Controversies in the clinical management of chronic pulmonary aspergillosis

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Shareable abstract (@ERSpublications)
Chronic pulmonary aspergillus infection has a range of clinical presentations. Clinical management options include observation, medical therapy, surgical therapy and minimally invasive procedures. https://bit.ly/4bVo3Iz

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Abstract

Chronic pulmonary aspergillosis has a range of manifestations from indolent nodules to semi-invasive infection. Patients may be asymptomatic or have chronic symptoms such as cough and weight loss or present with life-threatening haemoptysis. The physician can choose from a range of available therapies including medical therapy with antifungals, minimally invasive therapy with intracavitary antifungal therapy and surgery involving open thoracotomy or video-assisted thoracoscopic surgery. The patients with the most severe forms of pulmonary infection may not be surgical candidates due to their underlying pulmonary condition. The management of haemoptysis can include tranexamic acid, bronchial artery embolisation, antifungals or surgery. There are few controlled studies to inform clinicians managing complex cases, so a multidisciplinary approach may be helpful.

Clinical scenario 1

A 62-year-old man with a history of rheumatoid arthritis, receiving treatment with methotrexate, leflunomide and plaquenil was referred to the respiratory outpatient clinic for an assessment of a productive cough. He has a past history of pulmonary tuberculosis (TB) and completed directly observed treatment 3 years prior to the referral. He achieved clinical cure; however, he was left with a residual right upper lobe cavity at treatment completion (figure 1a). He underwent computed tomography (CT) chest which identified a new soft tissue density within the pre-existing right upper lobe cavity with a surrounding air crescent (figure 1b). Sputum examination was negative for acid-fast bacilli, TB PCR, TB cultures and fungal cultures. A provisional diagnosis of pulmonary aspergilloma was made. His symptoms were attributed to community-acquired pneumonia, and he was prescribed oral antibiotics. Given the response to treatment, no further management of pulmonary aspergilloma was initiated and he was discharged from the clinic.

What is the spectrum of disease caused by *Aspergillus* species?

Aspergillus species are saprophytic moulds ubiquitous in the environment [1]. In vulnerable hosts with immune compromise or underlying lung disease *Aspergillus* spp. can cause a spectrum of disease broadly categorised as allergic, invasive or chronic. Chronic pulmonary aspergillosis (CPA) can be further subdivided into nodules, aspergillomas, chronic cavitary aspergillosis, chronic fibrosing aspergillosis and subacute pulmonary aspergillosis although the distinctions between these categories can be unclear in clinical practice [1]. *Aspergillus fumigatus* is the most common species isolated in pulmonary aspergillosis; however, other *Aspergillus* spp. and other moulds including *Zygomycetes* and *Fusarium* spp. can also cause disease [1–3].

What are the diagnostic features of pulmonary aspergilloma?

Aspergilloma is a clinicopathological diagnosis requiring typical radiological features and microbiological or serological evidence of *Aspergillus* spp. involvement [4]. The typical appearance of pulmonary

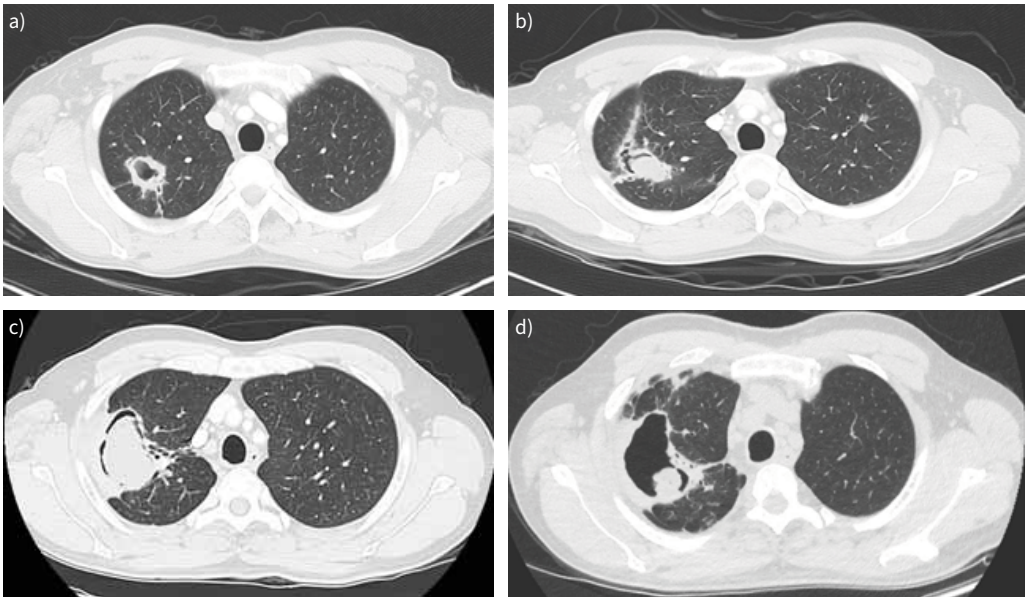

FIGURE 1 Computed tomography (CT) of the chest (clinical scenario 1). a) CT chest in 2014, showing the residual right upper lobe cavity following completion of tuberculosis treatment. b) CT chest in 2017, showing interval development of a soft tissue density within the pre-existing right upper lobe cavity. c) CT chest in 2021, showing interval enlargement of the right upper lobe cavity and soft tissue density. d) CT chest in 2023, showing a partial response with reduction in soft tissue density after 18 months of therapy with oral itraconazole.

