# British Thoracic Society Clinical Statement on *Aspergillus*-related chronic lung disease

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**Contents**

**Glossary of Terms**

ABPA Allergic bronchopulmonary aspergillosis
ABPM Allergic bronchopulmonary mycosis
AMB Amphotericin B
BAL Bronchoalveolar lavage
BTS British Thoracic Society
CCPA Chronic cavitary pulmonary aspergillosis
CF Cystic fibrosis
CFPA Chronic fibrosing pulmonary aspergillosis
CPA Chronic pulmonary aspergillosis
COPD chronic obstructive pulmonary disease
CSG Clinical Statement Group
CT Computer Tomography
ECG Electrocardiogram
Fbc Full blood count
FeNO Fractional exhaled nitric oxide
$FEV_1$ Forced Expiratory Volume in 1 second
GM galactomannan antigen
IgE or IgG Immunoglobulin E or G respectively
LABA Long-acting beta-agonists
LAMALong-acting muscarinic antagonists
LFTs Liver function tests
PEFR Peak expiratory flow rate
PCR Polymerase chain reaction
SAFS Severe Asthma with Fungal Sensitisation
SAIA Sub-acute invasive pulmonary aspergillosis
SOCC Standards of Care Committee
TDM Therapeutic drug monitoring
U&Es Urea and electrolytes

**Summary of clinical practice points** (Box 1)

**Clinical practice points for diagnosis of *Aspergillus*-related chronic lung disease**

1. Investigate potential cases of *Aspergillus*-related chronic lung disease using a combination of clinical, radiological, microbiological and serological markers to identify the presence of *Aspergillus* spp. and the likely associated pathology.
2. Perform a careful clinical evaluation of patients after identification of *Aspergillus* spp. from a respiratory sample to characterise whether this represents transient or asymptomatic colonisation or indicates an *Aspergillus*-related chronic lung disease.
3. Investigate radiological findings consistent with *Aspergillus*-related chronic lung disease addressing the diagnostic criteria listed in boxes 2, 3, and 4
4. Screen (or rescreen) for ABPA in patients with poorly controlled or unexplained deterioration in asthma, COPD, CF or bronchiectasis using total serum IgE and *Aspergillus* spp. specific serum IgE and/or *Aspergillus* spp. skin prick tests.
5. Seek advice from a clinician with significant experience in *Aspergillus*-related chronic lung disease where the diagnosis is not clear.
6. Physicians caring for patients with *Aspergillus*-related chronic lung disease should have access to appropriate diagnostic testing (e.g. *Aspergillus* serology, antifungal susceptibility testing, therapeutic drug monitoring [TDM]).

**Clinical practice points for management of aspergilloma**

1. Monitor patients with recently diagnosed aspergilloma for a minimum of 12 months for evidence of clinical or radiological progression.
2. Do not routinely offer surgical intervention or antifungal treatments for asymptomatic aspergilloma.
3. For patients with aspergilloma and the following complications consider surgical resection or antifungal therapy as described for the management of CPA (section 7):
   (i) recurrent or persistent minor haemoptysis
   (ii) an episode of major haemoptysis
   (iii) significant attributable systemic symptoms (e.g. fever, fatigue, night sweats, weight loss)
   (iv) progressive radiological change of the cavity wall (fulfils definition of CPA)
   (v) ongoing and/or future planned significant increases in immunosuppression (e.g. long-term oral corticosteroids or other systemic immunosuppressants, chemotherapy, organ or stem cell transplantation).

**Clinical Practice points for management of acute exacerbations of ABPA**

1. Use clinical assessment to determine if an acute exacerbation in a patient with ABPA is related to a flare of the underlying ABPA or an alternative cause.
2. Treat exacerbations caused by a flare of the ABPA with prednisolone 0.5mg/kg (ideal body weight) (maximum dose of 40mg) for up to two weeks, weaning to the maintenance dose or zero over 2 to 8 weeks tailored to the patient/clinical situation.

3. Consider temporary (no longer than 3 months) combined treatment with triazole therapy (**Box 5**) and prednisolone when weaning of oral corticosteroids leads to clinical deterioration.
4. Consider treatment with triazole therapy (**Box 5**) if systemic corticosteroids should be avoided, or fail to improve symptoms and restore lung function.

**Clinical Practice points for the chronic management of ABPA**

1. Optimise the general management of asthma and bronchiectasis according to BTS guidelines (including airway clearance, smoking cessation advice, avoiding other environmental triggers and exposure to *Aspergillus* spp.) and provide written action plans for treatment of exacerbations.
2. Monitor the response to treatment using clinical assessments supported by measuring total IgE and eosinophil counts, repeating the radiology (chest X-rays usually suffice, with CT scans as required), and monitoring lung function (peak flow and spirometry).
3. Titrate up inhaled corticosteroid and bronchodilator treatment to minimise symptoms and exacerbations, and maintain stable peak flow and/or spirometry recordings.
4. For patients with two or more exacerbations within 6 months requiring oral corticosteroids, failure to maintain stable $FEV_1$ / peak flows consider either:
   - long term oral prednisolone, with an initial dose 10mg/day weaning to 5mg/day after 3 months, and if disease control is maintained attempt weaning completely after 6 months
   - or trial of triazole therapy (Box 5)
   - or referral to severe asthma centre for evaluation for treatment with monoclonal antibodies
5. For patients with two or more exacerbations within 6 months requiring oral corticosteroids, or failure to maintain stable $FEV_1$ / peak flows despite monotherapy with maintenance prednisolone or antifungal therapy alone, consider combination treatment with oral prednisolone and an antifungal agent, or referral to severe asthma centre for evaluation for treatment with monoclonal antibodies.
6. Consider testing for adrenal insufficiency (e.g. measuring a 9am cortisol, and if abnormal perform a synacthen test) in patients either receiving two or more courses of oral corticosteroids in 6 months, or on maintenance oral corticosteroids for >6 months, or receiving long term (>6 months) triazole therapy in combination with inhaled corticosteroids.

**Clinical practice points for management of chronic *Aspergillus* spp. Infections**

1. Optimise the management of underlying lung disease and other comorbidities (e.g. diabetes) and if relevant consider whether immunosuppressive therapy can be modified.
2. Patients being considered for surgical intervention or long-term treatment with antifungal agents should be discussed with clinicians with significant expertise in *Aspergillus*-related chronic lung diseases.
3. Consider surgical resection for CPA lesions in patients with low operative risk and adequate lung function, particularly in patients with a poor response to

antifungal therapy or previous life-threatening haemoptysis.

