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Diagnosis, Therapy and Prophylaxis of Fungal Diseases

Review article

Chronic pulmonary aspergillosis

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Summary

Chronic pulmonary aspergillosis (CPA) is a group of consuming diseases usually presenting with prolonged and relapsing cough, dyspnoea and weight loss. Acute symptoms such as haemoptysis and bronchial or pulmonary haemorrhage may occasionally occur. CPA affects patients with underlying pulmonary conditions, for example, chronic obstructive pulmonary disease or mycobacteriosis or common immunosuppressive conditions such as diabetes. Precise epidemiology is unknown, and while prevalence is considered low the chronic and relapsing nature of the disease challenges the treating physician. Diagnostics largely rely on serologic *Aspergillus* precipitins and findings on thoracic computed tomography. The latter are manifold comprising cavity formation, pleural involvement and sometimes aspergilloma. Other markers for aspergillosis are less helpful, in part due to the non- or semi-invasive nature of these forms of *Aspergillus* infection. Various antifungals were shown to be effective in CPA treatment. Azoles are the most frequently applied antifungals in the outpatient setting, but are now compromised by findings of *Aspergillus* resistance. Long-term prognosis is not fully elucidated and may be driven by the underlying morbidities. Prospective registry-type studies may be suitable to systematically broaden our CPA knowledge base. This article gives an overview of the available literature and proposes a clinical working algorithm for CPA management.

Key words: Chronic cavitary pulmonary aspergillosis, chronic necrotising pulmonary aspergillosis, chronic fibrosing pulmonary aspergillosis, complex aspergilloma, semi-invasive aspergillosis, subacute aspergillosis.

Introduction

Chronic pulmonary aspergillosis (CPA) ultimately a rather rare condition continues to be a research area of scarce evidence. Establishing the correct diagnosis as well as treatment strategies are challenging to the consulted physician.

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Here, we aim to give an overview of the current literature and evidence for diagnostic and treatment strategies. We also propose a possible algorithm for CPA follow-up and management.

Methods

We performed a PubMed literature research using the terms '(Chronic[All Fields] AND ('pulmonary aspergillosis'[MeSH Terms] OR ('pulmonary'[All Fields] AND 'aspergillosis'[All Fields]) OR 'pulmonary aspergillosis'[All Fields])) NOT invasive[All Fields] AND English [All Fields]' which yielded 549 results on 24 June 2013. Of these, 122 were chosen for further analysis. Appropriate additional evidence was quoted as encountered.

NB. A substantial portion of research articles has been published in Japanese exclusively. We accessed

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abstracts in these cases. Classification of CPA subgroups in Japanese was quoted to differ from the classification in English language. English references or online links to official Japanese guidelines could not be retrieved.

Epidemiology and pathogenesis

Epidemiology and estimated burden of disease

During recent years consensus has emerged that severity and cause of pulmonary aspergillosis are largely determined by the state of host immunity. Known forms of pulmonary aspergillosis to date comprise allergic bronchopulmonary aspergillosis (ABPA), invasive bronchial aspergillosis, CPA and invasive pulmonary aspergillosis (IPA). These forms are thought to represent a continuum of disease and thus a considerable disease overlap exists.[1–5] While neutropenia remains the major risk factor for acute invasive forms of aspergillosis (IA),[6] preexisting pulmonary disease, especially when causing impaired pulmonary clearance predisposes for CPA,[1,5,7] an entity in patients who present with only minor immunosuppression. Underlying pulmonary diseases frequently found in CPA patients are diverse and include history of tuberculosis,[8,9] active atypical mycobacterial infection,[10–13] chronic obstructive pulmonary disease (COPD),[13–15] asthma, cystic fibrosis (CF), ABPA (a condition complicating, e.g. asthma and CF[16]), prior pneumothorax, treated lung cancer,[7] sarcoidosis,[17] pneumoconiosis,[18–20] emphysema, preformed bullae, pneumonia and thoracic surgery.[5,7,21–23]

Minor immunosuppression in CPA occurs in the form of corticosteroid use, alcoholism, diabetes mellitus and immunosuppressive treatment.[5,7,24,25]

In some cases, symptoms of CPA lead to the diagnosis of the original underlying pulmonary or immunological impairment, exemplary cases have been described for idiopathic pulmonary fibrosis and ankylosing spondylitis.[26,27] As CPA often arises in preformed cavities, it can also complicate other conditions which cause lung injury such as cryptococcosis and radiation therapy respectively.[28,29] Furthermore, aspergilloma has been reported to be associated with chronic hypersensitivity pneumonitis.[30]

According to the predisposing conditions, most cases of CPA occur in middle-aged patients,[5,7] but young CF patients[31,32] as well as younger adults, e.g. with history of tuberculosis[9] may be affected, too.

The greater part of CPA is due to infection with *Aspergillus fumigatus,*[33] but occasional cases of CPA caused by *Aspergillus niger*[34] as well as *Aspergillus flavus*[17,35] occur.[5] Infections with rare *Aspergillus* spp. are an exception.[36]

Interestingly, recent travelling is not commonly found in patient history.[5]

Demographic figures on burden of disease can only be estimated. Some rough approximation exists for the 5-year period prevalence of CPA as a sequel to pulmonary tuberculosis (1.17 million patients), complication of ABPA (345 000 patients) and sarcoidosis (71 900 patients).[16,37,38] These estimates, however, may vary with a precision of one log and unfortunately there are no available data on CPA complicating COPD patients, supposedly one of the largest patient subgroups.[7,14]

Subgroups of chronic pulmonary aspergillosis

In 2003, Denning *et al.* [7] and Franquet *et al.* [39] proposed the following new nomenclature for different presentations of CPA, largely defined by distinct radiological and histological findings.

