been described in noninvasive pulmonary aspergillosis [58].

TABLE 6 Antibody diagnosis of chronic pulmonary aspergillosis (CPA)

Population	Intention	Intervention	SoR	QoE	Ref.	Comment
Cavitary or nodular pulmonary infiltrate in non-immunocompromised patients	Diagnosis or exclusion of CPA	<i>Aspergillus</i> IgG antibody	A	II	[42, 43, 44]	IgG and precipitins test standardisation incomplete
		<i>Aspergillus</i> precipitins	A	II	[29, 43, 45–47]	Mostly in-house tests and poorly validated; uncertain sensitivity is the major problem
		<i>Aspergillus</i> IgM antibody	D	III	[48]	Few data
		<i>Aspergillus</i> IgA antibody	D	III	[49, 50]	
Intervention in context of asthma, ABPA or CF patients		<i>Aspergillus</i> IgE antibody	B	II	[10, 51]	Often detectable in CCPA irrespective of underlying condition, with a raised total IgE

SoR: strength of recommendation; QoE: quality of evidence; ABPA: allergic bronchopulmonary aspergillosis; CF: cystic fibrosis.

TABLE 7 Radiological diagnoses and follow-up of chronic pulmonary aspergillosis (CPA)

Population	Intention	Intervention	SoR	QoE	Ref.	Comment
Any features of cavitation, fungal ball, pleural thickening and/or upper lobe fibrosis	Raise suspicion of CPA for physicians	Radiological report must mention possible CPA	A	II	[10, 11, 24, 25, 40, 55, 56]	CPA is often missed for years and patients mismanaged; microbiological testing required for confirmation
Suspicion of CPA on chest radiograph	Diagnosis or exclusion of CPA	CT scan (contrast)	A	II	[55]	High quality CT with vessel visualisation
		PET scan	D	III	[57, 58]	Expert radiology advice
Follow-up on or off therapy		CT (low dose)	B	III	[15, 55]	General need to minimise radiation exposure, especially multiple CT scans
		Chest radiograph	B	III		
		Initial follow-up at 3 or 6 months or with change of status	A	II	[15, 59]	

SoR: strength of recommendation; QoE: quality of evidence; CT: computed tomography; PET: positron emission tomography.

Imaging findings

The imaging features of CPA result from a combination of the findings related to underlying lung disorders and changes secondary to *Aspergillus* infection itself, reflecting the chronic inflammatory and immune response to *Aspergillus* spp. [61]. CPA most commonly develops in a pre-existent bronchopulmonary or, less usually, pleural cavity, but also directly causes the formation and expansion of new cavities or nodules and rarely alveolar consolidation. Multiple underlying conditions may be present [62]. TB, NTM infection and ABPA remain the predominant risk factors for development of CPA, with COPD, prior pneumothorax or treated lung cancer also relatively common [26, 62]. Fibrocystic sarcoidosis [19], ankylosing spondylitis, pneumoconiosis [63] and progressive massive fibrosis in silicosis [64, 65] may also be implicated [40, 55, 66–69]. Changes secondary to the *Aspergillus* infection itself range from the typical appearance of a fungus ball within a lung cavity (single or simple aspergilloma) to complex pleuroparenchymal features that are related to a progressive destructive cavitary disease [61]. The distinctive hallmarks of CPA are new and/or expanding cavities of variable wall thickness in the setting of chronic lung disease with or without intracavitary fungal ball formation, often with pleural thickening and marked parenchymal destruction and/or fibrosis. *Aspergillus* empyema may be seen [11]. Associated enlargement of bronchial or non-bronchial systemic arteries and, less frequently, pseudo-aneurysms may lead to sometimes fatal haemoptysis.

Prior to aspergilloma formation, a mat of fungal growth on the interior surface of the cavity is common, with a distinctive appearance of a bumpy or irregular interior cavity appearance (figure 9). An aspergilloma typically starts as a surface infection following colonisation in a lung cavity or a bronchiectasis [56, 61]. Aspergilloma is a late manifestation of CPA [26]. Aspergilloma typically presents as an upper-lobe, solid, round or oval intracavitary mass, partially surrounded by a crescent of air, the “air-crescent” sign, mobile on prone position [40, 56, 67] (figure 10). It may also appear fixed and immobile as an irregular sponge-work filling the cavity and containing air spaces. Fungal strands, corresponding to mats of fungal growth detached from the interior of the cavity surface, may also be seen forming a coarse and irregular network with interstices (figure 9), which often coalesce to form the mature fungus ball [56]. Calcification may be seen in the fungal ball as flecks of density, as dense nodules or extensively throughout the aspergilloma [64, 56, 70]. Fungus balls do not enhance after *i.v.* injection of contrast media [71]. Adjacent pleural thickening is often observed [67]. Aspergilloma have been categorised as “simple” or “complex”, the latter corresponding to CCPA. Aspergilloma may coexist with any underlying condition [67]. There are some mimics of aspergilloma including necrotic lung carcinoma [72].