aspergilloma on CT imaging consists of a mass within a lung cavity with an air crescent between the mass and cavity wall. CT chest is superior to chest radiography for diagnosis of aspergilloma due to its ability to discern other differentials including lung carcinoma, abscesses and hydatic cysts. CT imaging may also detect invasion into surrounding tissue and satellite lesions [5].

Detection of *Aspergillus* spp. on culture or PCR of sputum, bronchoalveolar lavage (BAL) fluid or lung tissue provides supporting microbiological evidence of pulmonary aspergillosis. However, due to the ubiquitous presence of *Aspergillus* spp. in the environment, clinical correlation is required to differentiate airway colonisation and infection [1, 3, 6]. Positive fungal cultures from deep respiratory specimens, including BAL fluid and tissue biopsies are more specific for *Aspergillus* spp. infection [6].

An elevated *Aspergillus*-specific IgG is diagnostic and is the most sensitive serological assay in pulmonary aspergillosis, it is positive in more than 90% of cases of CPA [2, 6, 7]. *Aspergillus*-specific IgG also differentiates infection from colonisation [6]. A prospective observational case–control study showed *A. fumigatus*-specific IgG had a sensitivity of 63.5% and specificity of 98.3% in simple aspergilloma compared with controls with underlying lung disease [8]. However, false negative results can occur in immunocompromised states or disease caused by another *Aspergillus* spp. [2, 7]. Galactomannan antigen, in both serum and BAL fluid, is recommended in the diagnosis of invasive aspergillosis, especially in immunocompromised patients [2, 6]. In CPA, galactomannan antigen in BAL is more sensitive than serum, 77% compared with 66%, respectively, and only provides supportive evidence of disease [6, 7].

How does an aspergilloma differ from other forms of CPA?

The least aggressive forms of *Aspergillus* infection are nodules without cavitation and simple aspergillomas. Chronic cavitary pulmonary aspergillosis (CCPA), previously known as complex aspergilloma, involves one or multiple cavities, with or without fungal balls, which enlarge to become symptomatic [6]. CCPA can progress to chronic fibrosing pulmonary aspergillosis (CFPA), which involves cavitation and fibrosis over multiple lobes, or subacute invasive aspergillosis, which can progress over weeks due to immune compromise [1, 6]. In contrast to nodules and simple aspergilloma, CCPA and CFPA are associated with symptoms such as productive cough, dyspnoea, chest pain and haemoptysis, and systemic symptoms including anorexia, malaise, sweats and weight loss [1, 6]. The diagnosis of CPA is made using a

combination of radiology and *Aspergillus*-specific IgG. Tissue biopsy with evidence of fungal hyphae on histopathology is the gold standard in the diagnosis of *Aspergillus* nodules and invasive aspergillosis [6, 7].

Clinical scenario 1 continued

3 years following discharge from the clinic, the patient had poorly controlled rheumatoid arthritis and an escalation of immunosuppression was being considered. He was re-referred to the respiratory outpatient clinic for assessment and clearance prior to escalation of his immunosuppression given his history of treated TB. Clinically, he had an occasional cough, which was productive of white phlegm. However, he was otherwise asymptomatic from a respiratory point of view. Given the presence of respiratory symptoms, a progress CT of the chest was obtained to ensure stability of the right upper lobe cavity. This demonstrated an enlargement of the right upper lobe cavity and soft tissue density (figure 1c). BAL cultures were obtained which confirmed growth of *Aspergillus* spp. Due to the radiological progression and the potential need to intensify immunosuppression, a decision was made to commence treatment for pulmonary aspergilloma with oral itraconazole at 100 mg twice daily.

What are the indications for treatment of pulmonary aspergilloma?

The Infectious Diseases Society of America (IDSA) recommends treatment for aspergilloma which becomes symptomatic or demonstrates radiological progression such as cavity enlargement, thickening of the cavity wall, development of surrounding lung opacification, and an increase in the number of lesions [3, 6, 9]. Haemoptysis is a potentially life-threatening complication of aspergilloma with a reported incidence of 28–90% annually and a mortality rate of 2–14% [10, 11]. Clinical features which correlate with an increased risk of haemoptysis include the size of the lung cavity and the diameter of the fungal ball [12]. In contrast, the IDSA recommends that asymptomatic patients with a single aspergilloma and no disease progression over 6–24 months should continue to be observed [2].