Simple aspergilloma is a well known and circumscript entity referring to a fungus ball that occurs in a preformed cavity (e.g. after tuberculosis or in emphysema).[39] Because in treatment and outcome it differs significantly from the other forms described below, different opinions exist as to whether it actually is a subgroup of CPA (similar risk factors, similar symptoms) or should rather be regarded as a separate presentation of pulmonary aspergillosis (Fig. 1).

Chronic cavitary pulmonary aspergillosis (CCPA, formerly known as complex or complicated aspergilloma), an entity characterised by new and expanding thick-walled cavities with or without a fungus ball, may be an important differential diagnosis that sometimes only becomes evident in the cause of time through relapse of symptoms and on follow-up radiography. Pleural involvement may occur but is due to preformed fistula or pneumothorax and not to tissue or angioinvasion. It was first described as a distinct entity and named CCPA by Denning *et al.* [7].

The overlap in disease entities is best illustrated by chronic necrotising pulmonary aspergillosis (CNPA Fig. 2), a syndrome characterised by expanding thin-walled cavities with tissue invasion, but not angioinvasion on histological examination.[39,40] This entity is also termed sub-acute invasive aspergillosis[3–5] and may resemble IPA appearance on computed tomography scans.[26] Differing from CCPA, pleural involvement can occur subsequently to tissue destruction.[41] It was first described as a distinct entity and named CNPA by

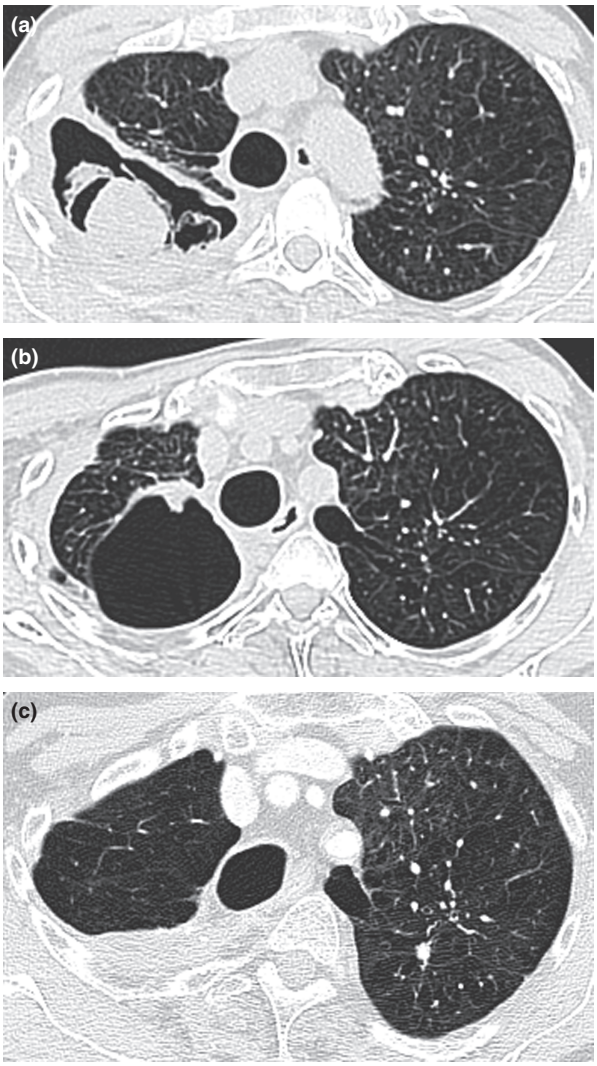

Figure 1 (a) Chest CT shows a fungus ball within a large thick-walled cavity in the right upper lobe. The aspergilloma had grown within that old cavity of former tuberculosis. Note severe emphysema of both upper lobes. (b) Chest CT reveals the empty cavity in the right upper lobe after surgical resection because of proven mobility of the aspergilloma. (c) Five years after resection, the empty cavity has diminished and a thickened dorsal pleura in the right upper lobe remains. At the time the patient complains about increased frequency of cough and expectorations, probably related to his underlying chronic obstructive pulmonary disease.

Binder *et al.* [5]. Chronic forms of aspergillosis were already described over 80 years ago.[42]

Over time, and especially under continued steroid treatment or in absence of antifungal therapy, fibrosis may complicate CCPA and maybe CNPA. Denning *et al.* [7] suggested to name this condition chronic fibrosing pulmonary aspergillosis (CFPA). To our knowledge, this term has not been widely adapted in literature.

Multiple 'simple aspergillomas' without thick walls or other typical features of CNPA or CCPA can occur, but are as yet a rare finding.[43]

When reviewing the literature it is important to remember that nomenclature change was only proposed in 2003, and that the entities above might overlap considerably. Hence, CPA terms used in available literature especially older publications might not comply with the criteria above. In fact, some older CNPA cases might be classified as CCPA with the diagnostic tools of today.[12]

Apart from this morphological definition, Al-shair *et al.* [44] recently proposed criteria for banding CPA according to clinical severity ranging from band 1 (outpatient and independent) to band 3 (wheelchair bound due to respiratory impairment and/or azole resistance and/or other). So far, however, this banding has only been used in assessing subjective well-being with standardised questionnaires. No data exist on its use in steering patient management.