The typical appearances of CCPA consist of unilateral or bilateral areas of consolidation (figure 11) associated with multiple expanding usually thick-walled cavities (figures 3, 4 and 8) that may contain one or more aspergillomas [26, 55], with concomitant pleural thickening of variable extent. The thickened pleura, frequently associated with abnormally dense extra pleural fat, may not be differentiated in some cases from the neighbouring alveolar consolidation or the wall of the cavities. These findings are frequently asymmetric and predominantly located in the areas with pre-existing anomalies related to the underlying pulmonary disease [10]. Radiological evolution, over time, is typically slower than that observed in SAIA

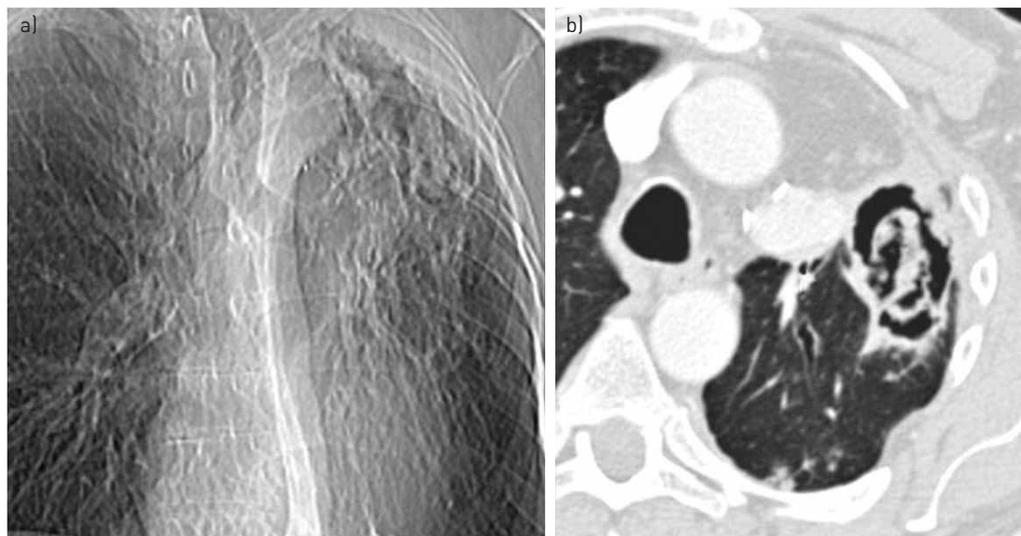


FIGURE 9 Cavity with irregular edge and aspergilloma presenting as a coarse and irregular network in a patient with a previous left upper-lobe resection. Note the apical pleural thickening bordering the cavity well seen on the topogram of the a) computed tomography scan. b) Axial view with lung window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

and may take several years (figure 3) [10]. Over time, if untreated, these cavities enlarge and coalesce, and the fungal balls may appear or disappear [11]. The differential diagnosis includes active TB [26], NTM, histoplasmosis, actinomycosis, coccidioidomycosis and lung carcinoma, the last sometimes associated concurrently with chronic (or invasive) *Aspergillus* infection [73, 74].

Chronic fibrosing pulmonary aspergillosis (CFPA) is the terminal fibrosing evolution of CCPA [26]. This situation may occur when CCPA remains untreated resulting in extensive pulmonary fibrosis (figures 4 and 12). The fibrosis may be limited to one or both upper lobes but also commonly involves the whole hemithorax [10]. There is no distinctive feature of fibrosis related to CPA, other than the cavitation and fungal balls seen in close proximity.

Aspergillus nodules (figures 6 and 13) are very similar in appearance to malignancy, coccidioidal nodules [75], NTM [76] and actinomycosis [77], as well as rheumatoid nodules [78, 79]. Most such lesions are rounded in

