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Carter, Charlotte; Kahai, Rasleen; Cunningham, Josie; Kilduff, Jennifer; Hough, Natasha; Baxter, Caroline

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Chronic pulmonary aspergillosis – a guide for the general physician

Charlotte Carter[a,*], Rasleen Kahai[b], Josie Cunningham[c], Jennifer Kilduff[d], Natasha Hough[e], Caroline Baxter[f], David Connell[g], Anand Shah[h]

[a] Registrar in respiratory medicine, Guy's and St Thomas' NHS Foundation Trust, London, UK
[b] Respiratory dietitian, Guy's and St Thomas' NHS Foundation Trust, London, UK
[c] Pharmacist independent prescriber, Frimley Park NHS Foundation Trust, Frimley, UK
[d] Physiotherapist in respiratory medicine, Guy's and St Thomas' NHS Foundation Trust, London, UK
[e] Consultant physician in respiratory medicine, Oxford University Hospitals NHS Foundation Trust, Oxford, UK
[f] Consultant physician in respiratory medicine, National Aspergillosis Centre, Manchester NHS Foundation Trust, Manchester, UK
[g] Consultant physician in respiratory medicine, NHS Tayside, Dundee, UK
[h] Consultant physician in respiratory medicine, Guy's and St Thomas' NHS Foundation Trust, London, UK, and MRC Centre of Global Infectious Disease Analysis, Imperial College London, London, UK

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ABSTRACT

This collaborative article presents a review of chronic pulmonary aspergillosis (CPA) from the perspective of a multidisciplinary team comprising of respiratory physicians, radiologists, mycologists, dietitians, pharmacists, physiotherapists and palliative care specialists. The review synthesises current knowledge on CPA, emphasising the intricate interplay between clinical, radiological, and microbiological aspects. We highlight the importance of assessing each patient as multidisciplinary team to ensure personalised treatment strategies and a holistic approach to patient care.

Introduction

Pulmonary aspergillosis is a spectrum of allergic and infective diseases caused by the fungal species *Aspergillus*. The phenotypic presentation of disease is dependent on underlying lung disease and the patient's immune system function. Table 1 describes in brief the variety of presentations of *Aspergillus*-related lung disease alongside typical presentation and findings. This article will be focusing solely on chronic pulmonary aspergillosis (CPA). The global prevalence of CPA varies depending on region with significant likely underdiagnosis, however recent estimates show a global annual incidence of more than 1,800,000, with 340,000 (18.5%) deaths.[1]

CPA complicates underlying current or historic lung disease in broadly immunocompetent patients. The diagnosis of CPA is reliant on a combination of serological, radiological and microbiological criteria with a heterogenous presentation.[2] Given the difficulty in both diagnosis and management of CPA the input of a multidisciplinary team (MDT) is recommended. To help illustrate this, in this article we will discuss a patient with CPA from the perspective of all the members of the MDT (Fig 1) that are often required to provide complex care.

Case presentation

A 65-year-old man presents to the respiratory clinic with a 6-month history of a persistent cough with occasional streaks of haemoptysis. He is an ex-smoker with a history of chronic obstructive pulmonary disease (COPD). Until recently his COPD was well controlled on inhalers, and he had not had an exacerbation for 1 year. He also reports increasing shortness of breath and a decreasing exercise tolerance. He is more fatigued and spends most of his day sat in a chair. He has reduced appetite and has lost 8 kg in weight in the last few months, giving him a body mass index (BMI) of 17.6. He has a past medical history of hypertension, atrial fibrillation and ischaemic heart disease and is currently taking ramipril, amlodipine, apixaban, atorvastatin, bisoprolol, aspirin and inhaled umeclidinium bromide/vilanterol. He has a CT scan which shows evidence of a right upper lobe cavity with a mycetoma on a background of emphysematous change and mild apical pleuroparenchymal fibroelastosis (PPFE). His sputum is persistently positive for *Aspergillus fumigatus* and his serological markers show an *Aspergillus* IgG of 170 mg/L (normal cut-off <40 mg/L).