Ways of *Aspergillus*–host interactions on a molecular level and predisposing immune defects

A great part of the literature currently available for this topic originates from various study centres in Japan[2,45–48] yielding the hypothesis that genetic predisposition may play a considerable role in the development of CPA. Evidence in this field is rare and sometimes contradictory.

Gliotoxins, encoded by multigene clusters, have been identified at the same time as part of the *Aspergillus* autoprotection system and as *Aspergillus* virulence factors for their toxicity towards mammalian cells. The single gene GliT is heavily involved in *Aspergillus* self-protection against exogenous gliotoxins.[49]

It has been shown in an experimental model that severity of host immune deficiency is mirrored directly by different grades of *Aspergillus* germination, tissue invasion and hence severity of infection. In a rabbit model, the main protective factor against tissue invasion was granulocyte activity.[6] Furthermore, myeloperoxidase and coenzyme nicotinamide adenine dinucleotide phosphate (NADP/H) were found to participate in early host defence against fungal pulmonary infection and their dysfunction rendered hosts more susceptible to fungal pulmonary infection.[50]

Possible alterations in the pro-inflammatory response against *Aspergillus* in CNPA which promote disease may be reduced CD40L and sCD40L as well as

increased IL-10.[51] Other evidence suggests genetically low production of IL-10 and TGF-beta1 to be associated with CPA predisposition.[52]

Some defects in innate immunity frequently found in CCPA have been characterised. A significant association between a toll-like receptor 4 allele variant and CCPA was reported.[53] A case series reported on an allele variant for mannose-binding lecithin (MBL) and surfactant protein 2 which was only present in CCPA patients.[54] Further data on MBL in CPA remain controversial: one study found elevated plasma levels to be associated with increased breathlessness,[55] whereas other studies suggested low levels to be associated with expression of CNPA.[56]

A report from 2008 describes a patient presenting with acute exacerbation of rheumatoid arthritis and underlying tuberculosis as well as CPA who was successfully treated with rituximab and had stable pulmonary conditions under voriconazole (VRCZ).[57] To date, little is known about B-cell immunity in CPA.

In one case CNPA has been observed as a late complication of AIDS when CD4 cells drop below 50 cells mm^{-3}.[8] To which extend CD4 lymphocytes interact with the common macrophage *Aspergillus* defence remains unclear.

Furthermore, interferon gamma production deficiency may be associated with sub-acute invasive aspergillosis.[58] Consequently, interferon gamma has been employed in some treatment strategies.

Diagnosis

As there are no specific markers for the broad entity CPA and even less for the CPA subgroups, diagnosis will always be drawn from a synopsis of typical predisposing characteristics, clinical findings (including clinical response to specific antifungal therapy) and further diagnostic data[59] – all the more as evidence for diagnostic efficacy from prospective randomised trials will necessarily be scarce.