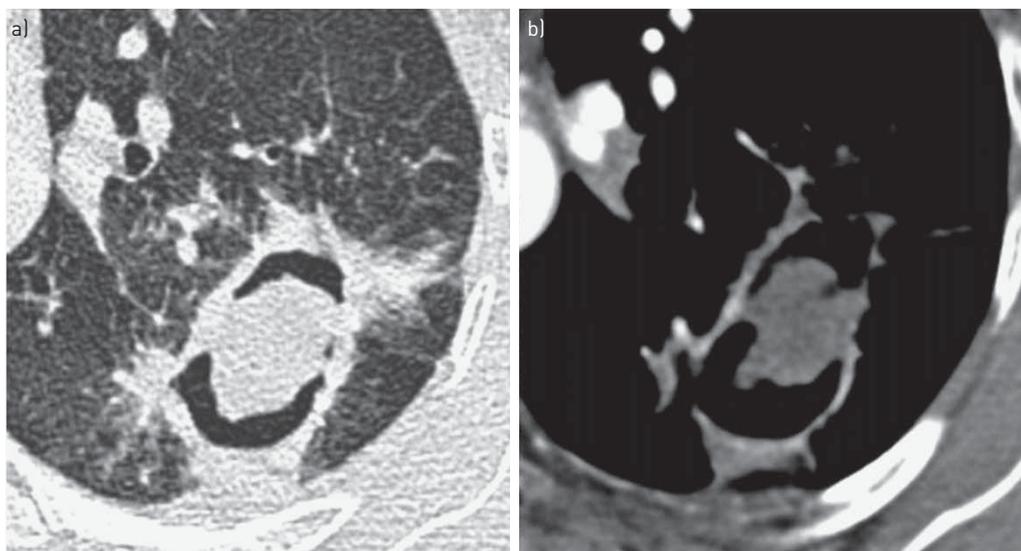


FIGURE 10 Aspergilloma in chronic, cavitary pulmonary aspergillosis. Axial view with a) lung and b) mediastinal windows. The fungus ball appears as a left upper lobe solid oval mass partially surrounded by a crescent of air, the “air-crescent” sign (a), within a thick-walled and slightly irregular cavity.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

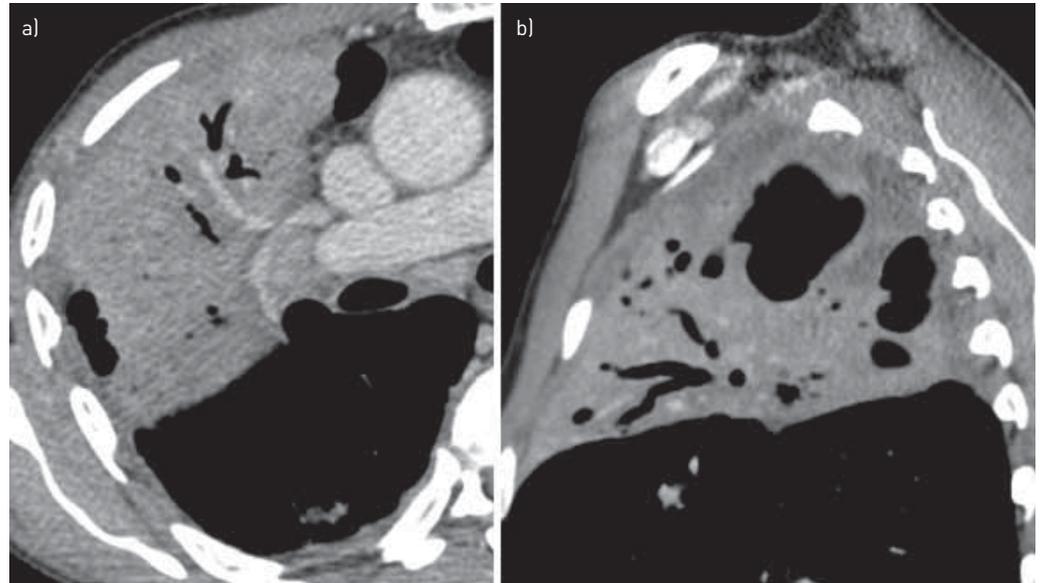


FIGURE 11 Chronic cavitary pulmonary aspergillosis of the right upper lobe. a) Axial view and b) sagittal reformat in mediastinal window show cavitary alveolar consolidation delimited inferiorly by fissures. Note the dense extrapleural fat.

appearance and may have low attenuation or cavitation within. Some have a spiculated edge. They may be single or multiple and have an area of central cavitation. There is no formal upper limit of size for an *Aspergillus* nodule, but larger mass lesions are also occasionally seen, typically with cavitation (figure 14).

In those with SAIA, the absence of any prior cavitary lesion is usual [6, 55, 67, 80]. Usually a single area of consolidation is found in an upper lobe which progresses over days or weeks with cavitation (figure 7) [40]. Sometimes the predominant feature is a thin walled cavity that expands over 1–3 months [10]. Pleural thickening and fungus balls may occur [24, 25] as well as pneumothorax and pleural effusion [81]. An air-crescent sign may be seen, a probable sign of the development of necrosis, thereby an indication of the worsening of the disease [82].

Despite these typical presentations, much overlap exists [61] between the three forms of disease, and one form of CPA may evolve into another over time [26]. It may be difficult or impossible to differentiate CCPA and SAIA without pathological evidence and/or further data on progression over time.

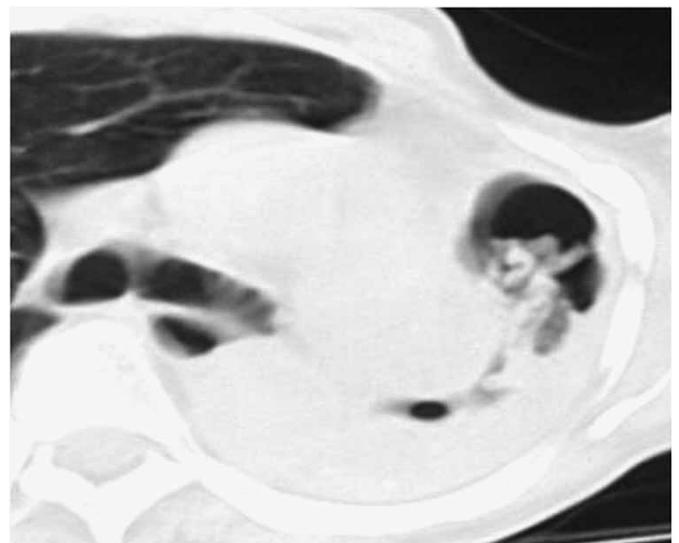


FIGURE 12 Chronic fibrosing aspergillosis with atelectasis and fibrosis of the whole left lung, secondary to untreated chronic cavitary pulmonary aspergillosis. The cavity contains strands of *Aspergillus*.