What are the treatment modalities for pulmonary aspergilloma?

Surgical resection

The IDSA recommends surgical resection of aspergillomas in symptomatic patients who are suitable candidates [2]. Surgical resection is associated with reduced haemoptysis risk, superior symptom control, improved overall survival and a lower risk of recurrence compared with conservative management [9, 13, 14]. However surgical resection requires adequate respiratory reserve and is associated with post-operative morbidity and mortality in 27–60% and 0.8–4% of cases, respectively [6, 10–12]. Given that aspergillomas more commonly occur in patients with underlying respiratory comorbidities, many patients will be unsuitable for surgery due to poor respiratory reserve and frailty [4].

The traditional approach to pulmonary resection in aspergilloma was *via* a posterolateral thoracotomy, as the inflammatory nature of the disease causes significant adhesions and therefore the risk of massive haemorrhage [15, 16]. However, video-assisted thoracoscopic surgery (VATS) approaches have been shown to be both safe and effective [15]. Thoracoscopic surgery is appropriate in simple aspergilloma without severe pleural adhesions or infiltration of the hilum when the underlying lung is minimally diseased [16].

Medical management

Medical management with antifungal treatment is indicated when surgery is not an option due to frailty, poor respiratory reserve or the number and location of the lesions [2]. Antifungal penetration to the site of infection is poor in chronic disease due to fibrotic tissue and reduced vascular supply, necessitating a prolonged duration of therapy [1, 17]. Relapse rates following cessation of therapy are high, with one study observing a relapse rate of 42% in CPA including aspergilloma [18]. Risk factors for relapse include bilateral disease and multiple aspergillomas [18]. Due to the high rates of relapse, many patients require long-term suppressive antifungal therapy [1, 6].

Which antifungal agents are effective for management of pulmonary aspergilloma?

Evidence relating to the effectiveness of antifungals in the management of pulmonary aspergilloma is limited to case series and unblinded trials. Due to small numbers, many studies pooled the results for aspergilloma and other forms of CPA which makes interpretation of the results more challenging. Options for antifungal therapies are summarised in table 1.

Triazoles

Triazoles, such as itraconazole, posaconazole and voriconazole, interrupt fungal membrane synthesis and are the main agents with activity against *Aspergillus* spp. [19]. Triazoles are considered first-line agents for management of chronic *Aspergillus* spp. infections due to demonstrated efficacy, oral route of

TABLE 1 Antifungal therapy for the management of aspergilloma

Agent	Treatment efficacy	Level of evidence	Common side-effects	Potential drug interactions
Triazoles				
Itraconazole [22–25]	Up to 60%	Case series and open label trials	Fluid retention, gastrointestinal (nausea and/or vomiting), hepatotoxicity and resistance profile	CYP3A4 and P-gP inhibitor
Posaconazole [27–30]	Up to 60%	Case studies and case series, pooled with other forms of CPA	Gastrointestinal side-effects (diarrhoea, nausea and/or vomiting), hepatotoxicity, hypokalaemia, pyrexia and QT prolongation	CYP3A4 and P-gP inhibitor
Voriconazole [31–37]	40–60%	Case studies and case series including aspergilloma pooled with other forms of CPA	Hepatotoxicity, photosensitivity, visual changes and hallucinations Association with skin malignancies with long-term use	CYP2C19, CYP2C9, CYP3A4 inhibitor
Echinocandins				
Micafungin and caspofungin [38–43]	Up to 50%	Open label trials	Local irritation at infusion site, infusion reactions and hepatotoxicity	Few drug–drug interactions
Polyenes				
Intravenous amphotericin [45, 46]	Up to 30%	Extrapolated from randomised control studies in CPA	Dose-dependent renal toxicity, infusion reactions and hepatotoxicity	Few direct drug interactions, but can lead to renal toxicity which impairs drug clearance

P-gP: P-glycoprotein; CPA: chronic pulmonary aspergillosis.

administration and comparatively tolerable side-effect profile [2]. The triazoles are cytochrome P450 and P-glycoprotein inhibitors, which leads to many drug interactions [20]. The optimal duration of therapy for triazoles is not established, however, a treatment period of at least 6 months is recommended [3].

Itraconazole is the most studied antifungal agent for management of aspergilloma [3]. The study populations and treatment regiments for these studies were heterogenous, however they have demonstrated response rates of up to 60% [21–24]. There is also evidence for itraconazole in the setting of invasive aspergillosis with trials demonstrating success rates of between 50 and 80% [22]. The most common side-effects arising from itraconazole use include fluid retention, nausea and/or vomiting, hepatotoxicity, and resistance profile [25].