* Address for correspondence: Charlotte Carter, Respiratory Department, Royal Brompton Hospital Sydney St, London, SW3 6NP
E-mail address: Charlotte.carter5@nhs.net (C. Carter).

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Table 1
An overview of Aspergillus-associated lung disease.

Disease	Common risk factors	Presentation	Common radiological manifestation	Typical serological findings	Treatment
Invasive pulmonary aspergillosis	Immunodeficiency	Non-specific - Fever - Cough - Sputum - Haemoptysis - Dyspnoea	Multiple nodules Ground glass changes Consolidation Halo sign	↑ Galactomannan ↑ β-d-glucan	Voriconazole, posaconazole, isavuconazole Amphotericin B
Chronic pulmonary aspergillosis	Structural lung disease eg COPD, tuberculosis	Chronic (>6 months) Constitutional symptoms Cough Haemoptysis	Aspergilloma Nodules Pleural thickening	↑ *Aspergillus* IgG	Itraconazole Voriconazole
Allergic bronchopulmonary aspergillosis	Asthma Cystic Fibrosis	Wheezing Pleuritic chest pain Brown plugs in sputum	Fleeting pulmonary infiltrates Central bronchiectasis	↑ Immunoglobulin E ↑ Eosinophils ↑ *Aspergillus* IgE ↑ *Aspergillus* IgG	Oral corticosteroids Itraconazole

Table 2
The diagnostic of CPA requires the presence of a number of the below features for more than 3 months and a lack of alternative diagnosis.

Symptoms	Radiology	Serology	Microbiology
Haemoptysis Cough Weight loss Structural lung disease	One or more cavities Aspergilloma Nodules	↑ *Aspergillus* IgG	*Aspergillus spp.*