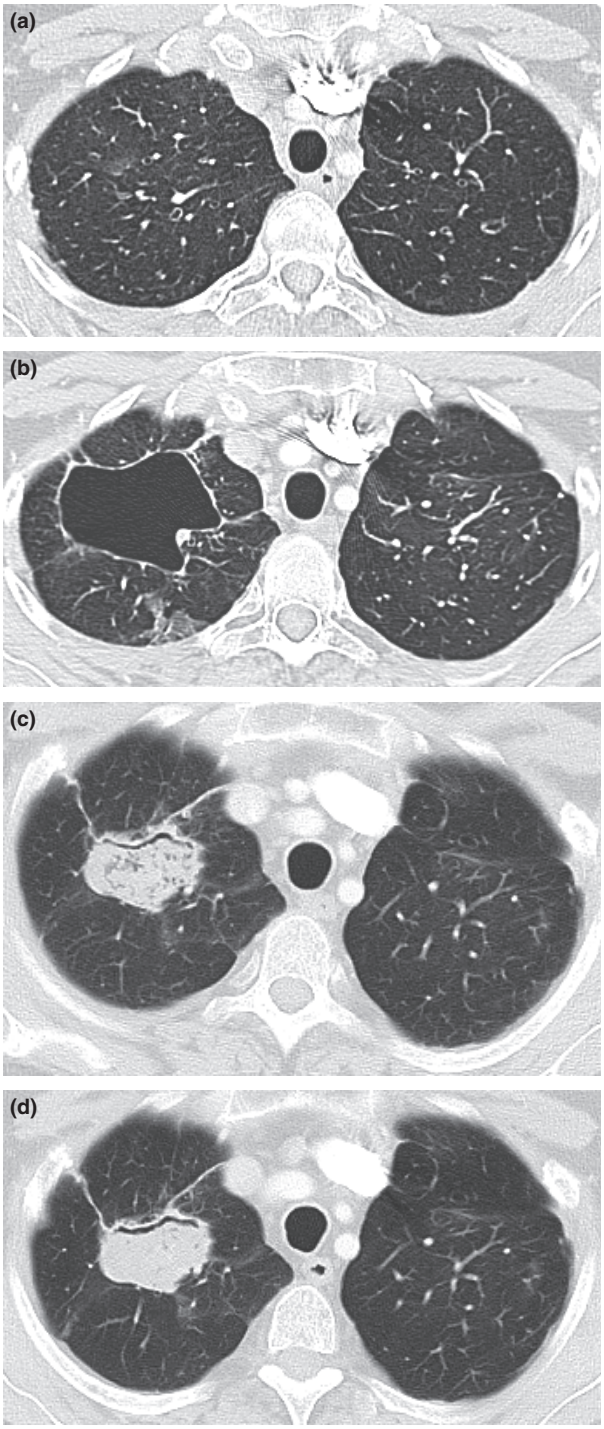

Figure 2 (a) Female 57a with allergic asthma and IDDM under steroid therapy. Histological diagnosis of CNPA was established 06/2010 after wedge resection left lung. Chest-CT at that time reveals an almost normal right upper lobe with slight ground glass opacification in the central part. Treatment with itraconazole. (b) Patient was switched from intraconazole to voriconazole after formation of triangular new infiltrates in the upper right lobe dorsal to a large thin-walled cavity in 05/2011, but went back onto intraconazole after severe hepatitis. (c) Formation of aspergilloma in the preformed cavity in 11/2012 under itraconazole 200 mg day^{-1}. Patient complains of relapsing pulmonary infections and occasional hemoptysis. (d) Stable radiologic findings under itraconazole 400 mg day^{-1} in 07/2013. Patient continues to experience pulmonary infections and occasional hemoptysis but feels overall improvement in general health. Treatment is continued with itraconazole 2 × 400 mg. Next regular follow-up CT planned after 6 months. Courtesy of *Radiologische Gemeinschaftspraxis am St. Josefs-Hospital,* Wiesbaden, Germany.

Excluding the presence of other pathogens is a basic requirement.[5] Due to the increasing reports of co-infection, atypical mycobacteria are exempt from this request.[10–13]

Clinical symptoms

Symptoms correspond to the chronic cause of the underlying disease. Most commonly reported are weight loss, chronic productive cough and shortness of breath, followed less frequently by chest pain, fatigue and fever. Acute clinical presentations with accompanying fever are more often due to CNPA.[5,7,17,44,60] Haemoptysis also frequently occurs and is a major contributor to CPA morbidity and mortality, especially in CNPA and aspergilloma.[17,61–63]

Definition of chronicity varies in literature. Early references propose 30 days,[5] lately three symptomatic months are used.[7]

Imaging studies

In the setting of typical symptoms and classical underlying host conditions as described above, a chest CT should be performed.

Chronic necrotising pulmonary aspergillosis is characterised by thin-walled cavities that expand over time (Fig. 2).[7,64] These cavities may or may not contain a fungus ball. Additional findings include parenchymal infiltration, abscess formation, pleural thickening and effusion,[5] sometimes bilateral[65] as well as the air-crescent sign.[5,66] In this sub-acute invasive form of aspergillosis, however, the air-crescent sign is probably merely a sign of necrosis development indicating worsening of disease. Note that this interpretation differs substantially from that of an air-crescent sign in neutropenic patients with IPA where it is thought to be a signal of neutrophil recovery.[67]

Classical findings of CCPA include formation of new, sometimes multiple thick-walled cavities over time with or without a fungus ball and infiltrates. Often pleural involvement can be observed.[7]

The distinction of simple aspergilloma can sometimes only be made in the course of time according to the evolvement of radiologic pathology. The fungus ball may be detached from the cavity wall and imitate an air-crescent sign.[29,39] Although rare, multiple aspergillomas can occur, therefore bilateral lung involvement on chest CT does not exclude aspergilloma.[39,43]

Additional signs of fibrosis characterise CFPA, a late stage complication of CCPA and CNPA.[1,7]

Antibody and antigen testing

Importantly, most patients with active CPA show elevated *Aspergillus* precipitins, i.e. antibody titres, and inflammatory markers.[7] Whereas early publications report 16/17 CNPA patients positive for *Aspergillus* precipitins, other data suggest that precipitins are more frequently found in aspergilloma (78%) than CNPA (14%).[59] Precipitins seem to correlate with the activity of disease, but may revert to negative in a few instances as serum levels vary in the cause of illness.[10] Hence, precipitin sensitivity might not permit detection of all CPA cases, but is still one of the most sensitive markers available.

Serum galactomannan assays are considerably less sensitive in CPA diagnostics than precipitins even when using the old cut-off index of $\geq$1.5 instead of $\geq$0.5.[68] Slightly higher sensitivity is achieved when testing for galactomannan in bronchoalveolar lavage (BAL) fluid of CPA patients.[69]

Elevated beta-D-glucan testing has not been extensively studied in CPA. Existing literature is largely published in Japanese language. It was found elevated in CPA, but to date is not considered a useful diagnostic tool due to low positivity rates.[68]

Serological findings may include elevated total IgE and elevated *Aspergillus*-specific IgE, but have been found in about 60–70% of patients only.[7]

Bronchoscopy including BAL should be pursued as well as direct optical airway assessment and biopsies of radiographic or bronchoscopic lesions even though the larger airways are uncommonly involved in CPA.[70]

Mycological evidence

Direct mycological evidence and culture should always be attempted, but are subject to numerous limitations. Finding *Aspergillus* spp. in BAL fluid can represent contamination due to ubiquitous *Aspergillus* conidia and should only be considered clinically significant in the setting of a clinical suspicion of aspergillosis.[59] Still, positive cultures are highly predictive of an underlying disease caused by *Aspergillus* and can be attempted from BAL fluid, sputum, biopsy or drainage fluid.[33] Isolation of *Aspergillus* cultures from urine has been reported in one case of advanced and lethal CNPA.[71]

Whenever feasible a biopsy of suspicious radiologic lesions should be performed as many fungal infections are missed by respiratory and serological sampling alone and information on the retrieved species and resistance pattern might be incomplete.[72] Histology of