Posaconazole is another ergosterol with activity against *Aspergillus* spp. Studies including pooled cohorts of chronic aspergillosis and aspergilloma demonstrated success rates of up to 60% with posaconazole therapy [26]. Larger studies in patients with invasive aspergillosis have demonstrated response rates of 42–45% and non-inferiority to voriconazole [27, 28]. The most common side-effects reported with use of posaconazole include diarrhoea, nausea, vomiting, hypokalaemia, pyrexia, liver function derangement and QT prolongation [29].

Voriconazole has demonstrated efficacy in management of CPA including aspergilloma with response rates of 40–58% [21, 30–34]. Voriconazole is also effective in managing invasive aspergillosis and was superior to amphotericin in a randomised control trial [35]. The potential acute side-effects include hepatotoxicity, photosensitivity, visual changes and hallucinations [36]. Although the mechanism is unclear, long-term use of voriconazole has been associated with development of skin malignancies which is an important consideration in immunocompromised patients [37].

Isavuconazole is a newer antifungal agent with broad anti-mould activity [2]. It has been shown to have fewer drug interactions and adverse effects compared with voriconazole when used in invasive aspergillosis and CPA [17]. However, issues with cost, lack of evidence around efficacy and therapeutic drug monitoring (TDM) limits its clinical utility at this stage [2, 17].

Echinocandins

The echinocandins are β-(1,3)-D-glucan synthase inhibitors which interfere with fungal cell wall synthesis and are currently considered salvage therapy for *Aspergillus* species infections [38]. The most common agents currently used for management of aspergillosis are caspofungin and micafungin with response rates of up to 50% [39, 40]. Larger studies have also found that caspofungin and micafungin are effective for

management of invasive aspergillosis with response rates of 45% and 72%, respectively [41, 42]. Echinocandins are well tolerated with the most common side-effects being local irritation, infusion reactions and hepatotoxicity. The main limiting factor for long-term use is the requirement for intravenous administration due to poor oral absorption [43].

Polyenes

Amphotericin is a polyene antifungal which acts through precipitating cell death through pore formation in the fungal cell wall [44]. The use of amphotericin in the management of *Aspergillus* spp. infections is limited by dose-dependent renal toxicity and the side-effect profile [45, 46]. Voriconazole is better tolerated and has also demonstrated non-inferiority in management of *Aspergillus* infections in a randomised control study [35]. Due to its poor side-effect profile compared with other agents, amphotericin is currently considered salvage therapy for *Aspergillus* spp. infections [2].

Intracavitary management

Percutaneous instillation of antifungal therapy *via* a catheter inserted into the cavity under CT guidance is another option for patients with inoperable aspergilloma [3, 47]. Published case series report control of haemoptysis in 85–100% of cases and radiological improvement in 50–73% of cases. One published protocol required repeated procedures with percutaneous instillation of amphotericin at 1–3-week intervals with a mean treatment course of 2.7 injections per patient. Reported complications of the percutaneous approach included cough (65%), pneumothorax (26%) and transient renal dysfunction (22%) [47]. Intracavitary antifungal therapy can also be delivered endobronchially or transbronchially *via* bronchoscopy [3, 6].

Clinical scenario 1 continued

The patient tolerated itraconazole well over 2 years with no perceived side-effects. Serial imaging demonstrated a reduction in cavity wall thickness and size of the soft tissue density (figure 1d). However, complete resolution was not achieved. The cardiothoracic surgery service was consulted regarding possible resection, but surgery was not advised given the response to itraconazole. The patient remains on long-term itraconazole with clinical and radiological surveillance given the ongoing need for immunosuppression for rheumatoid arthritis.

How long should antifungal treatment be used in patients with aspergilloma?

The optimal duration of antifungal treatment for pulmonary aspergilloma has not been defined. European guidelines on the management of CCPA recommend at least 4–6 months of treatment followed by reassessment [6]. Those with minimal response at this time point can consider extending the duration of therapy to 9 months or switching to another antifungal agent [6]. Patients that respond often require long-term antifungal therapy since studies have reported relapse rates of up 53% following cessation of therapy [48]. Given the high relapse rate, patients that discontinue antifungal therapy require radiological surveillance.

Is there a role for TDM or susceptibility testing in the management of pulmonary aspergilloma?

Therapeutic drug monitoring

TDM is recommended for itraconazole, voriconazole and posaconazole due to the variable, non-linear pharmacokinetics of triazoles, especially due to the high number of drug interactions [2]. Clinical failure with breakthrough infection is seen in suboptimal drug exposure and supratherapeutic drug levels can be associated with toxicity [2]. TDM allows tailored dosage recommendations based on an individual's serum drug concentration [49]. Trough levels are used as a surrogate marker for area under the concentration–time curve/minimum inhibitory concentration (AUC/MIC) ratios which have been shown to predict treatment outcomes in rat models [50].