4. Treat patients undergoing surgical resection of CPA with antifungal agents (triazole or echinocandin) for a duration of at least 2 weeks pre-operatively and 2 weeks post-operatively, extending therapy (eg for three months) if persisting infection is suspected.
5. Do not routinely offer antifungal therapy to patients with *Aspergillus* nodules identified by surgical excision or biopsy (e.g. to exclude suspected lung cancer) with no clinical or radiological evidence of progressive infection.
6. Consider antifungal therapy for cases of CPA not suitable for surgical resection, for *Aspergillus* bronchitis/bronchiolitis or tracheobronchitis, and for *Aspergillus* nodules with clinical or radiological evidence of progressive infection. Suggested agents are described in Box 5.
7. Assess antifungal treatment response 6 weeks to 3 months after initiating antifungal therapy depending on the individual patient and disease characteristics, then every three months using:
   (i) clinical assessment (e.g. weight change, malaise, cough, sputum, haemoptysis, and preferably a validated QoL score such as the St George's Questionnaire [71])
   (ii) TDM for patients receiving itraconazole, voriconazole, or posaconazole
   (iii) radiology (see point 10)
   (iv) additional tests according to clinical need, including sputum cultures, CRP, FBC, U&E, serum *Aspergillus* IgG, ECG, lung function tests and/or 6-minute walk tests.
8. In most instances, continue antifungal therapy for CPA for at least 12 months. Further treatment will depend on the clinical and radiological response, recurrence after stopping therapy, and other clinical factors (e.g. level of immunosuppression, side effects caused by antifungal agents and, background comorbidities). Treatment duration for SAIA could be shorter if there is rapid clinical improvement.
9. The duration of antifungal treatment for *Aspergillus* nodules, bronchitis/bronchiolitis or tracheobronchitis will vary depending on the clinical presentation, response to antifungal treatment, and whether relapses occur when stopping antifungals.
10. Consider repeat CT scans at 3 to 6 months after initiating antifungal therapy, at key management decision points, then annually whilst on antifungal therapy.
11. Monitor for disease relapse 3 months after stopping antifungal therapy then 3 to 6 monthly thereafter for a minimum of 12 months.
12. Consider further discussions with clinicians with significant expertise in *Aspergillus*- related chronic lung diseases for patients with poor response to first- or second-line antifungal therapy.
13. Patients and their carers with chronic aspergillus infections can benefit from patient support groups, details of which should be provided by their local specialist clinician.

**Clinical practice points for use of antifungal therapy for chronic *Aspergillus*-related lung disease:**

1. Take a thorough drug history from all patients to inform on the choice of antifungal prescribed.
2. Consider altering existing medications to avoid potential drug interactions.

3. For patients starting a triazole consider reducing the dose of inhaled corticosteroid therapy to reduce systemic side effects, depending on type of corticosteroid (a) fluticasone, budesonide, mometasone – initial 50% dose reduction, (b) beclomethasone, ciclesonide – no dose adjustment needed; monitor for side effects.
4. Consider testing for adrenal insufficiency (eg measuring a 9am cortisol, and if abnormal performing a synacthen test) in patients receiving triazole therapy and either maintenance oral corticosteroids for >6 months, long term inhaled corticosteroids, or receiving two or more courses of oral corticosteroids in 6 months for exacerbations of airways diseases.
5. For patients receiving triazole therapies, request pre-treatment ECG and baseline bloods (LFTs, FBC and U&Es). Repeat the LFTs and request therapeutic drug levels after 2 to 4 weeks along with an ECG for patients with pre-treatment prolonged QTc or additional risk factors for a prolonged QTc (e.g. long term azithromycin). Repeat LFTs / U&Es and TDM at 3 months then 6 (itraconazole and voriconazole) or 12 (posaconazole) monthly, or after dose / formulation changes, or interacting medicines are started or stopped.
6. Counsel patients receiving antifungal agents about common and important side effects, and what to do if a potential side effect occurs.
7. Persist with one formulation of itraconazole or posaconazole, and if changing between capsules/tablets or the liquid formulation use TDM to ensure correct dosing.

## 1. Need and scope of this clinical statement

*Aspergillus* spp. cause a wide range of acute, sub-acute and chronic lung conditions, some of which can lead to progressive loss of lung function and death. More extensive use of immunosuppression in medical practice has increased the number of patients at risk of *Aspergillus* spp. lung infections. The diagnosis and management of *Aspergillus*-related lung disease is often complex, and the optimum management of patients with *Aspergillus*-related lung disease will usually require involvement of subspecialty expertise. The purpose of this clinical statement is to summarise the management approach to patients with *Aspergillus*-related chronic (defined as lasting 3 months or more) lung disease. Not covered in detail are: (i) acute invasive infections caused by *Aspergillus* spp.; (ii) chronic infections caused by non-*Aspergillus* fungi; (iii) Severe Asthma with Fungal Sensitisation (SAFS); and (iv) hypersensitivity pneumonitis caused by exposure to *Aspergillus* spp. (Farmer's lung) which is best characterised as a form of interstitial lung disease rather than infection [1, 2].

## 2. Methodology

The Clinical Statement Group (CSG) was chaired by Dr Caroline Baxter and Professor Jeremy Brown. Membership was drawn from respiratory medicine physicians, nurse specialists, pharmacists, infectious disease physicians and medical mycologists, and included input from all nations of the United Kingdom. The overall content was developed to reflect the scope approved by the BTS Standards of Care Committee (SOCC) and is summarised through Clinical Practice Points (presented in **Box 1**). A final edited draft was reviewed by the BTS SOCC before posting for public consultation and peer review on the BTS website in July 2024. The revised document was re-approved by the BTS SOCC in October 2024 before final publication.

## 3. General background

*Aspergillus* spp. are saprophytic environmental fungi which grow as branching hyphae and spread by distributing airborne spores, termed conidia. Human exposure to inhaled *Aspergillus* spp. conidia is almost ubiquitous, and in subjects with a normal immune system conidia reaching the lung are rapidly cleared with no health consequences. However, in patients with immunosuppression and / or structural lung disease the inhaled conidia can germinate to cause active lung infection, with the morphology and speed of progression of infection varying markedly depending on host immune function. Inhaled *Aspergillus* spp. can also generate an allergic response to fungal antigens resulting in inflammatory lung disease. Due to this dependence of disease phenotype on host immune status, *Aspergillus* spp. cause a wide range of chronic lung conditions including asymptomatic colonisation, allergic bronchopulmonary aspergillosis (ABPA) and several types of chronic infection (**Table 1** and **Figure 1**). Transition from one form of infection to another can occur (e.g. aspergillomas evolving to more invasive forms of infection), and allergic and active infection disease subtypes may co-exist. Although *Aspergillus fumigatus* is the predominant species in the UK, other *Aspergillus* spp. (e.g. *A. niger*, *A. terreus*, and *A. flavus*) can also cause *Aspergillus*-related chronic pulmonary disease.