CPA varies depending on underlying illness and may include inflammation, caseous material and fungal hyphae. Bronchocentric granulomatosis, a destructive, granulomatous lesion of the bronchi and bronchioles that is usually associated with asthma and ABPA, was described to occur in a case of CNPA.[40] Importantly, CNPA is the only subgroup in which tissue invasion occurs.[5,40] Its subacute nature is probably due to the lack of angioinvasion which is a typical pattern of invasive aspergillosis (Fig. 3) in the severely immunosuppressed. Aspergilloma and CCPA can present with hyphae and detritus within elements of the mycetoma, cavity walls, however, are not invaded by the fungus hyphae.[7]

Culture and PCR allow for more specific diagnosis, the latter being by far more sensitive with excellent specificity. But even between culture methods significant differences in performance exist, the diagnostic yield being highest from undiluted specimen as compared to standard procedures.[73,74] PCR offers highest sensitivity and significantly faster results. This will be especially important in infections with drug-resistant *Aspergillus* to allow for minimal delay of appropriate treatment. Spiess *et al.* [75] established a PCR assay that detects mutations which mediate azole resistance in the *A. fumigatus* cap51A gene directly from clinical samples.

Pitfalls: Some evidence exists that antibiotics reduce the diagnostic yield of *Aspergillus* findings in respiratory samples including PCR.[74] Secondly, it is important to consider that in aspergillomas, multiple isolates of *Aspergillus* may be found of which some, but not all may be azole resistant,[72,76] and that furthermore a fungus ball may be composed not only of *Aspergillus* but of different types of fungi.[77]

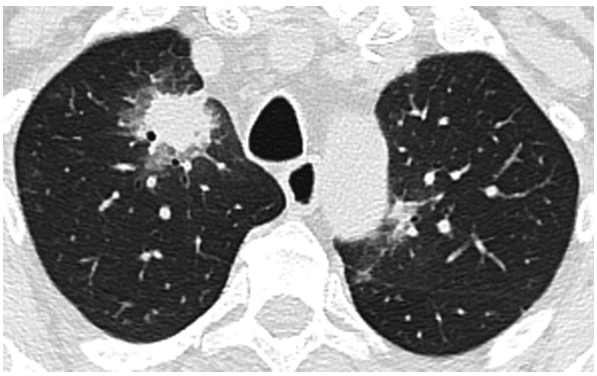

Figure 3 Bilateral invasive aspergillosis in the upper lobes can be seen on chest CT. The larger right-sided infiltrate with its spiculated nodule is surrounded by ground-glass opacity. This 'halo sign' represents fungal vessel invasion.

New diagnostic methods

Aspergillus-specific IgG antibodies can be detected either by counterimmunoelectrophoresis (CIE) or enzyme immune assays (EIA). The latter showed good sensitivity in a publication from 2012, but antibody titres detected did not correlate with CIE titres. Titre changes observed over 6 months in the CIE were mirrored in 92% and 72%, respectively, of the patients tested with the two commercially available EIAs. The EIAs furthermore differed in the inter-assay coefficient of variation.[78]

2-Pentylfuran, a metabolic by-product of *A. fumigatus*, can be detected in the breath of patients with *A. fumigatus* infection or colonisation with at least comparable sensitivity to culture. Since 2009, however, no new evidence in this field has been published.[79]

Diagnostic detection of other *Aspergillus* antigens than galactomannan is an area of constant research as much for CPA as for acute invasive aspergillosis. The latest publication from 2012 proposes a potential role for thioredoxin reductase GliT[a] in future *Aspergillus* diagnostics.[80]

To our knowledge, *Aspergillus* lateral flow device from BAL to date has only been tested in acute aspergillosis.[81–85]

Data of *Aspergillus* species identified via mass spectrometry instead of sequencing exist but this is yet far from clinical routine.[80,86]

Differential diagnosis

Other consuming illnesses such as tuberculosis, sarcoidosis or malignancy may mimic the cause and clinical presentation of CPA. Likewise, however, CPA and aspergilloma are important differential diagnoses in suspected malignant findings[47,87,88] and cases of suspected tuberculosis.[64] Often the physician is challenged with the presentation of several active diseases at the same time, for instance, in CPA complicating lung cancer[89] or atypical mycobacteria.[10–13] Case reports described actinomycosis mimicking CNPA,[90] and scedosporiosis mimicking aspergilloma.[91]

Treatment options and prognosis

As in most chronic diseases, the therapeutic approach to an individual patient may change considerably in the course of time. To our knowledge, no curative

[a]GliT = part of the gliotoxin gene cluster.

treatment approaches exist for CCPA, CNPA and CFPA.

Watch and wait

In stable subclinical disease watchful waiting may be indicated as much for simple aspergilloma as for CCPA and maybe CNPA.[2,7,92]

Surgery

Classically in patients eligible for surgery a simple aspergilloma is cured by resection of the cavity and the fungus ball[92] (Fig. 1). However, CCPA might mimic simple aspergilloma, so surgery should always be considered carefully and is not without risk. Spillage of *Aspergillus* to the pleural space complicating surgical procedures has been reported to occur frequently rendering perioperative antifungal treatment mandatory.[5,7,93] Removal of a simple aspergilloma by interventional bronchoscopy without surgery had favourable outcome in an elderly patient unfit for surgery.[94] In a retrospective series of 89 surgical patients who underwent bi-lobectomy, segmentectomy, pneumonectomy and cavernostomy for pleuropulmonary aspergilloma five postoperative deaths occurred in symptomatic patients but no major postoperative complications were found in the asymptomatic group.[95]

While satisfactory surgical outcome in CNPA has been reported after short-term follow-up,[5] the significant negative long-term impact of surgery in predamaged parenchyma needs to be considered as well.[7,17,93] In 2001, a report of 10 patients proposes aggressive pulmonary resection as an effective long-term palliation in critically ill patients with CNPA.[96] Another publication favours early surgery for a circumscript CNPA lesion with fistula and pleural involvement.[41] Other data, however, report major postoperative complications in 40% of surgically treated patients.[5] Bearing in mind that in CNPA surgery does not offer definite treatment it should only be performed in distinct clinical situations such as a late-stage palliative treatment option or intervention in complicated courses.