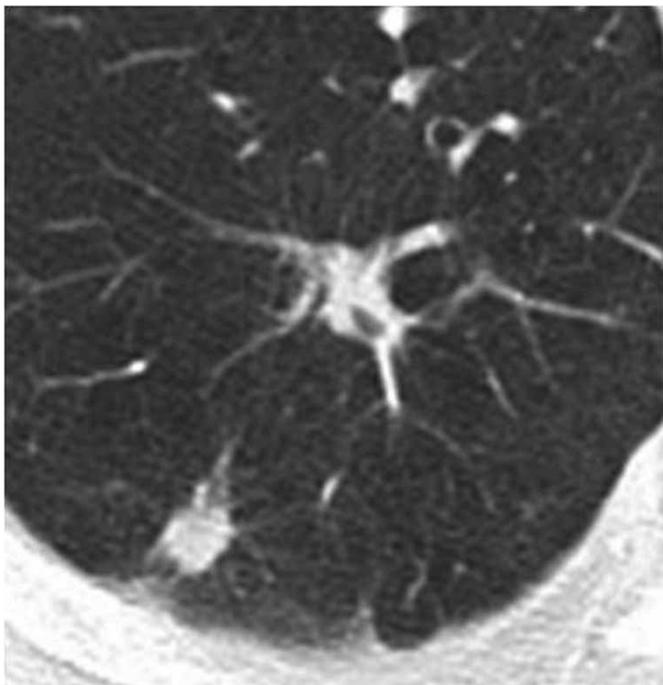


FIGURE 13 Axial view of lung window at the level of the right upper lobe. Nodule of the right, upper lobe, with irregular and slightly spiculated borders that was surgically resected and proven to be an *Aspergillus* nodule.

Treatment and follow-up

Oral triazole therapy of CPA

Most of the data guiding the management of CPA are based on cohort studies (either prospective or retrospective) or case reports with the exception of two prospective phase II trials of oral therapy; one a randomised controlled study of two *i.v.* antifungal agents [14], the other oral azole therapy randomised against no antifungal therapy [83]. Most of the cohort studies do not clearly separate out the various subsets of CPA. No study has been done directly comparing two oral triazole drugs. Drug efficacy analysis has relied on a composite “score” including clinical, radiological and mycological responses, which probably vary from one study to another. Drug safety analysis requires both plasma therapeutic antifungal (SoR A and QoE II) (table 8) and serological monitoring, in addition to clinical assessment of adverse events, which is not often fully described or done in published studies. These limitations impact on the recommendations here.

The decision to treat CPA with oral triazole therapy depends on patient’s type of disease or clinical phenotype and eligibility for surgical treatment. As a general recommendation, outpatient oral triazole therapy likely provides some therapeutic benefit in cases of progressive and/or symptomatic CPA. Quality of life measures, such as the St. George’s Respiratory Questionnaire [84, 85] or the Respiratory Symptoms Score [15], may guide the decision-making process.

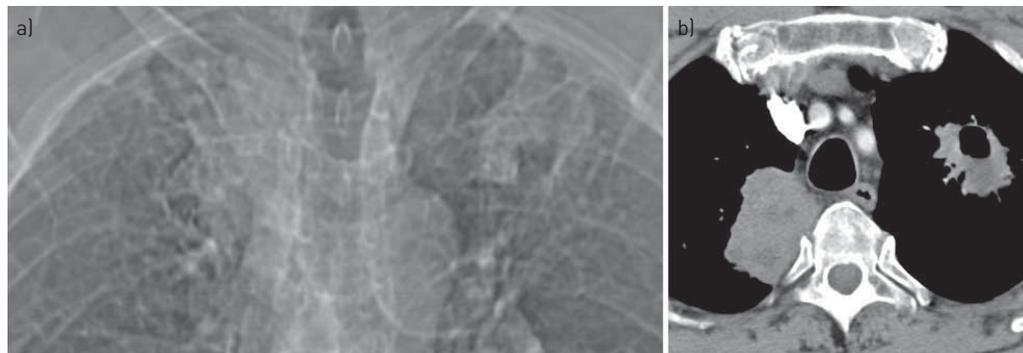


FIGURE 14 Chronic pulmonary aspergillosis presenting as bilateral upper lobes lung masses partly necrotic and cavitory on the left. a) Topogram of the chest computed tomography. b) Axial view in mediastinal window with contrast media administration.