The IDSA recommends initial TDM monitoring once a steady state is achieved, 4–7 days after initiation of antifungal therapy, with ongoing TDM monitoring to assess for drug toxicity and patient compliance [2, 50]. Duration of TDM monitoring depends on clinical progress and duration of therapy [2]. For TDM to have clinical utility, there must be established therapeutic ranges to guide dosing and a sensitive drug level assay available with a short turn-around time [2]. At this stage, more evidence is required prior to TDM for isavuconazole [2]. It is also not recommended for echinocandins or amphotericin [17].

Susceptibility testing

Antifungal susceptibility testing of fungal isolates is performed at mycology reference laboratories using EUCAST (European Committee on Antimicrobial Susceptibility Testing) clinical breakpoints or CLSI (Clinical and Laboratory Standards Institute) epidemiological cut-offs [2]. Antifungal susceptibility testing is not routinely performed on *Aspergillus* isolates in initial infection [2]. However, it is recommended in

suspected antifungal resistance due to treatment failure with clinical or radiological progression once patient compliance and subtherapeutic antifungal levels are excluded [2, 6]. Similarly, antifungal susceptibility testing should be performed if cultures remain positive while on triazole therapy [6]. Resistance to azoles had been reported in up to 30% of isolates in Europe, with emerging triazole resistance [17].

Clinical scenario 2

A 57-year-old female presents for investigation of recurrent episodes of pleurisy and reduced exercise tolerance. She reports modified Medical Research Council (mMRC) grade 1 dyspnoea, walking slower on the flat and breathless when climbing two flights of stairs. She denies cough, haemoptysis, or weight loss. She is an ex-smoker with 30 pack-year history and has continued to smoke marijuana for the past 35 years. Her other comorbidities include treated Hepatitis C and opioid dependence, she is on methadone as opioid replacement therapy. On examination her weight is 64.7 kg and her height is 161 cm. Her breath sounds are vesicular, and her oxygen saturation is 97% on ambient air. There is no lymphadenopathy, and she appears euvolaemic. Baseline post-bronchodilator spirometry demonstrated moderately severe airflow obstruction (forced expiratory volume in 1 s of 1.3 L (55% predicted); forced vital capacity of 1.9 L (64% predicted)) without bronchodilator reversibility, mild pulmonary restriction (total lung capacity 1.78 L (71% predicted)) and moderately reduced diffusing capacity of the lungs for carbon monoxide corrected for haemoglobin (63% predicted). An initial CT chest demonstrated biapical sub-pleural fibrosis.

She commenced daily inhaled tiotropium for COPD, with some benefit. However, she experienced a dry mouth and constipation in combination with methadone. Within 18 months, the patient reported an episode of low-volume haemoptysis, <50 mL haemoptysis in 24 h, that resolved spontaneously, and 15 kg weight loss. Over this period there was significant change in her CT chest imaging: progressive biapical sub-pleural fibrosis with increasing cavitation and nodular thickening particularly at the left apex (figure 2). There was associated progressive traction bronchiectasis and peribronchial thickening in addition to mild centrilobular emphysematous changes. Further investigation was delayed due to patient preference. Over the next 2 years the patient developed a productive cough and had a further three episodes of low-volume haemoptysis, treated with courses of oral antibiotics. She stopped smoking marijuana. Serial CT chest over this time demonstrated further progression with a new thick-walled cavity in the left lung apex, containing some debris. Sputum samples demonstrated negative microbiology on standard culture, fungal and acid-fast bacilli analysis. Blood tests show elevated IgE (1107 $kU{\cdot}L^{-1}$) and *Aspergillus*-specific IgE and IgGs. Other investigations including antinuclear antibody, antineutrophil cytoplasmic antibody, extractable nuclear antigen, immunoglobulins, double stranded DNA, C3/C4, HIV serology were unremarkable. BAL detected *Aspergillus* DNA and positive *Aspergillus* galactomannan. TB-PCR, acid-fast bacilli and standard culture were negative. A diagnosis of CCPA was made and the patient was commenced on oral voriconazole, after she was transitioned from methadone to buprenorphine/naloxone to reduce the potential for drug interactions with antifungal therapy. A voriconazole dose of 100 mg twice a day achieved a therapeutic voriconazole level in this patient.

Over 12 months of voriconazole therapy her cough improved, and she had a weight gain of 6 kg. However, there continued to be radiological progression of CCPA and eventual recurrence of frequent low-volume haemoptysis (figure 3a). Antifungal therapy was ceased after 18 months, and serial CT chest demonstrated an enlarging left upper lobe cavity. She then experienced large volume haemoptysis of >150mL in 24 h requiring radiologically guided embolisation of blood vessels to the left upper lobe.

At the time of the large volume haemoptysis surgical resection of the aspergilloma was considered. It was felt that surgical excision would present a substantial risk of prolonged air leak and other postoperative complications, given the extensive multilobar bronchiectasis, poor nutritional status and underlying emphysema. The patient declined surgery and was managed with long-term voriconazole and regular sputum clearance techniques. Episodes of haemoptysis were managed with short courses of tranexamic acid and oral antibiotics. A decade after her initial presentation, she continues to report a reasonable exercise tolerance with mMRC grade 2 dyspnoea, stable weight and has avoided repeat bronchial artery embolisation.