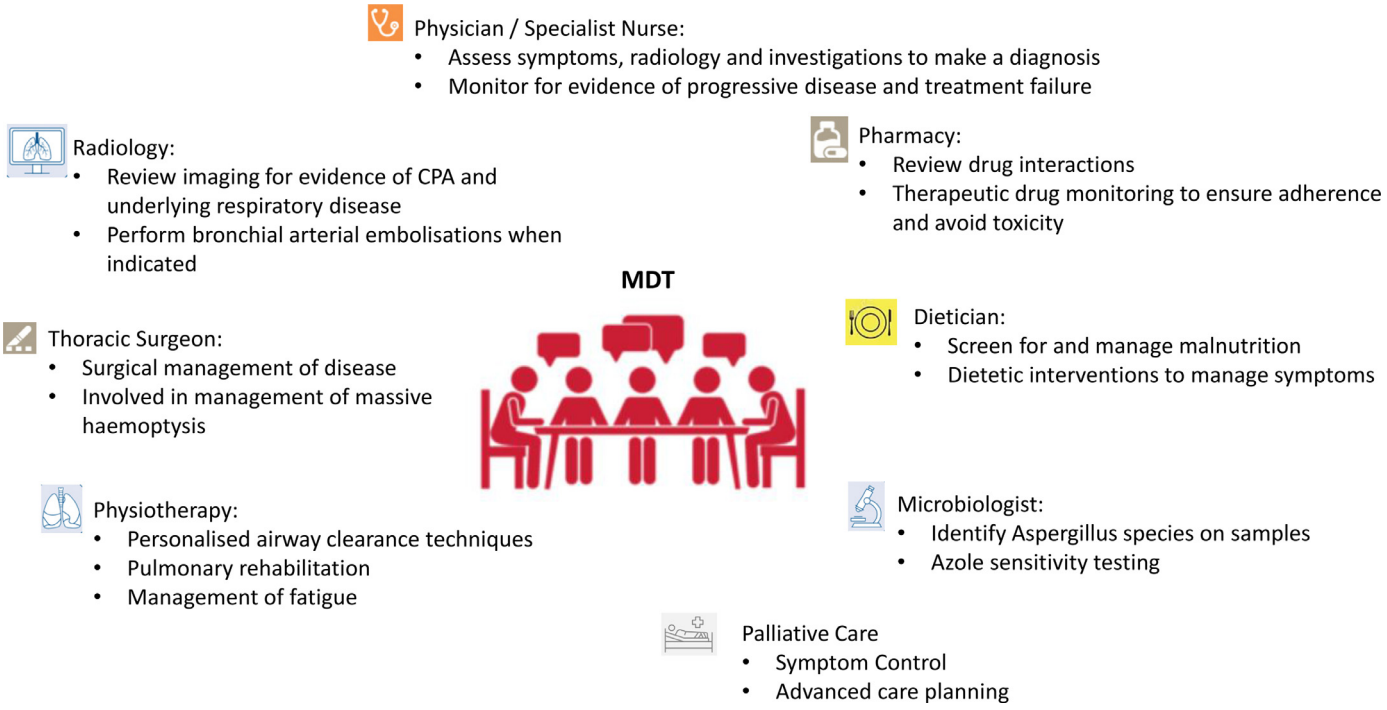

Fig 1. Roles of members of the multidisciplinary team in managing chronic pulmonary aspergillosis.

Case management by the clinician/specialist nurse

This patient has a diagnosis of CPA based on their symptoms, radiological appearances, serology and persistently positive microbiology. The diagnosis of CPA can be challenging given the requirement of a constellation of compatible radiology, microbiology and serological findings together with relevant symptoms. In cases with diagnostic difficulty an MDT may be required for consensus. To ensure the correct diagnosis is made, the patient should be actively investigated for lung cancer and non-tuberculous mycobacterial (NTM) disease as these can present similarly to and can co-exist with CPA. Table 2 gives a summary of the key findings in patients with CPA.

Patients can present at any age, although it is more commonly seen in males from middle age onwards. A history of structural lung disease secondary to tuberculosis or NTM, sarcoidosis, lung cancer, or COPD are risk factors for developing CPA and should alert clinicians to consider it as a differential diagnosis in patients presenting with chronic respiratory symptoms.[3]

This patient has the classical features of CPA, which include a history of cough (which is often productive), weight loss and haemoptysis.

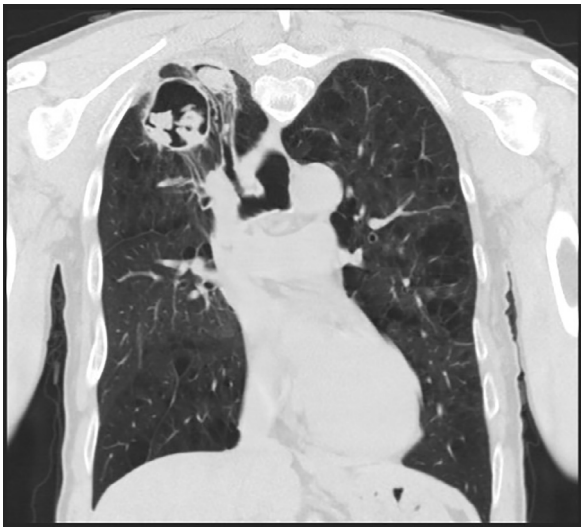

Fig 2. Coronal slices of the patient's CT scan.

Symptoms must have been present for longer than 3 months and may be accompanied by non-specific features such as fever, chest pain, lethargy and night sweats.[4] The symptoms may develop over months to years and are easily mis-diagnosed as exacerbations of the underlying respiratory disorder. Haemoptysis may be a significant feature of CPA and can range from small volume haemoptysis to large volume life threatening haemoptysis (more than 150 ml in 24 h).

The clinician's role in these patients is to ensure they make the correct diagnosis and start appropriate treatment at the right time. The decision to start treatment can be based on many factors, but is usually guided by progression of symptoms, and/or radiology. An MDT approach to management is key as complications such malnutrition and haemoptysis can feature alongside a declining quality of life. The main aims of treatment alongside resolution of disease, are improving symptoms and quality of life, prevention or treatment of complications, and prevention of progressive lung disease/damage.[5] The specific drug treatments are discussed later in this article.