Oral itraconazole therapy may be useful in preventing or treating life-threatening haemoptysis (SoR A and QoE II) [86–88]. Oral itraconazole treatment was superior to conservative treatment in stabilising the clinical and radiological manifestations in patients with CCPA, with comparatively minimal risk in terms of tolerance [83]. Oral triazole therapy for CCPA is now considered the standard of care. Oral voriconazole is also effective for CCPA with an acceptable tolerability in several studies as primary therapy (SoR A and QoE II) or after itraconazole (either because of failure or intolerance) (SoR A and QoE II) [15, 30, 89–92]. A retrospective cohort study supports the evidence that oral posaconazole may be a potential alternative treatment (SoR B and QoE II) [59].

CFPA is generally the end result of untreated CCPA associated with subsequent development of extensive pulmonary fibrosis. Long-term treatment with itraconazole may be beneficial in stabilising patients' general condition, with limited impact on breathlessness [10].

We unequivocally recommend treatment of SAIA as acute invasive aspergillosis; please refer to the 2016 ESCMID Aspergillosis and other guidelines. Some cases of SAIA have responded to long-term oral itraconazole in some cohort studies [31, 86, 87, 93, 94]. A prospective multicentre study of CPA patients treated with voriconazole confirmed data obtained in a preliminary study showing that voriconazole efficacy was significantly greater in patients with SAIA than in those with CCPA [15, 90, 95].

Duration of antifungal therapy for CPA

In CCPA, response to antifungal therapy is generally slow. However, most patients who respond have done so by 6 months [59] [table 9]. Thus, a minimum of 4–6 months oral triazole therapy is recommended initially (SoR A and QoE I). Patients who deteriorate in this period should be deemed failures and an alternative regimen used. Those with minimal response should have this initial trial period extended to 9 months; almost all patients who are destined to respond will have done so by that time (SoR C and QoE III) [59]. In responders, continuing therapy, which may be indefinite long-term suppressive treatment, is usually required and translates into better outcomes (SoR B and QoE II) [83]. Those with only stable disease may not benefit from long-term therapy, but each case must be assessed on its merits, with factors such as respiratory disability, tolerability of medication, need for alternative interacting medication and cost taken into account. As prevention of haemoptysis and further fibrosis are key goals of therapy, even patients with stable disease may benefit by not deteriorating further. Relapse is common, but not universal, on discontinuation of therapy [83].

Intravenous alternatives for the treatment of CPA

Antifungal *i.v.* therapy for CPA can be used in patients with progressive disease and in those who fail, are intolerant of triazoles or who have triazole resistance (table 10). In addition, some studies addressing *i.v.* antifungal therapy for CPA acknowledge a strategy of infection control through an *i.v.* induction phase followed by an oral maintenance therapy with antifungal drugs. Amphotericin B or echinocandins are alternative drugs to triazoles and are exclusive *i.v.* drugs.

An equivalent response to treatment (60% *versus* 53%, respectively) as well as a significantly improved safety profile was observed during a short-term course (2–4 weeks) of *i.v.* micafungin in comparison with *i.v.* voriconazole in CPA patients [14]. Within the echinocandin class, a small double-blinded randomised controlled trial has shown caspofungin to be as effective as micafungin in improving health status in the CPA subset [97]. Cyclical courses of caspofungin, combined with oral maintenance therapy by triazoles between infusions, have been proposed in the specific setting of complex sarcoidosis-related CPA [102].

CPA patients receiving a short-term course of *i.v.* liposomal amphotericin B (mean daily dose and duration of 3 mg·kg⁻¹ and 17 days, respectively) after prior azole therapy experienced a clinical response in

TABLE 8 Oral triazole therapy of chronic pulmonary aspergillosis

Antifungal agent and dose	Strength of recommendation	Quality of evidence
Itraconazole 200 mg twice daily, adjust with therapeutic drug monitoring	A	II
Voriconazole [#] 150–200 mg twice daily, adjust with therapeutic drug monitoring	A	II
Posaconazole 400 mg twice daily (liquid); 300 mg once daily (tablets)	B	II

[#]: lower doses advised in those aged >70 years, low weight, significant liver disease and those of North East Asian descent who may be slow metabolisers.

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% of the cases although associated with 32% rate of acute kidney injury [103], which may not improve. The *i.v.* amphotericin B deoxycholate carries limited or no benefit for CPA patients [10, 31].

Local cavity therapy for CPA

If surgical resection is not a treatment option to control recurrent haemoptysis, instillation of antifungal agents in an aspergilloma cavity could be considered, in those without a haemorrhagic diathesis (SoR C and QoE II). Several clinical reports have described the resolution of aspergilloma through the instillation of antifungal agents into pulmonary cavities, when systemic use of antifungals is ineffective or prevented by adverse events [104–113]. Instillation of antifungal agents may be delivered through an endobronchial catheter under bronchoscopic guidance, *via* a percutaneous transthoracic needle or catheter placed into the aspergilloma cavity. Ordinarily a percutaneous catheter is placed in the cavity avoiding repeated bronchoscopy and a shorter period of therapy [107].