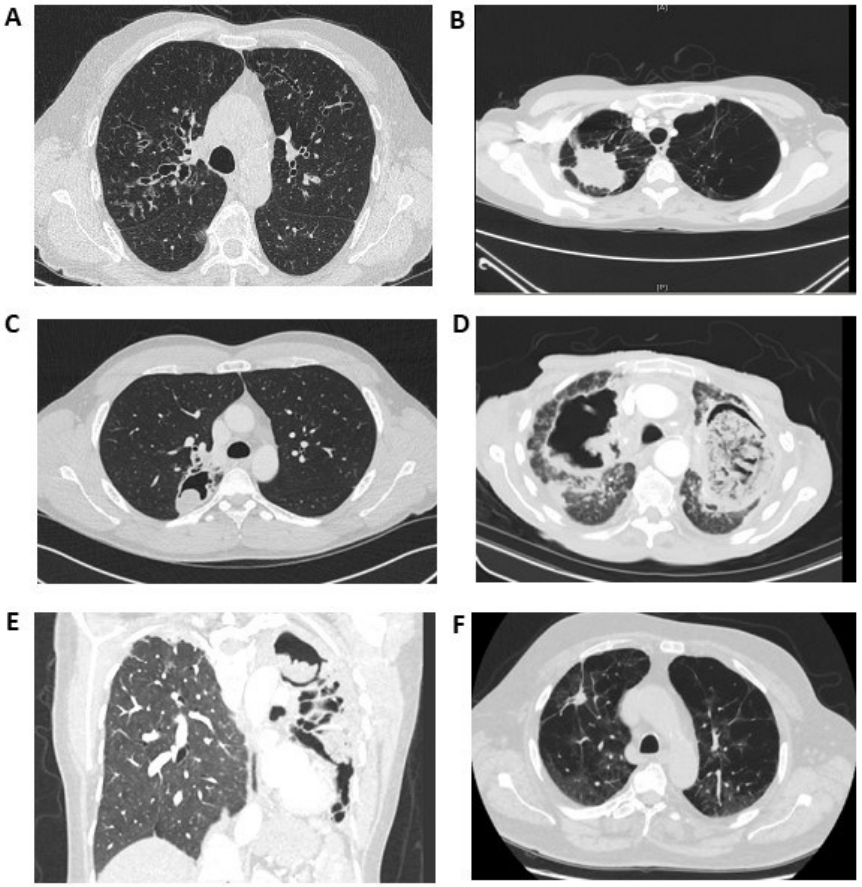
**Table 1 Classification of *Aspergillus*-related chronic lung disease**

| **Clinical manifestation** | **Sub-type** | **Main risk factors** |
|---|---|---|
| Colonisation | n/a | Pre-existing lung disease |
| Aspergilloma | Simple<br>Complicated (e.g. haemoptysis) | Pre-existing cavities |
| Allergy | ABPA[1]<br>SAFS[2] | Asthma, bronchiectasis, CF, COPD<br>Asthma |
| Chronic infection | Forms of CPA[3]:<br>(i) SAIA[4]<br>(ii) CCPA[5]<br>(iii) CFPA[6]<br>Nodules<br>Airways infections (*Aspergillus* bronchitis / bronchiolitis or tracheobronchitis) | <br>Immunosuppression<br>Pre-existing lung disease<br>Pre-existing lung disease<br>Unclear<br>Immunosuppression, pre-existing lung disease |

[1]allergic bronchopulmonary aspergillosis
[2]severe asthma with fungal sensitisation
[3]chronic pulmonary aspergillosis
[4]subacute invasive aspergillosis
[5]chronic cavitary pulmonary aspergillosis
[6]chronic fibrosing pulmonary aspergillosis

## Figure 1 :Exemplar CT scans of different types of *Aspergillus*-related chronic lung disease

**Figure 1:** Exemplar CT scan appearances of different forms of *Aspergillus*-related chronic lung disease. (A) ABPA with marked bilateral upper lobe bronchiectasis, including proximal disease. (B) SAIA macronodule in a patient with background emphysema. (C) Right upper lobe posterior aspergilloma with a well-defined thin cavity wall and an intracavity mycetoma. (D) Bilateral large cavities caused by CCPA showing less well-defined cavity walls, surrounding inflammatory changes, and in the left cavity a poorly formed intracavity mycetoma. (E) CFPA with considerable volume loss and pleural thickening affecting the left lung, and an associated upper lobe cavity containing a mycetoma. (F) A right upper lobe well-circumscribed *Aspergillus* nodule in a patient with severe emphysema.



## *4.* Classification and diagnostic criteria for sub-types of *Aspergillus*-related chronic lung disease

Respiratory manifestations of *Aspergillus* spp. include colonisation, disease related to an allergic response to *Aspergillus* spp. (ABPA and SAFS), and infection (**Table 1**). The epidemiology of these conditions is poorly understood, with limited data on incidence and prevalence. Several microbiological and serological markers are important for clarifying a diagnosis of *Aspergillus*-related chronic lung disease (**Table 2**), and the diagnostic criteria for *Aspergillus*-related chronic lung diseases are summarised in **Boxes 2, 3 and 4**. A diagnosis of *Aspergillus*-related chronic lung disease should generally be considered when: (i) an *Aspergillus* spp. is identified from a respiratory tract sample; (ii) assessing for ABPA in people with chronic airways disease; and (iii) there are abnormal radiological appearances compatible with one form or another of *Aspergillus*-related chronic lung disease. Diagnostic pathways for each of these are shown in **Figure 2**.

### 4.1 *Aspergillus* spp. colonisation of the respiratory tract (diagnostic criteria Box 2)

A positive respiratory sample culture for an *Aspergillus* spp. may represent transient or intermittent colonisation of the respiratory tract without disease or a diagnosis of one of the pathological conditions caused by *Aspergillus*-related lung disease. Hence, analogous to the situation for non-tuberculous mycobacteria, a positive respiratory sample culture for *Aspergillus* spp. needs careful clinical and radiological evaluation to characterise any potential associated underlying pathology. In the absence of clinical or radiological evidence of disease and without underlying immunosuppression, a positive culture can be regarded as either a sample contaminant or non-pathological (often transient) colonisation with *Aspergillus* spp. and requires no further investigation or treatment. A positive galactomannan (GM) antigen or *Aspergillus* PCR in a bronchoalveolar fluid (BAL) sample are alternative tests to a positive *Aspergillus* spp. culture that indicate the presence of *Aspergillus* spp. in the lung.