Given the complexity of the condition, communication of diagnosis, findings and prognosis is imperative. Likewise, it is critical to ensure there is ongoing access to specialist care and input, a specialist nurse where available, has an essential role in facilitating continued access to high quality care and clear transparent communication.

Radiology

The CT thorax in this case shows some of the classical features of CPA. There is a right upper lobe cavity with a mycetoma on a background of emphysema. Fig 2 shows a coronal slices of this patient's CT scan. This patient also has evidence of pleuroparenchymal fibroelastosis (PPFE) which can be associated with CPA often with progressive fibrotic lung disease being a feature. A CT thorax is the most useful modality of imaging for patients with CPA.

There is significant radiological heterogeneity across cross-sectional imaging in patients with CPA. The most characteristic feature is a fungal ball (an aspergilloma); however, in a recent study only 25% of patients have evidence of this.[6] More rarely CPA can present with only nodules on CT imaging which can be cavitated in appearance. Without treatment, cavities will often continue to enlarge and new cavities will form.[7] Nodules are often associated with surrounding pleural thickening and areas of parenchymal consolidation/fibrosis.

In a subset of patients CPA can be characterised by additional fibrosis of one of more lobes of the lung, which can appear like consolidation without any defining features. It can be associated with PPFE like changes (including pleural thickening and subpleural fibrosis) with progression of disease leading to progressive fibrotic destruction of the affected lobe(s).

Serial CT scans may be useful to show progression over time and response to therapy. Although definitive studies to show radiological response to treatment have not been performed, previous retrospective analysis and recent consensus statements have suggested a reduction in cavity and pleural wall thickening, and a reduction in mycetoma size as prognostic markers associated with treatment success.[8,9]

CPA can be complicated by haemoptysis, in many cases this can be managed with oral therapies. In more severe or recurrent cases CT bronchial angiography (CTBA) is useful to identify the source of bleeding (which is usually from the systemic circulation). Radiologically guided bronchial arterial embolisation is an effective treatment.

Mycology

This patient has persistent growth of *A fumigatus* in his sputum. Although adding to the constellation of diagnostic findings suggestive of CPA, a positive fungal culture in isolation is not diagnostic given the presence of *Aspergillus* ubiquitously in the environment. Importantly, however, it does allow antifungal sensitivity testing to be performed, which can be critically important given the increasing global relevance and emergence of azole resistance. This is of particular importance in patients with a prior history of azole therapy where the likelihood of azole resistance is increased.

CPA is most commonly caused by *A fumigatus*, but CPA due to *A niger* or *A flavus* is occasionally seen. Repeated culture positivity may increase the likelihood of underlying pathology but again would need to be confirmed by clinical, radiological, serological or histopathological findings. The sensitivity of *Aspergillus* detection in respiratory cultures is variable, so negative culture in the context of a suspicious presentation does not exclude infection. Sensitivity can be improved by use of PCR detection although its use is limited particularly when distinguishing between colonisation and infection.[10]

Quantitative serological tests for IgG antibodies specific to *A fumigatus* are key in making a diagnosis of CPA. The detection of anti-*Aspergillus* antibodies has been reported to have a positive predictive value of 100%[11] when distinguishing infection from colonisation with isolation of *Aspergillus* in respiratory samples in non-immunocompromised patients. It is positive in >90% of cases of CPA[12] although can be falsely negative in non-fumigatus *Aspergillus* infection or immunocompromise. It is therefore used in conjunction with the clinical and radiological picture, and if clinical suspicion is high but there is a negative IgG, this does not exclude the diagnosis.