The antifungals used for instillation include amphotericin B (as paste or solution), azoles (miconazole, itraconazole), sodium iodide and nystatin (as paste with amphotericin B). The reported short-term response rates have varied from 70% to 100%. Amphotericin B is the drug of choice (50 mg in 20 mL 5% dextrose solution) (SoR C and QoE II) and the instilled amount depends on cavity space available. Direct leakage into the bronchial tree needs to be avoided by patient positioning. Complications include cough, chest pain, pneumothorax or endobronchial reflux, which is problematic in those with poor respiratory reserve. If successful, instillation of antifungal agents should result in the cessation of haemoptysis and pain, conversion of cultures of sputum for *Aspergillus* spp. to negative, decreased *Aspergillus* antibody titre and occasionally the disappearance or regression of an aspergilloma.

Follow-up

Follow-up imaging is one means of assessing progress of CPA. The chest radiograph and CT give complementary information. Reduced dose CT (to minimise radiation dose according to the ALARA principle (As Low As Reasonably Achievable)) [74, 114] is optimally used for follow-up CT. Follow-up imaging, which is recommended every 3–6 months after beginning antifungal treatment [15, 59] and then less often, or with any major change of clinical status (SoR B and QoE III) (table 9). Radiological change

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.

is slow and very little change is visible in <3 months on CT scans or chest radiographs. Signs of improvement are reduced pleural thickening, less material or fluid in a cavity, a smoother interior cavity wall, and a smaller nodule or area of pericavitary consolidation. Features of failure include an expanding cavity, new cavities, or coalescing cavities, formation of an aspergilloma, and increased consolidation adjacent to a cavity. Key judgments on the efficacy of treatment include assessing the extent of consolidation, cavity wall thickness and size, fungus ball(s) and pleural thickening by comparing exact equivalent anatomical lesions. Volumetric quantification of the lesions with software is also feasible.

Corticosteroid therapy and CPA

Inhaled or systemic treatment with corticosteroids is one of the major risk factors for CPA, posing significant progression or dissemination risk [115]. Without adequate antifungal therapy, corticosteroid therapy accelerates disease progression. Patients with underlying diseases such as sarcoidosis, rheumatoid arthritis, COPD, ABPA or asthma may, however, be dependent on immunosuppressive therapy including corticosteroids. Prednisolone 5–30 mg·day⁻¹ or other immunosuppressive therapy may carefully be considered for symptom control [74] only if patients are adequately treated with antifungals (SoR B and QoE II).

Interferon- γ immunotherapy for CPA

Many, often subtle, immune defects are noticed in CPA, but interferon (IFN)- γ deficiency is the only one that can be substituted. Impaired production of IFN- γ and interleukin (IL)-12, necessary to produce IFN- γ , were demonstrated in a set of 30 CPA patients [116]. However, normal response pathways were observed following *in vitro* stimulation of whole blood with a variety of stimuli to interrogate the IL-12 and IFN- γ -dependent pathways. Impaired IFN- γ -mediated immune response was noticed in two patients with progressive CPA despite adequate antifungal therapy [117]. This observation opens doors towards IFN- γ substitution in CPA patients. Adjunctive IFN- γ therapy (50–60 μ g subcutaneously, three times weekly) resulted in clinical improvement in both cases [117]. Another observational study reported on three patients with stable or improved disease following adjunctive therapy with IFN- γ [10]. Due to the limited number of cases described in the literature and the absence of controlled studies, no recommendation is possible.

Therapies for haemoptysis in CPA

CCPA and simple aspergilloma may be complicated by mild (common), moderate or life-threatening haemoptysis [61]. Mild and moderate haemoptysis usually responds to tranexamic acid (typically 500 mg three times daily), although not licensed for this indication (SoR A and QoE III) [118, 119]. Tranexamic acid interferes with clot dissolution because it inhibits fibrinolysis and so increases infarction potential. A low rate of strokes has been reported after its use. Sometimes it is not well tolerated, with gastrointestinal upset the most common problem.

In patients with moderate or severe haemoptysis, embolisation may be necessary, either as a temporising measure before surgery, or as a definitive treatment. In CPA, bleeding is from an abnormal and novel vascular nexus of small vessels derived from the systemic circulation, in proximity to the affected area(s). Vessels are usually derived from the bronchial circulation but may come from other arteries; intercostal, subclavian, or internal mammary. It is common for multiple abnormal connections to be present. Successful embolisation semi-permanently occludes these vessels.

Patients with a communication between an intercostal and the anterior spinal artery can only be embolised safely if the catheter is introduced well past the anterior spinal artery.