### 4.2 Aspergilloma (diagnostic criteria Box 2)

Fungi within pre-existing pulmonary cavities can grow to form an intracavitary body termed a mycetoma. Most mycetomas are caused by *Aspergillus* spp. and are called aspergillomas. Other pathogens reported to cause mycetomas include *Candida*, *Coccidioidomycosis*, and *Paecilomyces* [3-5]. Lung parenchymal cavities (mainly formed by previous tuberculosis or sarcoidosis) are the commonest sites for aspergillomas, but they can occasionally form in chronic pneumothoraces, enlarged airways or bullae. The diagnosis is based on the distinct radiological appearances of an intracavity body (a mycetoma) (Figure 1C) with no evidence of radiological progression over time. Patients may have a positive *Aspergillus*-specific IgG and/or culture positive respiratory samples, but neither is required for the diagnosis. Most patients are asymptomatic and are termed simple aspergillomas. However, aspergillomas can cause minor or major (potentially life-threatening) haemoptysis; when associated with haemoptysis or other chronic respiratory symptoms, they are termed complicated aspergillomas. If there is radiological progression of the cavity over time, the diagnosis is chronic pulmonary aspergillosis (CPA) rather than aspergilloma (section 4.4). A change in size of the aspergilloma contained within a cavity does not indicate evolution to CPA.