Galactomannan, a part of the fungal cell wall, can also be tested on BAL samples with sensitivity of 75–85% and specificity of 75–80%; serum galactomannan is not recommended due to the low sensitivity of the test. β-d-Glucan is a component of the cell wall of all fungi excluding zygomycetes, it is not widely used in the diagnosis of chronic pulmonary aspergillosis as it is associated with a high rate of false positives.

Dietitian input

For CPA, a low body mass index (BMI) has consistently been associated with increased mortality and is an independent predictor of prognosis.[13] As such, it is imperative that this patient with a low BMI and recent history of weight loss receives dietitian input. In patients with COPD the body mass index, airflow obstruction, dyspnoea and exercise capacity index (BODE) index[14] recommends that patients should be aiming for a BMI of at least 21 kg/m^2. Weight loss, and particularly loss of muscle mass, is associated with risk of infection and respiratory failure.[15]

Table 3
The options for available anti-fungal medications, dosing, key interactions and the necessary monitoring[2,22–24].

Drug	Form	Dose	Key interactions	Monitoring requirements at baseline and during treatment	Therapeutic drug monitoring (TDM)		
					Type of level	Timing of level post initiation / dose adjustment	Target level
Itraconazole	Oral	400 mg BD for 24 hours, then 200 mg BD	• Carbamazepine • Diazepam / midazolam • Omeprazole / esomeprazole • Paxlovid® • Phenytoin • QT interval prolongation (eg macrolides, quinolones, antipsychotics, ondansetron) • Rifampicin / rifabutin • Sirolimus / tacrolimus / ciclosporin • Vinca alkaloids • Warfarin	• **Bloods** (LFTs, U&Es, FBC, CRP) at baseline, weekly for first month and then monthly during treatment. If not feasible then after 2 weeks of treatment and then each follow-up clinic visit. • **ECG** at baseline and then 2 weeks after initiation or dose change. • **Aspergillus markers** (Total IgE, Aspergillus IgE, Aspergillus IgG, eosinophil count) Baseline and with each follow up clinic visit	Trough or Random	4–7 days	0.5–4 mg/L
Voriconazole	Oral	<40 kg: 200 mg BD for 24 hours, then 100 mg BD >40 kg: 400 mg BD for 24 hours, then 200 mg BD			Trough	Within first 5 days	1–6 mg/L
	IV	6 mg/kg BD for 24 hours, then 4 mg/kg BD					
Posaconazole	Oral	300 mg OD (capsules) 400 mg BD (liquid)			Trough or Random	3–8 days	>1 mg/L
Isavuconazole	Oral / IV	200 mg TDS for 48 hours then 200 mg OD			Trough	After 3–4 weeks	2–4 mg/L
Caspofungin	IV	<81 kg: 70 mg OD for 24 hours, then 50 mg OD >81 kg: 70 mg OD	• Hepatotoxicity (eg statins, tetracyclines, valproate) • Phenytoin •Rifampicin	• **Bloods (**LFTs, FBC, creatinine, serum potassium, calcium and magnesium, glucose) • Blood pressure daily	N/A	N/A	N/A
Anidulafungin	IV	200 mg OD for 24 hours then 100 mg OD	• Hepatotoxicity as above	• **Bloods** (LFTs, FBC, creatinine, potassium, glucose) • Blood pressure daily	N/A	N/A	N/A
Micafungin	IV	<40 kg: 2 mg/kg >40 kg: 100 mg OD	• Hepatotoxicity as above	• **Bloods** (LFTs, FBC, renal function, electrolytes)	N/A	N/A	N/A
AmBisome® Amphotericin B (liposomal)	IV	1 mg/kg test dose, then 3 mg/kg OD	• Nephrotoxicity (eg aciclovir, ACE inhibitors) • Ototoxicity (eg aminoglycosides, vinca alkaloids) • Hypokalaemia / torsade de pointes (eg citalopram) • Digoxin	• **Bloods** (LFTs, U&Es, creatinine, potassium, magnesium, FBC)	N/A	N/A	N/A

CRP = C-reactive protein; FBC = full blood count; LFT = liver function tests; U&E = urea and electrolytes

Biochemistry

For patients who may not have exposure to sunlight, vitamin D is a vital nutrient to support bone health. If a patient has lost a lot of weight over a short period of time, there may also be a refeeding risk.