Bronchial artery embolisation is a difficult procedure requiring a skilled interventional radiologist. Fifty to 90 percent of embolisation procedures are successful, depending in part on the radiologist [120–123]. Recurrent haemoptysis occurs in 30–50% of patients over 3 years [123] but it is likely that relapse can be minimised with successful long-term antifungal therapy. Complications include chest wall pain, stroke with cortical blindness or impaired vision, chest wall or spinal cord infarction, as well as renal impairment and allergic reactions to the contrast dye. If *i.v.* amphotericin B is being administered, doses should be withheld for 24–48 h after bronchial artery embolisation, to avoid additive nephrotoxicity.

Indications for surgery in CPA

Surgical resection of aspergilloma is a definitive treatment option for patients with adequate pulmonary function (SoR A and QoE II) (table 11) [124, 125]. Success of the procedure depends on the ability to fully resect the aspergilloma without spillage of fungal elements into the pleural space. As such, recurrence of disease and haemoptysis are rare in simple aspergilloma while CCPA carries a lower success rate [124–126].

Surgery should be considered in all patients with severe haemoptysis. Experience of the surgical team with aspergilloma resection is pivotal to optimise the odds of a favourable outcome. Catheter embolisation of bronchial arteries may be life saving for severe haemoptysis, prior to surgery (SoR B and QoE II) [135]. Yet,

as this approach is rarely completely effective for very severe haemorrhage, it is rather a bridge towards definite elective surgery. Prior to possible elective surgery, careful patient selection [125] is warranted as many patients are physically debilitated contributing to a higher risk of death and peri- and post-operative complications. In this regard special emphasis should be given to cardiopulmonary function. Malnourished patients should have supplemental feeding to improve nutritional status before surgery, including the use of nasogastric or percutaneous endoscopic gastrostomy feeding if oral supplementation is inadequate. In patients not deemed candidates for surgery because of a high risk profile, bronchoscopic removal of the aspergilloma should be considered (SoR B and QoE III) [136, 137].

Potential complications of aspergilloma resection include persistent air-leak, persistent pleural space, empyema, pneumonia, wound infection, bronchopleural fistula, respiratory failure, massive haemorrhage, and death [127, 138]. Risk of peri- or post-operative complications and mortality are significantly higher in patients with multi-cavity disease (CCPA) compared with simple aspergilloma [9, 127, 128]. The type of disease also affects the long-term outcome. In simple aspergilloma 10-year survival rates range between 69 and 90% while morbidity and mortality is higher in CCPA, where the 10-year survival rate is ~63–80% [125, 127, 129, 138].

With better surgical techniques, treatment outcomes have improved in recent years [130]. Procedures include bullectomy, segmentectomy, sublobar resection, wedge resection, lobectomy, pleurectomy, pneumonectomy. Video-assisted thoracic surgery (VATS) may reduce the number of complications and length of hospitalisation and has been suggested as an alternative procedure to open surgery for the resection of simple aspergilloma and multicavity disease without infiltration of the hilum (SoR B and QoE II) [129, 132]. Unexpected peri-operative issues may necessitate conversion to thoracotomy (bleeding, dense fibrous adhesions, fused interlobar fissure, or hilar lymphadenopathy) [132]. Some patients with extensive disease may require thoracoplasty with simultaneous cavernostomy and muscle transposition flap (SoR C and QoE III) [133, 134].

Antifungal therapy can be administered to prevent *Aspergillus* empyema or to avoid recurrence of disease when complete resection is not possible [125], but there is no evidence to support this role of adjuvant triazole antifungal therapy following definitive surgical removal of a single aspergilloma [139, 140], although a more nuanced approach is warranted in our view [125]. Simple aspergilloma that can be resected without spillage of fungal material probably does not require adjuvant antifungal therapy (SoR D and QoE II) [139, 140]. If spillage of fungal infection is anticipated because of the complexity of the surgical procedure, antifungal therapy can be administered in the weeks preceding surgery (SoR A and QoE III). Fungal cultures should be taken intra-operatively and part of the aspergilloma or cavity submitted for culture, especially if the patient has had prior antifungal therapy. In case of peri-operative spillage, the pleural space can be washed out with either amphotericin B deoxycholate or taurolidine (SoR B and QoE III) [125]. In such cases antifungal therapy is best continued in the post-operative period (SoR A and QoE III). Post-operative antifungal treatment may be usefully guided by: whether cultures taken peri- or post-operatively are positive or hyphae are seen in resected lung parenchyma (as opposed to the cavity); peri-operative difficulty in lesion removal with a risk of extension to contiguous lung segment(s) and/or pleura; and suboptimal surgery (residual lesions). No recommendation can be made about the duration of antifungal therapy in case of failure to completely resect the aspergilloma and should be individualised.

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.