**Figure 2:** Diagnostic pathways for suspected *Aspergillus*-related chronic lung disease

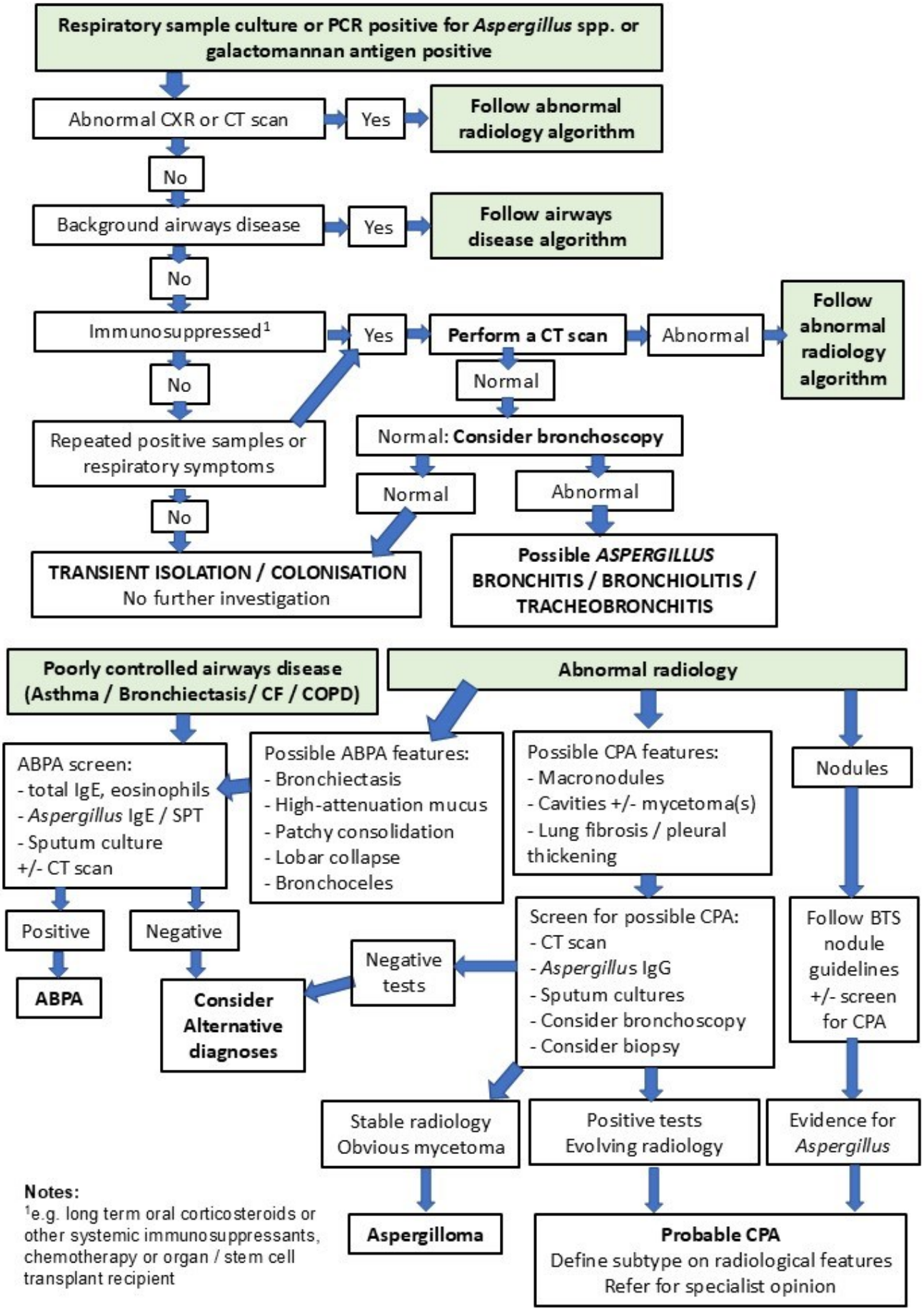


**Table 2: Interpretation of diagnostic tests**

| Disease form | | Diagnostic tests |
|---|---|---|
| Colonisation | Radiology | No radiological changes suggestive of *Aspergillus* lung disease |
| | Microbiology | Positive sputum/BAL culture/PCR for *Aspergillus* spp. or GM |
| | Serology | Total IgE and *Aspergillus* IgE normal |
| | | *Aspergillus* IgG may be raised |
| ABPA | Radiology | Typical radiological changes are common (see **Box 3**) |
| | Microbiology | Often positive sputum/BAL culture for *Aspergillus* spp.[1] |
| | Serology | Positive *Aspergillus* spp. specific IgE or skin prick test |
| | Other | Total IgE at least >500 IU/ml |
| | | Eosinophil count often raised >0.5x$10^9$/L |
| | | Lung function evidence of airflow obstruction |
| Aspergilloma | Radiology | Mycetoma visible on chest X ray or CT scan |
| | Microbiology | Often positive sputum/BAL culture for *Aspergillus* spp.[1] |
| | Serology | *Aspergillus* spp. specific IgG usually raised |
| CCPA/CFPA | Radiology | Radiological changes of progressive cavitary +/- fibrotic parenchymal or pleural dis |
| | | with or without concurrent aspergilloma |
| | Microbiology | Often positive sputum/BAL culture for *Aspergillus* spp.[1] |
| | | Serum GM usually negative |
| | Serology | *Aspergillus* spp. specific IgG almost always raised and may be used to monitor response to treatment |
| | | Total IgE and specific *Aspergillus* IgE may or may not be raised |
| | Other | Confirmed by histological demonstration of *Aspergillus* spp. hyphae in lung parenchyma from CT-guided, bronchoscopic or surgical biopsy |
| SAIA | Radiology | Radiology demonstrates expanding macro-nodules or focal consolidation |
| | Microbiology | Often positive sputum/BAL culture for *Aspergillus* spp.[1] |
| | | BAL and serum GM may be positive |
| | Serology | *Aspergillus* spp. specific IgG usually raised |
| | Other | Confirmed by histological demonstration of *Aspergillus* spp. hyphae in lung parenchyma from CT-guided, bronchoscopic or surgical biopsy |
| *Aspergillus* nodules | Radiology | Usually detected by CT scan and requires exclusion of malignancy. |
| | Microbiology | Sputum/BAL usually negative: positive from biopsy/resection samples |
| | Serology | *Aspergillus* spp. specific IgG may be elevated or normal |
| | Other | Diagnosis confirmed by histology (CT guided or surgical biopsy) |
| *Aspergillus* bronchiolitis / bronchitis / tracheobronchitis | Radiology | Usually have CT changes of airway inflammation +/- nodules |
| | Microbiology | Positive sputum/BAL culture for *Aspergillus* spp., often recurrently[1] |
| | Serology | *Aspergillus* spp. specific IgG usually raised |
| | Other | Confirmed by evidence of *Aspergillus* infection on endobronchial biopsy |

[1]GM and/or *Aspergillus* PCR in BAL and sputum may be positive but at present are not validated as alternatives to a positive culture when making a diagnosis of *Aspergillus*-related chronic lung disease

**Box 2: Diagnostic criteria for *Aspergillus* spp. colonisation and aspergilloma**

Non-pathological *Aspergillus* spp. colonisation:

(a) Repeated positive culture, GM, or PCR for an *Aspergillus* spp. from a respiratory tract sample

(b) **And** absence of any clinical, radiological, or serological evidence of *Aspergillus*-related chronic lung disease

Aspergilloma:

(a) Radiological evidence of a mass with the air crescent sign in a well-defined thin-walled cavity

(b) **And** no radiological evidence for CPA suggested by the cavity wall morphology and/or progressive enlargement of the cavity size over time

(c) Asymptomatic – **simple Aspergilloma**
Associated with major or minor haemoptysis or chronic symptoms – **complicated Aspergilloma**

(d) Supportive but non-essential criteria:
- Positive *Aspergillus* IgG
- Positive A*spergillus* spp. culture, GM, or PCR from respiratory samples

### 4.3 Allergic bronchopulmonary aspergillosis (ABPA) (diagnostic criteria Box 3)

ABPA is caused by allergic hypersensitivity to inhaled *Aspergillus* spp. spores resulting in a variable clinical syndrome of airways obstruction and bronchiectasis. ABPA is most commonly diagnosed in patients with underlying atopy or airways disease (asthma, cystic fibrosis [CF], bronchiectasis, or chronic obstructive pulmonary disease [COPD]) but can rarely occur in patients without these conditions. The diagnosis is dependent on serological evidence of IgE-mediated hypersensitivity to *Aspergillus* spp. with a raised serum total IgE (>500 IU/ml, although frequently >1000 IU/ml) and a raised *Aspergillus* spp. specific serum IgE and/or a positive *Aspergillus* spp. specific skin prick test. In both bronchiectasis and CF a diagnosis of ABPA is associated with more severe disease and faster progression [6].

Confirming a diagnosis of ABPA can be difficult and discussion with a clinician with sub-specialty expertise in *Aspergillus*-related lung disease may be necessary. Sensitisation to non-*Aspergillus* fungal pathogens (termed allergic bronchopulmonary mycosis, ABPM) with a raised total serum IgE but normal or weakly positive specific IgE or IgG to *Aspergillus* spp. causes a similar clinical picture but is much less common than ABPA [7, 8]. In patients with poor asthma control and a positive serological IgE response but who do not fulfil the other ABPA diagnostic criteria, SAFS should be considered (not discussed further in this document).

Early detection and management of ABPA can prevent progression. ABPA should be considered in patients with:

- difficult to control or severe asthma or other causes of airways obstruction
- a new diagnosis or unexplained clinical deterioration of bronchiectasis or CF
- typical radiology findings (**Box 3)**
- visible mucoid impaction on bronchoscopy or who produce bronchial casts
- a positive respiratory culture for *Aspergillus* spp.
- raised total serum IgE and/or positive *Aspergillus* spp. IgE or skin prick test.

A diagnosis of ABPA requires a combination of clinical and immunological features [7, 9-12]. The three core criteria are: (a) presence of obstructive airways disease, (b) high total serum

total IgE (>500 IU/ml), (c) and positive *Aspergillus* spp. specific IgE (>0.35 kUA/$L^{-1}$) or skin prick response (**Box 3**). A highly raised serum total IgE is a sensitive marker for a diagnosis of ABPA, and a cut off of >500 (although commonly far higher) is the current international consensus [13]. Lower levels of total IgE may also be significant if other criteria are met. Total IgE levels tend to fall when patients are well controlled, and can be used to monitor response to therapy [14]. *Aspergillus* spp. specific serum IgE or skin prick testing are essential to confirm a diagnosis of ABPA. Interpretation of the relative importance of a positive result indicating ABPA as a driver for poor asthma control requires a broader screen for other aeroallergens using specific IgE and skin prick test. *Aspergillus* spp. specific serum IgE levels do not correlate with response to treatment [14]. A positive *Aspergillus* IgG or positive respiratory sample cultures for *Aspergillus* spp. are common in ABPA, but are not required for the diagnosis [15].