There are a number of CPA complications such as air-leakage, fistulas, superinfections and massive pulmonary haemoptysis[61–63,97] which might necessitate surgical interventions or bronchial arterial embolisation. A large number of cases with haemoptysis may actually be managed conservatively, although postural drainage is likely required. Some patients experience recurrent and life-threatening bleeding. Although embolisation is effective in the immediate control of bleeding, little is known about its long-term efficacy in CPA.[98] Partial lung resection in acute haemoptysis in CPA does not seem to offer additional benefit, e.g. effective prophylaxis of recurrence.[62] Again, as most cases of CPA follow a chronic course with deteriorating lung function, resection of functional lung parenchyma and reduction in vital capacity needs to be carefully weighed against.

Interventional treatment such as drainage is indicated for fluid-filled cavities and persistent pleural fluid or empyema.[5]

Antifungals

Various antifungals have been on trial for CPA since 1988, with oral azole treatment representing its mainstay. Intravenous echinocandins such as micafungin (MCFG) and caspofungin have been suggested to have fewer adverse effects than azoles[99] but their use is limited because of their intravenous application route.

Izumikawa *et al.* [2] have published an algorithm which reserves oral azole treatment for outpatients and suggests admission and intravenous echinocandins first line for 2–4 weeks for clinically more severely impaired patients. There is some published evidence that oral maintenance therapy with azoles after intravenous antifungals is of clinical benefit.[100]

Systemic antifungals have no primary role in the treatment of aspergilloma.[101,102] Currently, the Infectious Disease Society of America basically recommends systemic oral azoles for CCPA and CNPA, but no systemic therapy for aspergilloma.[102] Frequently itraconazole (ITCZ) is used first line. An increasing prevalence of resistance might necessitate changes in management.

Itraconazole was already successfully implied in a randomised trial for treatment of ABPA where it was shown to lead to clinical improvement without added toxicity.[103] Given at 200 mg per os $2\times$ day^{-1} it also yielded superior results when compared to supportive therapy alone in a small a randomised open-label trial for CCPA ($N = 31$).[104] In 1990, 13/14 CNPA patients of a mixed population (49 patients total with aspergilloma, CNPA and IPA) improved significantly (6) or were reported as cured (7) with ITCZ 200–400 mg $1\times$ day^{-1}.[105] In a non-comparative multicentre study of the efficacy and safety of ITCZ intravenous infusion (200 mg $2\times$ day^{-1} for 2 days, then $1\times$ day^{-1} for 3–12 days) followed by ITCZ capsules (200 mg $2\times$ day^{-1}), 9/17 patients showed radiological improvement, but 2/17 had to stop treatment because

of congestive heart failure.[106] There are some further isolated case reports on the successful treatment of CNPA and aspergilloma with ITCZ where full text is available in Japanese[106–108] or German[24] language. One case report from Japan presents an aspergilloma successfully treated with intracavitary ITCZ.[109]

A single publication reports the possible association of diffuse alveolar haemorrhage with systemic ITCZ treatment in a CPA patient.[110] Inhaled ITCZ is currently only used on an experimental level, yielding satisfactory tissue absorption in rats.[111]

Voriconazole. Efficacy and safety of oral VRCZ were last tested in an open-label non-comparative multicentre trial in France ($N = 41$) which showed a 32% global success rate with higher response rates in CNPA (53%) than CCPA (14%) and overall acceptable toxicity after a 12-month follow-up (no attributable deaths, discontinuation of therapy due to toxicity in seven patients) for a minimum of 6 months oral therapy with VRCZ 200 mg (100 mg for patients weighing <40 kg) twice daily, after a loading dose of double the maintenance dose on day 1.[60] Intravenous VRCZ 6 mg kg^{-1} twice on day 1 followed by 4 mg kg^{-1} twice daily compared to MCFG 150–300 mg once daily given for 2–4 weeks was effective in 53% of 47 Japanese patients in a prospective randomised multicentre open-label trial.[99] Similar efficacy was found in a retrospective analysis ($N = 24$) from France with a 58% response rate after a 6–10 months follow-up.[112] Another retrospective analysis ($N = 16$) resulted in response rates of 62% with VRCZ after ITCZ treatment failure, however, follow-up was only conducted for up to 3 months.[113]

In aspergilloma patients unfit for surgical treatment VRCZ might help relief symptoms.[114] One successful VRCZ treatment in a sepsis patient with co-infection of *Aspergillus* and *Staphylococcus epidermidis* has been reported.[115]

The most common adverse effects of VRCZ are visual and digestive disturbance and elevated liver enzymes. Plasma trough levels vary considerably regardless of oral or intravenous application of VRCZ. Adverse effects correlated with trough levels higher than 4 μg ml^{-1} and treatment failure with trough levels lower than 1.4 μg ml^{-1} or peak levels lower 2.8 μg ml^{-1}[1116] (full text in Japanese). Few case reports highlight reversible peripheral neuropathy after drug discontinuation in CPA patients. In these correlation of trough level and toxicity was not addressed.[117] A single case report from Japan raised the hypothesis that lung toxicity in a CNPA patient might have been caused by VRCZ.[118]

Posaconazole (PSCZ) is also effective in CPA patients with a 46% response rate at 12 months and acceptable toxicity (15%) but to date there is only a single and retrospective study available[14] limiting its current role to being an alternative treatment to VRCZ.