Diet

It's important to understand nutrition impact symptoms and to try and tackle symptoms one by one.

Nutrition and mood are bidirectionally linked, understanding enjoyment of food and how food impacts everyone's quality of life, including cultural and social preferences is important.

Nutritional requirements include a higher protein intake (if no renal impairment), aiming for 1.2–1.5 g/kg.[16] A pragmatic approach around energy requirements may need to be taken as anecdotally, towards the end stages of disease, people with CPA become extremely catabolic.

Pharmacy

Various treatment options are available for the management of *Aspergillus* lung disease – see Table 3.

Azoles are the only oral drugs with anti-*Aspergillus* activity. Itraconazole or voriconazole are currently considered first line options as they have been shown to be effective in improving/achieving stability in clinical and radiological outcomes CPA.[17] Posaconazole and isavuconazole are used as second-line drugs if there is failure to respond to therapy, azole resistance or significant drug side effects.[18,19] Intravenous therapy may be used in cases of relapse, acute illness or antimicrobial resistance.[20] Recent data suggest that 12 months of therapy is superior to 6 months with regards to subsequent disease relapse.[21] Effectiveness should be assessed at 6-months, and if there is progressive disease then therapy may need to be changed or augmented.

Azoles have significant side effects; for example, voriconazole is associated with photosensitivity and may not be suitable in patients with certain occupations. It is important to review side effects and the tolerability of the azole medication of a regular basis, particularly as many patients relapse on cessation of the drug.

Therapeutic drug monitoring

Determining the levels of a particular medication in the bloodstream is known as therapeutic drug monitoring (TDM). This is recommended with azoles due to their inherent pharmacokinetic variations, drug expose-response, drug exposure-toxicity relationships and is useful when assessing interactions.[22-24]

Initial TDM is advised as per Table 3 and then periodically during clinical reviews to ensure adherence and efficacy while minimising tox-

icity.[23,24] Azoles, amphotericin and caspofungin are also known to potentially elevate liver function tests (LFTs), so it is vital to monitor these throughout treatment.[24] The LFT derangement is typically reversible on discontinuation of therapy.

Interactions

Azoles are known to affect cytochrome P450 (CYP450), an isoenzyme crucial for the metabolism of a wide spectrum of drugs.[23,24] As a result, there is potential to interact with many pharmaceutical agents, and it is important to involve pharmacists as part of an MDT-led approach.

Azole resistance and antifungal stewardship

Globally there is evidence of emerging anti-fungal resistance which is associated with poorer outcomes. Close monitoring in azole monotherapy is essential and in vitro susceptibility testing should be carried out in all culture-positive cases.[17] Azole resistance can be acquired via long-term use of azole therapy or may already be present due to environmentally derived mutations.[17,25,26]

There is limited evidence for the recommended treatment options in azole-resistance isolates and should be made on a case-by-case basis with the involvement of locally available expertise. Good anti-fungal stewardship will monitor and direct the use of anti-fungal agents to try and achieve good clinical outcomes while avoiding harm and preventing further resistance.[27]

Physiotherapy

This patient has both CPA and COPD with worsening symptoms, particularly breathlessness, and a declining functional status. The involvement of a physiotherapist is key to attempt to improve symptoms and his quality of life. There is a lack of evidence to guide physiotherapy management but as CPA typically occurs in the presence of a respiratory comorbidity, good clinical practice points can be extrapolated from existing literature in related disease groups.

In this group, fatigue is particularly important,[28] as a symptom of CPA as well as a side effect of antifungal treatment. Patients can also experience airway inflammation and bronchoconstriction. This may be related to *Aspergillus* exposure or their underlying respiratory condition.

Sputum production

Sputum production is not a principal symptom of CPA and many patients with CPA will not necessarily require regular airway clearance technique (ACT). However, in this case, COPD guidelines recommend ACTs be taught in the case of sputum production.