Patients with ABPA almost invariably have lung function evidence of airways disease, which can have varying degrees of reversibility. Serial spirometry or peak expiratory flow rate (PEFR) measurements are essential for monitoring disease severity and treatment response. Fractional exhaled nitric oxide (FeNO) may be significantly elevated in ABPA [16]. Acute pulmonary exacerbations are common, and can present with: (i) exacerbations due to standard triggers of the underlying airways disease (e.g. respiratory viral infection); (ii) infective exacerbations of bronchiectasis; and / or (iii) exacerbations related to flares of ABPA (defined in section 5.1).

**Box 3: Diagnostic criteria for ABPA**

ABPA is an *Aspergillus*-related chronic lung disease caused by allergic hypersensitivity to inhaled *Aspergillus* spp. spores resulting in a variable clinical syndrome of airways obstruction and bronchiectasis.

Core criteria required for a confirmed diagnosis:

(a) Presence of underlying obstructive airways disease (eg asthma, COPD, bronchiectasis or CF) or other compatible clinic-radiological presentation (see below)
(b) **And** high total IgE (>500 IU/ml, although frequently >1000 IU/ml):
(c) **And** *Aspergillus* spp. specific IgE >0.35 kUA/$L^{-1}$ and/or a positive skin prick test

Compatible clinic-radiological features:

(a) Production of mucous plugs / bronchial casts/ visible mucoid impaction on bronchoscopy
(b) Typical radiological changes (**Figure 2**):
    - Chest radiograph: Fleeting opacities or consolidation, segmental / lobar collapse, finger in glove opacities (bronchoceles), signs of bronchiectasis (tram lines and ring shadows). Normal in 50% of patients with ABPA.
    - CT lung scans: bronchiectasis (typically in a proximal distribution), mucous impaction (can be calcified, or show the hyperattenuated mucus sign), centrilobular nodules, mosaic attenuation. Can be normal.

Additional features suggestive of ABPA:

(a) Raised peripheral eosinophil count > $0.5x10^9$/L
(b) Raised serum specific IgG to *Aspergillus* spp.
(c) Identification of *Aspergillus* spp. in a respiratory sample

**4.4 Chronic Pulmonary Aspergillosis (CPA) (diagnostic criteria box 4)**

CPA is defined as chronic (>3 months) progressive pulmonary infection caused by an *Aspergillus* spp. CPA most commonly occurs in patients with underlying lung disease. There is a wide spectrum of disease - from evolution of aspergillomas into active infection, to slowly progressive *de novo* infection in patients with pre-existing lung disease to more rapidly progressive infection in immunosuppressed patients. Patients often have malaise, fatigue, weight loss, fevers, night sweats, haemoptysis (which can be life-threatening), cough, and progressive breathlessness. A diagnosis of CPA requires radiological appearances consistent with CPA and microbiological, serological, and/or histological evidence of *Aspergillus* spp. infection (**Box 4**). To help guide management CPA can be separated into the following subsets largely based on radiological appearances **(Figure 1)** and rate of progression [17]:

Commoner CPA sub-types:

*4.4.1 Sub-acute invasive pulmonary aspergillosis* (SAIA, also termed *semi-invasive pulmonary aspergillosis* or *chronic necrotising pulmonary aspergillosis*): SAIA is a more rapidly progressive form of CPA usually affecting patients with some degree of immunosuppression. Similar to acute invasive aspergillosis, the radiological changes are dominated by macronodule(s) or patches of consolidation (sometimes with a surrounding 'halo' sign of lower attenuation consolidation), but in SAIA these enlarge over weeks to months rather than days to weeks. Due to the faster speed of progression compared to other forms of CPA, SAIA frequently needs urgent and more aggressive treatment, which can often be curative.

*4.4.2 Chronic cavitary pulmonary aspergillosis (CCPA):* In CCPA the radiological changes are dominated by single or multiple cavities which progressively expand due to local invasion of the cavity wall by *Aspergillus* spp. and the consequent inflammatory response. CCPA can arise *de novo* or develop from a pre-existing aspergilloma (especially in patients who become immunosuppressed). The cavity wall is less distinct than aspergillomas, and often has surrounding inflammatory change, lung fibrosis or pleural thickening. The patient usually has background lung disease causing parenchymal damage such as emphysema, tuberculosis or sarcoidosis. CCPA is probably the commonest form of CPA and is relatively slowly progressive, but is often hard to cure. Serum *Aspergillus* IgG is almost invariably raised, although caution in interpreting low/normal levels in those with IgG deficiency must be made.

*4.4.3 Chronic fibrosing pulmonary aspergillosis (CFPA):* CFPA is best considered a subset of CCPA with an associated strong lung and/or pleural fibrotic component. The radiological changes are dominated by loss of lung volume with fibrotic change within the lung and / or progressive pleural thickening, usually associated with progressive CCPA cavities.

**Box 4: Diagnostic criteria for chronic *Aspergillus* spp. infection**

Chronic (>3 months) focal progressive pulmonary infection caused by an *Aspergillus* spp., usually associated with chronic lung disease and / or some degree of immunosuppression.

CPA (SAIA, CCPA, and CFPA):

(a) Suggestive radiological changes present for over three months with evidence of progression (**Figure 2**) including:
(i) SAIA: enlarging macronodule(s) ~~>3cm in diameter~~ or areas of consolidation +/- surrounding ground glass opacity (the 'halo sign'), +/- cavitation
(ii) CCPA: single or multiple cavities with a poorly defined thickened wall, +/- with surrounding consolidation, +/- containing aspergillomas or frond like soft tissue (representing *Aspergillus* material), +/- lung fibrosis and/or pleural thickening with progressive lung volume loss.
(iii) CFPA: pronounced pleural thickening and/or lung fibrosis with progressive lung volume loss, +/- single or multiple CCPA cavities

(b) **And** evidence of *Aspergillus* spp. infection with at least one of the following:
(i) Positive A*spergillus* spp. culture from respiratory samples,
(ii) Histological confirmation of *Aspergillus* invasion of lung tissue
(iii) Positive serum specific *Aspergillus* spp. IgG (almost all patients with CCPA or CFPA, and the majority of patients with SAIA)

*Aspergillus* bronchitis/bronchiolitis disease

(a) Positive culture for *Aspergillus* spp. from respiratory samples +/- histological evidence of *Aspergillus* spp. infection in bronchial biopsies
(b) **And** localised CT scan changes of airway wall thickening, +/- peri-bronchial inflammation, 'tree in bud' change (often migratory), or nodules <1cm that may cavitate
(c) **And** negative biochemical markers for ABPA (total IgE, *Aspergillus* spp. specific IgE)
(d) Supportive criteria are:
- underlying immunosuppression and/or chronic lung disease
- clinicoradiological response to treatment with antifungal agents