How can haemoptysis be managed in CPA?

Haemoptysis is a common complication of CPA and may manifest as mild, moderate, or life-threatening bleeding. Management of haemoptysis in CPA is patient specific, varies based on bleeding volume and frequency, and can include medical, surgical and interventional radiology strategies.

Medical management of haemoptysis in CPA includes the off-label use of oral, nebulised or *i.v.* tranexamic acid and oral antifungal therapy. Control of CPA disease activity with antifungal therapy may decrease the risk of haemoptysis, and long-term antifungal therapy is a useful adjunct to prevent recurrent bleeding [6, 51]. In the acute setting, medical therapy is commonly used to treat non-massive haemoptysis and in some cases as a bridge to definitive management of massive haemoptysis [6, 49]. Tranexamic acid inhibits fibrinolysis, thus interfering with clot breakdown and oral or *i.v.* tranexamic acid significantly reduces haemoptysis bleeding time and volume [52, 53]. The duration of tranexamic use is balanced against a low risk of seizure and the risk of venous thrombosis, although this is not well studied in haemoptysis cohorts [53]. There is limited randomised control trial evidence suggesting that nebulised

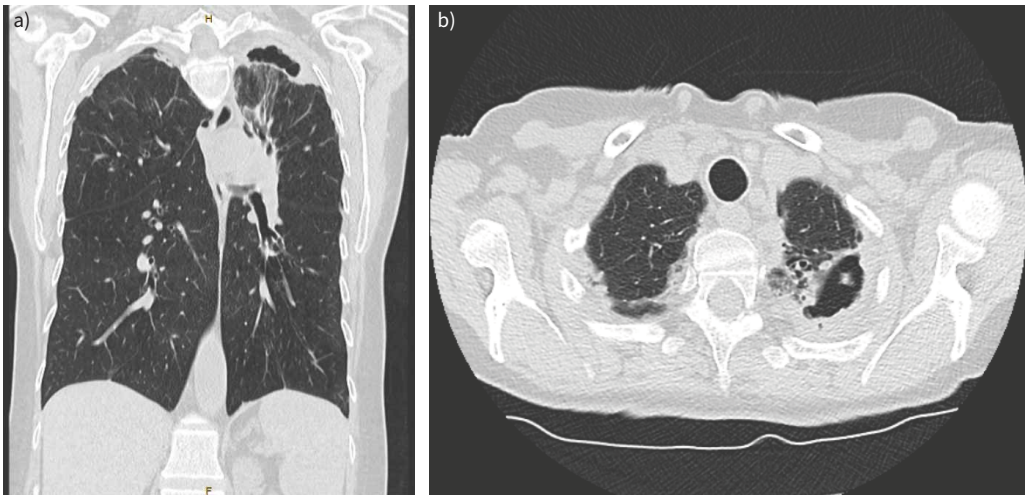

FIGURE 2 Computed tomography (CT) of the chest in 2014 (clinical scenario 2). a) The coronal view reveals a thick-walled cavity at the left apex, left upper lobe fibrosis and retraction. b) The axial view reveals debris in the left apical cavity, with adjacent peribronchial thickening.

tranexamic acid can also be safely and effectively used to manage non-massive haemoptysis with few side-effects [54].

Instillation of antifungal agents directly into the local CPA cavity can be considered if surgical resection is not a treatment option for recurrent haemoptysis; however, evidence of effectiveness is limited to case series [4, 48].

Surgery is considered the primary choice for management of massive or recurrent haemoptysis, and in many cases can be curative. The source of bleeding in CPA is usually an abnormal vascular complex adjacent to the affected area, derived from the systemic circulation and commonly continuous with the bronchial circulation [55]. Surgical resection is more likely to achieve long-term management of haemoptysis than either medical or interventional radiological approaches [6]. However, patients with CPA are often comorbid with pre-existing lung disease and are more likely to develop complications such as respiratory insufficiency [56]. The need for pre-operative optimisation and planning for major thoracic surgery may delay definitive treatment.