Follow-up of *Aspergillus* nodule after resection surgery

Usually the diagnosis is made histologically after excision biopsy, sometimes by percutaneous or other biopsy with removal (table 12). If an *Aspergillus* nodule is single and completely excised, the patient does not require antifungal therapy (SoR B and QoE III), unless immunocompromised (SoR A and QoE III), which is common in rheumatoid arthritis for example. While quantitative *Aspergillus* IgG serology is attractive as a monitoring tool for *Aspergillus* nodule, no substantive data support its use. If a single nodule is not completely resected (i.e. diagnosed by percutaneous biopsy), close follow-up of the lesion is required both with quantitative *Aspergillus* IgG serology, inflammatory markers and radiology at 3-monthly intervals to determine if antifungal therapy required (SOR B and QoE III). In those with multiple nodules, when one is removed but others remain, antifungal therapy is advised (SOR B and QoE III) with the expectation that there will be a reduction in size of most or all nodules over time, and that an increase in size may represent another disease process, such as a malignancy. Close radiological follow-up (initially 3 monthly) is required to ensure there has been no progression. In all cases, corticosteroid exposure should be minimised.

Discussion

The realisation that patients with CPA may benefit from long-term antifungal therapy and conversely have a high 5-year mortality (75–80%), without any intervention, has driven the need for earlier and more precise diagnosis. The 1970s–1990s surgical resection or “medical management” (in reality–inaction) dichotomy of management has been replaced in the 2010s with multiple management choices, once the diagnosis has been made. For those patients unwilling or unable to undergo resection surgery, cure is elusive, and even those thought to be cured with surgery may relapse. Thus, the vast majority of patients with CPA require chronic disease management. In most, the primary dual aims of therapy are reduction of symptoms and prevention of progression. Occasional patients are both asymptomatic and do not progress even without therapy. At the other end of the spectrum are highly symptomatic patients, whose disease appears to progress despite high intensity antifungal therapy, sometimes with combined immunotherapy. Arresting progression, and in particular minimising loss of lung function, is a key goal of therapy, not always achieved; likewise weight gain, reduction in fatigability, reduced cough and sputum production, haemoptysis and breathlessness are all valuable benefits of long-term antifungal therapy, also not always achieved.

These detailed guidelines are the first to set out all the diagnostic, surgical and medical management and monitoring steps of clinical management of CPA. The guidelines are possible because of multiple publications from all over the world on different aspects of CPA. Some of the SoRs have been guided by authors with extensive clinical experience in the clinical management of CPA. No doubt further research and high quality publications, as well as new diagnostic and therapeutic tools, will refine these recommendations and in decades to come, what we propose today will seem archaic. However, what is clear is that clinicians struggle with many aspects of confirming a diagnosis of CPA and implementing successful therapeutic regimens.

CPA is a disease of the lungs and, as such, the vast majority of new cases come to light in respiratory clinics or hospital wards. The primary role of the respiratory physician and thoracic radiologist is to suspect CPA and then to initiate testing to establish the diagnosis, or an alternative diagnosis. The mycology (and/or immunology) laboratory plays a key role in assisting this diagnostic process. If surgery is the chosen therapeutic path, then several risk assessments are required to prevent pleural recurrence and ensure cure. If surgery is precluded or not selected, long-term antifungal therapy may be initiated and the long-term management should be entrusted to a physician experienced in antifungal therapy or team with the dual

TABLE 12 Follow up of *Aspergillus* nodules after resection surgery

Population	Intention	Intervention	SoR	QoE	Ref.	Comment
<i>Aspergillus</i> nodule not treated with antifungal therapy	To identify progression early and/or carcinoma of lung if multiple lesions	3–6 months clinical follow up with low dose imaging, inflammatory markers and <i>Aspergillus</i> IgG / precipitins	A	III	[125, 141]	Not necessary if entire single nodule resected
Post-lobectomy/pneumectomy	To detect recurrence early	3–6 month, then 6-monthly for 3 years with inflammatory markers and <i>Aspergillus</i> IgG/precipitins	A	III	[125]	No predictors of recurrence yet described; full re-evaluation if consistent increase in <i>Aspergillus</i> IgG titres

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

skills of antifungal prescribing and managing respiratory complications of the underlying pulmonary diseases. The characteristics of CPA, *i.e.* long-term antifungal therapy requiring therapeutic drug monitoring, toxicity and antifungal resistance monitoring, and determining antifungal failure, are naturally infectious diseases requiring expertise, but such physicians may not have the depth of experience required in the underlying pulmonary conditions such as COPD, sarcoidosis, severe asthma *etc.* Co-infections are a common problem in CPA and are sometimes highly complex, especially NTMs. Different units will address this duality of expertise required in different ways, but all will need high quality mycology laboratory support to monitor antifungal therapy and antifungal resistance. These realities of complex multiyear care for CPA are intrinsic to these guidelines, although not overt in terms of recommendations. As with many complex clinical conditions, experience and larger patient numbers will probably improve outcomes.

Very many patients with CPA live in low and middle income countries and develop CPA following pulmonary TB. Not all the recommendations of this guideline can be implemented in low and middle income countries because of a lack of capacity. We have not “down-graded” our recommendations because of this problem, but would rather encourage our colleagues practicing in these environments to adopt as far as is possible these guidelines and try and develop services using the best tools available. For example, surgical resection may be preferable to long-term antifungal therapy, even if the risk is higher.

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