*Aspergillus* tracheobronchitis:

(a) Suggestive macroscopic appearances of the trachea +/- major bronchi on bronchoscopy (erythematous plaques, ulceration, pseudomembrane formation)
**And** positive culture +/- histological evidence of *Aspergillus* spp. infection in bronchial biopsies
(b) A supportive criterion is a significant degree of background immunosuppression

*Aspergillus* spp. nodules:

(a) Well defined single or multiple pulmonary nodules < 3 cm diameter
(b) **And** identification of *Aspergillus* spp. from histological sampling of the nodule
(c) **And** exclusion of alternative causes e.g. malignancy

**4.5 Rarer forms of chronic pulmonary *Aspergillus* spp. infection (diagnostic criteria Box 4)**

*4.5.1 Aspergillus bronchitis/bronchiolitis infection*: Patients with underlying lung disease and / or milder degrees of immunosuppression can develop infection of the medium and small airways with *Aspergillus* spp. which we have termed *Aspergillus* bronchitis/bronchiolitis. There are only very limited published data on this entity [18]. *Aspergillus* bronchitis/bronchiolitis can cause cough, chronic sputum production, haemoptysis, shortness of breath, and wheeze that persists over weeks. Diagnosis depends on computer tomography (CT) scan appearances of radiological evidence of varying areas of focal peribronchial inflammation and small nodules combined with positive respiratory sample cultures or histological evidence for *Aspergillus* spp infection on bronchial biopsies. Simultaneous exclusion of alternative infective causes (mainly bacterial bronchitis) is important. The patients generally have normal total IgE levels and a negative *Aspergillus* spp. specific IgE, although serum *Aspergillus* spp. specific IgG is often positive [18]. Patients should have a symptomatic and radiological response to antifungal treatment, which helps confirm the diagnosis.

*4.5.2 Aspergillus tracheobronchitis*: A more severe form of *Aspergillus* airways infection is infection of the trachea and main bronchi, termed *Aspergillus* tracheobronchitis. *Aspergillus* tracheobronchitis is usually one manifestation of acute invasive aspergillosis, but can also rarely affect less severely immunosuppressed patients and lung transplant recipients (often occurring at the bronchial anastomosis). Patients present with a relentless cough. The diagnosis is confirmed by bronchoscopy which shows distinctive macroscopic appearances of the trachea and / or major bronchi, positive cultures for *Aspergillus* spp., and/or histological evidence of *Aspergillus* invasion in bronchial biopsy samples. Serum *Aspergillus* spp. specific IgG and GM antigen may be positive but are not validated for the diagnosis. The mortality is high unless effective treatment is started rapidly.

*4.5.3 Aspergillus nodules*: *Aspergillus* nodules can occur in the context of active CPA/ABPA (61), but they can also present as a separate clinical entity as single or multiple parenchymal lung nodules (< 3 cm in diameter) that may not follow the same pathological evolution as CPA [19] but instead are usually indolent and asymptomatic. The nodules are usually well-defined, predominantly affect the upper lobes (>60%) [20], and have a diameter that is significantly smaller than SAIA macronodules with a mean of 21 mm. *Aspergillus* nodules have been reported to be cavitary in 35% of cases but it is not known if these represent early or previously active CCPA [19]. *Aspergillus* nodules are frequently diagnosed at resection or biopsy of a radiological nodule being investigated as suspected lung cancer [18]. The natural history of *Aspergillus* spp. nodules if untreated can vary; many cases are non-progressive, but in some patients they represent an early SAIA or CCPA lesion and close follow-up is necessary. Patients usually have underlying lung disease rather than significant immunosuppression. The diagnosis is based on radiological appearances and the histology of nodule biopsies or resections. *Aspergillus* IgG is positive in 40-70% cases [20, 21].

The above diagnostic categories should be considered as part of a spectrum of overlapping presentations of *Aspergillus*-related chronic lung diseases that assist management decisions. Some cases do not easily fit into these categories, and evolution of the clinical pictures between categories is not uncommon. With the increasing range of immunosuppressive agents used in medical practice less common presentations may become more frequent. In addition, patients may have co-existing diagnoses of ABPA and CPA [22]. Diagnosis requires an accurate

assessment of the radiology combined with clinical, microbiological and serological data (**Table 2, Box 4**) and is often difficult. Subspecialty input from physicians and radiologists with specific experience in *Aspergillus*-related chronic lung disease is often necessary to make an accurate diagnosis of CPA. The differential diagnosis often includes lung cancer, other chronic pulmonary infections (e.g. tuberculosis, nocardia), and inflammatory lung nodules or cavities (e.g. vasculitis, rheumatoid nodules); these conditions need to be actively considered and excluded during the diagnostic work up.