Radiologically guided interventional procedures such as bronchial artery embolisation (BAE) may be rapidly accessed in tertiary centres, providing either definitive haemostasis or a temporising measure in the emergency setting. In retrospective cohort studies of haemoptysis in CPA, BAE provided excellent short-term

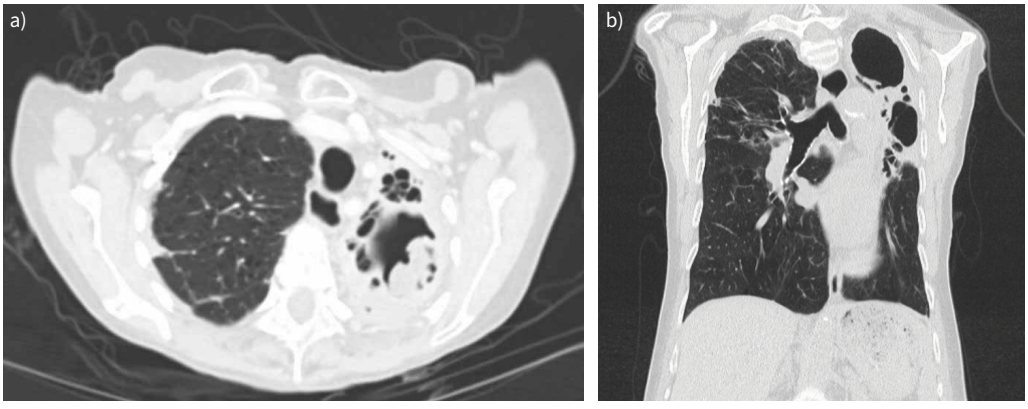

FIGURE 3 a) Computed tomography (CT) of the chest in 2020, the axial view shows progressive destruction of lung in the left apex with a fungus ball in a large cavity. b) CT of the chest in 2023, the coronal view shows progressive destruction of the left upper lobe, pleural thickening and bronchiectasis.

management of haemoptysis at 1 month; however, within 2 years, half of patients re-bled [40, 55]. This risk of re-bleeding is higher when the underlying CPA disease is uncontrolled and is more likely in CCPA than simple aspergilloma. BAE is a difficult procedure requiring a skilled proceduralist and can be complicated by stroke, spinal cord or chest wall infarction, and chest wall pain, as well as contrast-related allergy or renal toxicity. It is often a difficult clinical decision whether to offer surgical management or pursue BAE and medical management, and a multidisciplinary approach is recommended [6].

What are the indications for surgery in the management of CPA?

In pulmonary aspergillosis surgical management is aimed at eradicating the mycetoma, the underlying cavity and any diseased parenchyma to control symptoms, prevent recurrent haemoptysis, and potentially prolong life [13, 14, 57]. The success of these interventions is dependent on the ability to completely resect the affected tissue without spillage of infected material into the pleural space [6]. Current European Respiratory Society (ERS) guidelines suggest surgical management should be considered in all patients with pulmonary aspergillosis who are symptomatic with severe haemoptysis and have adequate lung function [6]. This is especially true in cases of simple aspergilloma [14], as CCPA presents a clinical challenge due to the need for more complex surgery and often worse underlying lung disease [15]. Assessing adequacy of lung function for surgery is complex and requires a multidisciplinary approach. It incorporates not just formal lung function testing, but also considers a patient's underlying lung disease, comorbidities and frailty [6]. Patient selection is contingent on maintaining the balance between the risks associated with the disease and the risk of surgery [13].

Historical literature examining the outcomes of surgical management of aspergillosis suggested high morbidity and mortality rates (up to 60% and 43%, respectively) [13]. As surgical techniques have progressed over the past few decades recent studies have shown surgical resection, most commonly lobectomy, to be not only safe, but an effective treatment option [13, 16]. From the 2000s onwards, morbidity and mortality rates have improved to 22.5% and 0–4%, respectively [13, 15], and modern series show good efficacy and safety profiles in appropriately selected patients with technically well executed procedures [13, 57–59]. Outcomes post-surgery were shown to be equivalent or better in asymptomatic patients, suggesting that operating earlier, when the disease process and underlying disease may be less severe, may improve patient outcomes [14, 57, 60].

Like all pulmonary resections, the optimal extent of surgical resection depends on maintaining a balance between effective removal of diseased tissue, with a risk of recurrence if it is incompletely removed, and minimising excessive tissue removal for preservation of pulmonary function. Anatomical resections are considered the gold standard of care, to allow full clearance of the lobe and reduce recurrence with additional wedge resections of adjacent lobes if the lesion bridges the fissure [15]. Lobectomy is the most common procedure for aspergilloma and CCPA reported in the literature. More extensive resections, such as bilobectomy or pneumonectomy, may be considered in multiple or extensive lesions where the lung parenchyma has been severely damaged, or if the remaining lobe is small and fibrotic [10, 13, 58]. The morbidity and mortality of these procedures is not as well established as standard lobectomy, with conflicting reports in the literature as to its outcomes [13, 61]. Sub-lobectomy, or wedge resection, may be considered in small, peripheral lesions where the underlying lung tissue is healthy. Sub-lobar resections may preserve lung function, and are associated with improved post-operative patient function, hastened recovery and have fewer overall complications. Sub-lobar resections are ineffective for large central lesions and may have a higher risk of air leak and recurrence post-operatively [10].