Amphotericin B (AMB) continues to play an important role especially in the light of currently emerging azole-resistant *Aspergillus* spp. Successful first-line therapy intravenously as well as – experimental – instillation into a cavity has been reported.[5,7,70] AMB has also been used in a multimodal treatment approach to irrigate pleural space after upper lobe resection for complicated CNPA in a patient with comorbidities.[97] Successful inhalational treatment in combination with other antifungals has been reported occasionally.[119,120]

Micafungin is an echinocandin antifungal whose safety and efficacy have been evaluated in two prospective trials in Japan.[99,121] Although efficacy rates were similar to those of VRCZ (60% vs. 68%) in both studies, respectively, treatment-emergent adverse events occurred less frequently with MCFG (26.4% vs. 15.8%). In the current available literature, one isolated case of acquired pure red cell aplasia in CPA may have been associated with MCFG.[48] MCFG may become even more important in future treatment efforts on azole-resistant *Aspergillus* spp.[122]

Caspofungin has been studied significantly less in CPA than MCFG. In a prospective randomised, double-blind study of a mixed Japanese patient population (candidiasis and aspergillosis) it yielded a favourable outcome in 46.7% of the CPA patients compared to 42.2% favourable CPA response with MCFG.[123] To date, it has no primary role in therapy of CPA. MCFG may be considered in severely ill patients as an alternative agent.

Supportive treatment

Supportive treatment largely relies on expert opinion and common experience.

Oral glucocorticoids may be useful in patients with deteriorated respiratory situation after starting antifungal therapy.[7,104] Special late stage cases might warrant oxygen and – in case of cachexia – optimised diet and food supplements.[7,104] Some patients might benefit from antitussives.[7,104] Interferon gamma s.c. is likely most beneficial for those patients with an interferon gamma production defect.[7,58] Argawal *et al.* [104] were able to show that antifungal treatment was clearly superior to supportive treatment alone.

Assessing treatment outcome

Clinical response to treatment is expected no sooner than after 12 weeks.[124] Usually efficacy assessment focuses on radiological response (complete or partial, unchanged, worsened) and clinical signs (improved, unchanged, worsened).[121] To our knowledge, correlation of these categories with outcome and prognosis to date has not been systematically studied over longer follow-up periods.

The St. George Respiratory Questionnaire in combination with the medical research council dyspnoea scale can be used to assess subjective well-being and health status.[44,125]

Apart from the overall clinical impression, CT criteria for disease remission focus on diminishing peri-cavitary infiltrates, stable or declining pleural thickening and thin-walled empty cavities stable in size.[7,44,60,99] To a certain extent, precipitins seem to reflect activity of disease as they may sink below detection limit in stable disease and have been reported to increase suddenly in disease reactivation.[7]

There are some important considerations that should always be made in the case of treatment failure.

Importantly and especially depending on underlying chronic pulmonary disease a co-infection with another pathogen should be excluded. Mycobacterial co-infection is not uncommon.[13] Unfortunately, concomitant tuberculosis treatment with rifampin and rifabutin induces azole metabolism. Rare cases of other pathogens might mimic the clinical pattern of CPA.[91]

Bacterial co-infection should be considered especially in the acutely ill patient[115] or upon fluid levels in a cavity.[126] When combining anti-infectives, drug–drug interactions are frequent (e.g. prolongation of QT interval for combinations of azoles, fluoroquinolones and macrolides.[127]).

Recurrence of haemoptysis may be a sign of treatment failure, but could also represent a persistent vascular network that cannot be expected to resolve through antifungal therapy alone.[98]

Change in antifungals might be required in case of resistant *Aspergillus* strains, which might occur (e.g. after long-term treatment with ITCZ).

Azole-resistant Aspergillus spp

Emerging azole-resistant *Aspergillus* spp. pose a serious threat to CPA treatment, as azoles are the sole currently available oral antifungals and thereby mainstay of CPA maintenance therapy.

Azole-resistant *Aspergillus* has been recovered from numerous patients.[72,76] Hypotheses differ as to whether this is mainly due to induction of resistance during sub-therapeutic drug levels or selection during prolonged azole exposure, especially after long-term exposure to ITCZ.[76,128,129] In general, resistant organisms may be of acquired agricultural origin.[130]

Some but not all strains with ITCZ resistance show cross-resistance to PSCZ and VRCZ or even pan-azole resistance.[76,128,129]

Outcome and prognosis

During the first year of follow-up, there is reasonable treatment success in about half of the CPA patients.[44,60,99] In the case series reporting long-term outcome mortality ranged from 37% to 67% after 10–18 years.[7,46,92] Older age, systemic comorbidities, corticosteroids, a body mass index of <18.5 kg m^{-2} and a C-reactive protein level of ≥ 5.0 mg dl^{-1} at baseline were risk factors for all-cause mortality.[46] Additional factors are acute or chronic co-infection and degree of pulmonary involvement and/or destruction.[61]

Despite effective disease containment, current antifungals appear unable to eradicate *Aspergillus* from the lung in CNPA.[131] Likely this is due to the underlying continuous chronic immune impairment of the affected host.

Even if no curative resection is attempted, the evolution in simple aspergilloma is often less dramatic with slow aggravation over decades. Spontaneous aspergilloma liquefaction with consequent development of wheezing and fibrosis have been described.[132] It remains difficult to interpret the succession of chronic allergic and chronic fungal pulmonary disease. One may ask: Is the case report of chronic hypersensitive pneumonitis (CHP) complicated by the finding of an aspergilloma or did the long-term *Aspergillus* exposure from the aspergilloma cause CHP[30]?