Haemoptysis

Many patients with CPA will experience haemoptysis. There is no evidence or guidance published surrounding the physiotherapeutic management of haemoptysis. A Delphi consensus, described in the Cystic Fibrosis Trust guidelines, provides a framework to assist with modification and personalisation of treatment in the context of haemoptysis for individuals who perform airway clearance techniques.[29]

Exercise and pulmonary rehabilitation

Exercise should be advised and prescribed in line with the World Health Organization recommendations for individuals with chronic disease.[30] Given this patient's co-existing diagnosis of COPD, pulmonary rehabilitation should be offered to improve health related quality of life and functional capacity.

Thoracic surgery

Surgical resection of CPA can be used to provide curative intent, improve quality of life, control infection and attempt to prevent haemoptysis.[2] Surgical resection is most commonly undertaken in patients with simple aspergillomas with good baseline function as it can provide a cure.

Advances in thoracic surgery techniques have led to better outcomes and reduced post-operative complications. Patients with more complex symptomatic disease are more likely to have complications. The mortality rate in a study of 33 patients from one centre over 11 years was 24%.[31] Given the complexity of the surgery and risk of possible complications, surgeons with experience of chronic pulmonary aspergillosis surgery are key. There is a risk of relapse post-surgery, anti-fungal therapy before and after surgery has been shown to reduce the risk of relapse.[32] A nuanced patient-based approach on the pre- and post-operative length of treatment should be taken.

Surgery should always be considered in patients presenting with major haemoptysis but patients may end up with a bronchial arterial embolisation as a bridge to possible elective surgery.

In lower resource settings surgery may be used as first line treatment in centers with experience, in part due to the availability and expense of azole medications. A systematic review of CPA managed surgically in Africa showed low mortality rates.[33]

Palliative care

This patient's 5-year mortality is approximately 50%.[34] This is higher than if he were diagnosed with idiopathic pulmonary fibrosis or many solid organ cancers. The mortality rate of CPA is impacted by numerous factors, many of which are not modifiable.[34]

Patients with CPA have a high symptom burden including fatigue and breathlessness. There is currently no evidence base for palliative care input in these patients and therefore funding for and access to palliative care services can be extremely difficult. Early referral to inpatient and outpatient services can help patients manage their symptoms and improve quality of life measures.

Conclusion

This case highlights the challenges in CPA diagnosis and management and how a multidisciplinary approach can help tackle this. One particular challenge is the insidious presentation which can be difficult to distinguish in the context of a patient's underlying lung disease. There is heterogeneity in cross-sectional imaging and the presentation can mimic a number of other respiratory conditions including lung cancer and NTM. The initiation and continuation of treatment is complex, particularly in an aging population with multiple health conditions. The involvement of a pharmacist is key in ensuring safe azole prescriptions. Communication with the local mycology teams to raise the concern of fungal infection can ensure appropriate investigations to detect *Aspergillus spp*. This is of increasing importance as global azole resistance emerges. Patients can have a number of complications and progressive disease can impact on negative on their quality of life. Members of the MDT can positively impact a number of symptoms and cure disease in some cases. However, in other patients' clear communication regarding prognosis and early involvement of palliative care services is vital.

Key points

- The diagnosis of chronic pulmonary aspergillosis is based on a combination of clinical presentation with suggestive features in the history, radiological findings, microbiology and serological tests.

- The input of a specialist MDT is vital in ensuring the best individualised management for patients
- Azole use is associated with significant interactions and side effects. Close therapeutic drug monitoring is required to avoid side effects and toxicity.
- There is evidence of increasing triazole resistance and patients with resistant strains of *Aspergillus spp*. have a higher risk of mortality. Sensitivity analyses should be done where possible in patients, this may be facilitated with close links with/discussions with regional mycology laboratories.
- Consider early palliative care referral for patients with CPA to help manage their symptom burden and for consideration of advanced care planning.

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