Other procedures described for patients with poor respiratory reserve, who are unable to tolerate anatomical resection, include wedge resection of bullae, cavernostomy or cavernoplasty, apicolysis with myoplasty or thoracoplasty, or transplant in the case of end-stage chronic lung disease [10, 15, 58].

How effective is surgical management of CPA?

Complete surgical resection of infected tissue is effective in reducing or eradicating symptoms of aspergillosis, which may be life-threatening and unpredictable, and delivers a satisfactory long-term prognosis with a likelihood of permanent cure [10, 13, 58, 60]. Symptoms such as cough, haemoptysis and dyspnoea have all been shown to improve with surgical intervention, therefore increasing quality of life [14]. Long-term survival is considered acceptable, with 5-year and 10-year survival rates reported as 85–93% and 92%, respectively. Patients undergoing surgery demonstrate better overall long-term survival than those managed medically alone. Complications predominantly depend on the condition of the underlying lung [13, 14, 61].

Published recurrence rates of aspergillosis post-operatively are highly variable: 0.6–57% [10, 14, 58, 61]. This may be due to differences in patient selection, the extent of disease ranging from simple aspergillomas

to CCPA, the extent of resection, and improvements in both surgical technique and antifungal therapy. The risk of recurrence is higher in the early post-operative period (33% in the first 3 years) compared with late recurrence (8% in 3–10 years), higher in patients receiving immunosuppression and lower in patients who receive antifungal therapy prior to resection [14].

Role for peri-operative antifungal therapy

The current ERS guidelines do not recommend adjuvant antifungal therapy for simple aspergillomas, but it may be considered prior to complex surgery, or in the event of inadequate resection or fungal spillage intra-operatively [6]. Similarly, the IDSA recommend that peri-/post-operative antifungal therapy is not routinely required, but if the risk of surgical spillage of the aspergilloma is moderate (related to the location and morphology of the cavity) antifungal therapy with voriconazole (or another mould-active azole) or an echinocandin is suggested to prevent *Aspergillus* empyema [2]. Post-operative antifungal treatment should be guided by positive intra-operative cultures, the presence of hyphae in resected tissue, or the risk of extension of disease to other areas of parenchyma. In addition to this, antifungals may be directly administered to the pleural space or cavitary lesion [6].

Studies suggest that patients who receive antifungal therapy at any point prior to, or in combination with, surgery have longer disease-free survival than those without pre-operative antifungals, however this benefit is not seen if antifungals are administered only after surgery [14, 61]. Establishing the diagnosis of aspergillosis prior to surgery, and instituting appropriate antifungal therapy early, may be key to reducing the risk of relapse after surgical management.

What are the controversies in patient selection for surgery?

CPA occurs in immunocompetent patients whose lungs are vulnerable to fungal infection due to underlying chronic pulmonary disease. Predisposing factors for simple aspergilloma and CPA include TB, non-TB mycobacterial lung disease, bronchiectasis, emphysema, sarcoidosis, lung abscess and lung cancer [56]. This cohort is at higher risk of morbidity and mortality associated with thoracic surgery. Selecting patients with CPA who will benefit from surgery is a balance between fungal disease activity and risk of haemoptysis, and the risk of surgical complications and adequacy of respiratory reserve. In a retrospective study of pulmonary aspergillosis patients selected for surgical resection, there was no peri-operative or 1 month mortality reported; however, complications were frequently observed. Morbidity included prolonged air-leak (23%), empyema (20%), respiratory failure requiring tracheostomy or reintubation (13%) and was more common in CCPA patients [9]. While surgery remains the mainstay of treatment for simple aspergilloma, conferring a high chance of cure and acceptable morbidity, the outcomes for CCPA are less conclusive and surgery is usually performed to manage massive haemoptysis (table 2).

Conclusion

CPA has a range of manifestations including aspergillomas and CCPA. Patients may be asymptomatic or have chronic symptoms, such as cough and weight loss, or present with life-threatening haemoptysis. The physician can choose from a range of available therapies including medical therapy with antifungals, minimally invasive therapy with intracavitary antifungal therapy and surgery involving open thoracotomy or VATS. The patients with the most severe forms of pulmonary infection may not be surgical candidates due to their underlying pulmonary condition. The management of haemoptysis can include tranexamic

TABLE 2 Summary of treatment options for chronic pulmonary aspergillosis (CPA)

Condition	Treatment options
Aspergilloma	Observation Surgical resection Antifungal therapy Intracavitary antifungal therapy
CCPA/CFPA	Antifungal therapy Surgical resection Peri-operative antifungal therapy
Haemoptysis secondary to CPA	Oral/nebulised/*i.v.* tranexamic acid Antifungal therapy Surgery Bronchial artery embolisation

CCPA: chronic cavitary pulmonary aspergillosis; CFPA: to chronic fibrosing pulmonary aspergillosis.

acid, BAE, antifungals or surgery. There are few controlled studies to inform clinicians managing complex cases, so a multidisciplinary approach may be helpful.

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