Degrees of haemoptysis vary. Several fatal cases due to haemoptysis in CNPA patients have been published.[17,61–63] More acute courses appear in the CNPA setting.[40] One case of acute respiratory distress syndrome has been reported, too.[133]

Approach to management

It seems obvious that according to the variable evolution of symptoms and disease progression, follow-up management will be guided by clinical presentation.

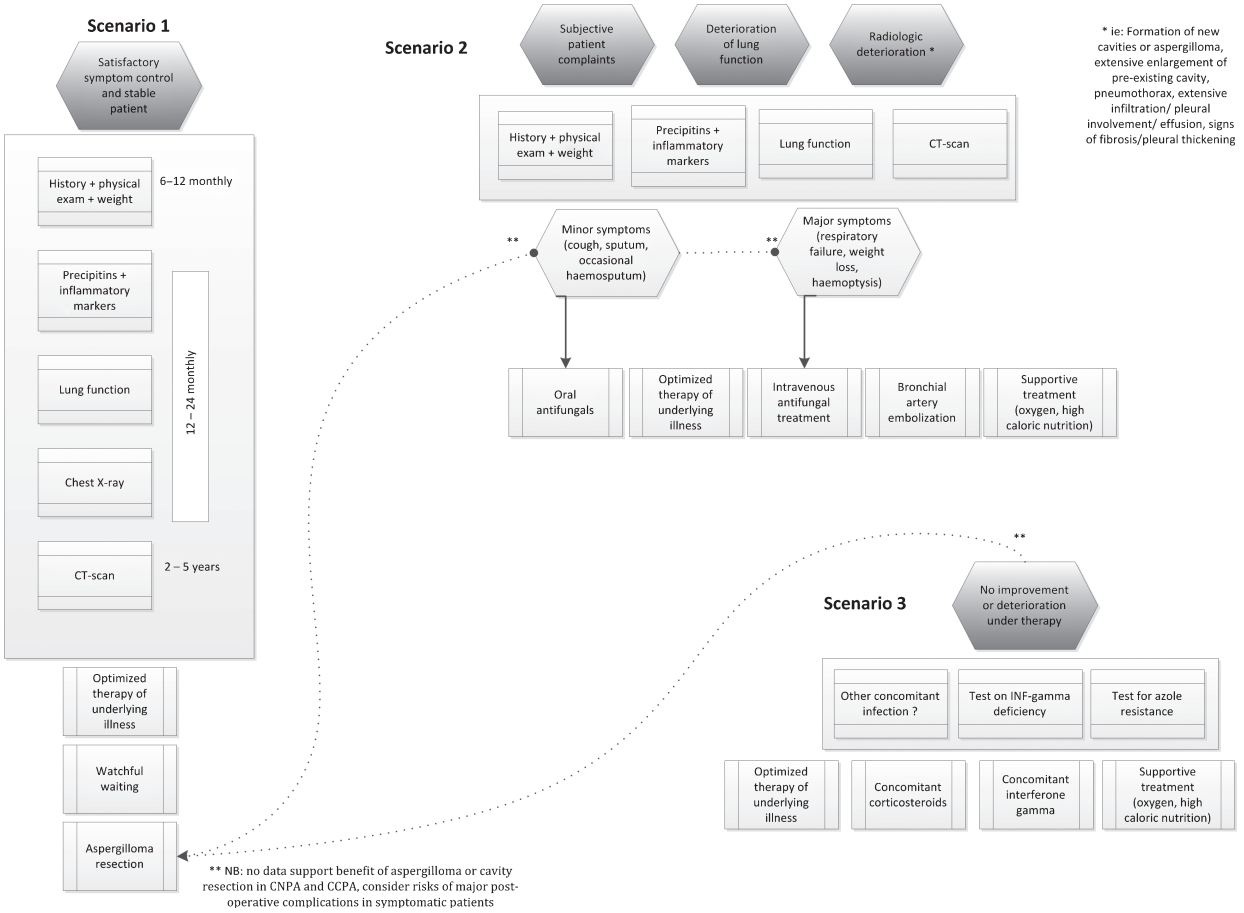

Figure 4 Proposed algorithm for chronic pulmonary aspergillosis (CPA) follow-up management.

Tools to assess the softer and more subjective data on clinical well-being and participation in daily living include the MRC dyspnoea scale (MRC scale) and the St. George's Respiratory Questionnaire. Both have been implemented in assessing health status in COPD patients and other chronic pulmonary diseases and yield reproducible and valid data in CPA patients as well.[125]

Apart from a medical history with special focus on common CPA symptoms and red flags such as haemoptysis, and weight loss, also precipitins and radiographic changes are follow-up tools. It has been proposed to repeat precipitin as well as inflammatory markers (C-reactive protein and erythrocyte sedimentation rate) every 3 months as it correlates with disease activity. X-rays are suggested every half year, followed by CT scan in the case of new clinical findings. Chest CT should be the technique of choice in a major change of clinical well-being. CT follow-up scans can be repeated yearly or less frequently in stable patients.[134]

There are no data or long-term evaluations on follow-up management. We aim at establishing a prospective cohort study to help filling this data gap during the years to come. In the meantime, we propose the algorithm in Fig. 4 for standardised follow-up management.

Conflicts of interest

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KES and KH have no conflicts of interest to declare. CB received lecture honoraria from Astellas and Merck/MSD.

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