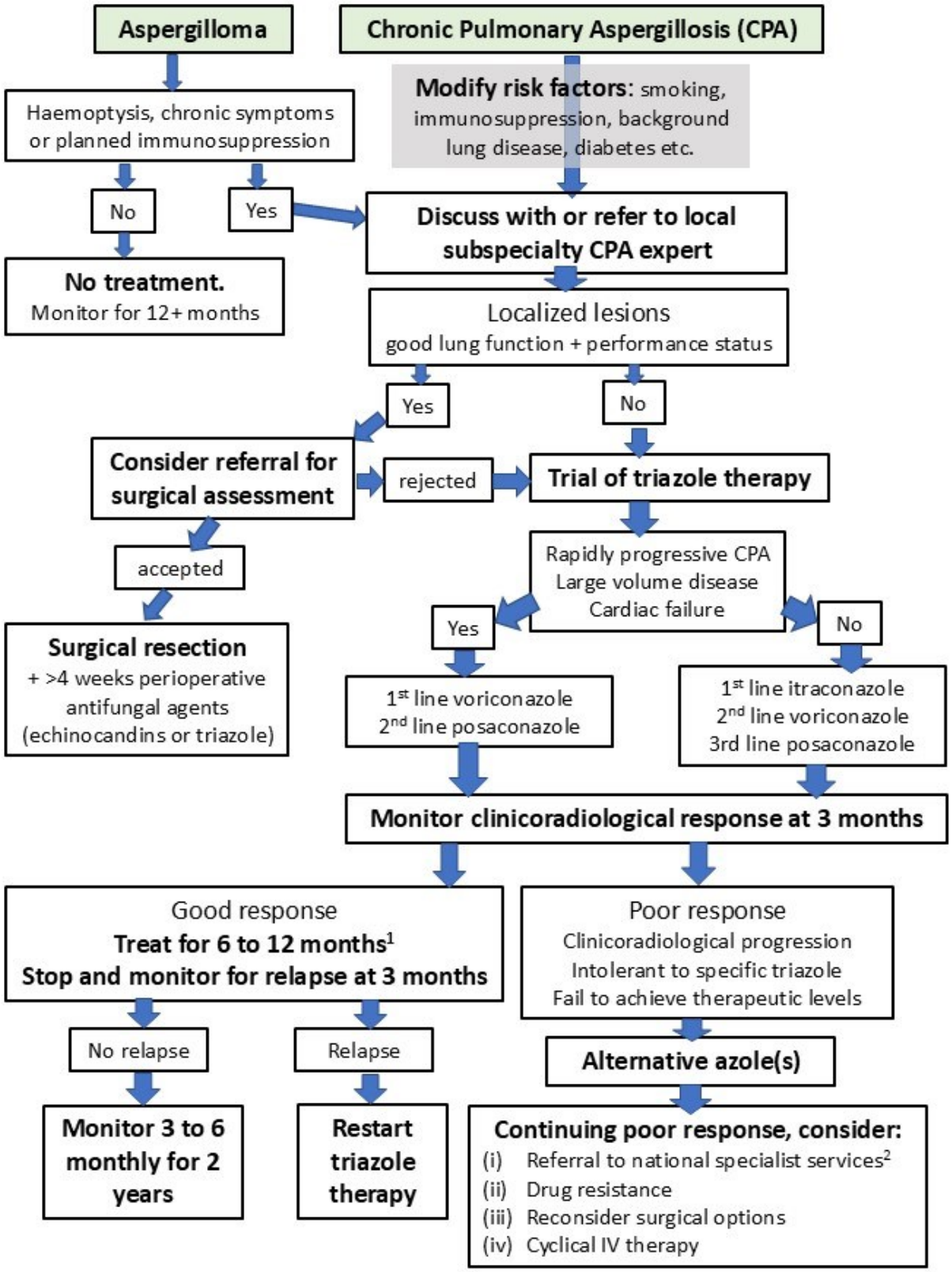
**Clinical practice points for diagnosis of *Aspergillus*-related chronic lung disease (Figure 2)**

1. Investigate potential cases of *Aspergillus*-related chronic lung disease using a combination of clinical, radiological, microbiological and serological markers to identify the presence of *Aspergillus* spp. and the likely associated pathology.
2. Perform a careful clinical evaluation of patients after identification of *Aspergillus* spp. from a respiratory sample to characterise whether this represents transient or asymptomatic colonisation or indicates an *Aspergillus*-related chronic lung disease.
3. Investigate radiological findings consistent with *Aspergillus*-related chronic lung disease addressing the diagnostic criteria listed in boxes 2, 3, and 4
4. Screen (or rescreen) for ABPA in patients with poorly controlled or unexplained deterioration in asthma, COPD, CF or bronchiectasis using total serum IgE and *Aspergillus* spp. specific serum IgE and/or *Aspergillus* spp. skin prick tests.
5. Seek advice from a clinician with significant experience in *Aspergillus*-related chronic lung disease where the diagnosis is not clear.
6. Physicians caring for patients with *Aspergillus*-related chronic lung disease should have access to appropriate diagnostic testing (e.g. *Aspergillus* serology, antifungal susceptibility testing, therapeutic drug monitoring [TDM]).

## 5. Management of Aspergilloma (Figure 3)

The majority of pulmonary aspergillomas do not cause symptoms and do not require surgical intervention or antifungal treatment. Major haemoptysis is managed acutely by supportive measures and considering treatment with tranexamic acid, bronchial artery embolization, and / or surgical resection [23, 24]. For patients with complicated aspergillomas associated with major haemoptysis or repeated minor haemoptysis first-line therapy is treatment with antifungals, with the most published evidence for using oral itraconazole [23, 25, 26]. The evidence base for either percutaneous or transbronchial instillation of antifungal agents is limited [27]. Single aspergillomas (or aspergillomas limited to one lobe) in patients with adequate lung function and performance status can be cured by surgical resection [24, 28, 29]. However, the reported post-operative mortality is as high as 4% and the future risk of life-threatening haemoptysis is hard to quantify after a single episode of major haemoptysis or in patients with ongoing minor haemoptysis [30]. Hence the decision to offer surgical resection is complex, and in general should be reserved for patients with a history of recurrent major haemoptysis despite treatment with antifungal agents, or in patients with new or increased immunosuppression (due to the potential for the aspergilloma to progress to CPA).

**Figure 3:** Management of aspergilloma and CPA




**Notes:**

[1]Duration of treatment: (i) 12 months for CCPA and CFPA; (ii) for SAIA, nodules and airways disease duration will depend on the exact clinical picture and the clinicoradiological response to treatment, although the minimum period will usually be 6 months.

[2]At present provided by the National Aspergillosis Centre which is commissioned by NHS England for the treatment of CPA in England and Scotland. Advice will also be provided for CPA patients from other regions.

**Clinical practice points for management of aspergilloma**

1. Monitor patients with recently diagnosed aspergilloma for a minimum of 12 months for evidence of clinical or radiological progression.
2. Do not routinely offer surgical intervention or antifungal treatments for asymptomatic aspergilloma.
3. For patients with aspergilloma and the following complications consider surgical resection or antifungal therapy as described for the management of CPA (section 7 and **Box 5**):
   (i) recurrent or persistent minor haemoptysis
   (ii) an episode of major haemoptysis
   (iii) significant systemic symptoms (e.g. fever, fatigue, night sweats, weight loss)
   (iv) progressive radiological change of the cavity wall (fulfils definition of CPA)
   (v) ongoing and/or future planned significant increases in immunosuppression (e.g. long term oral corticosteroids or other systemic immunosuppressants, chemotherapy, organ or stem cell transplantation).

## 6. Management of ABPA

Treatment can be divided into that targeted against an acute exacerbation of symptoms, and maintenance therapy used to optimise symptom control, maintain lung function, and prevent acute exacerbations whilst reducing the requirement for treatment with oral corticosteroids to limit the associated side effects.

### 6.1 Treatment of acute exacerbations of ABPA

Patients with ABPA who present with worsening respiratory symptoms or new radiological changes need careful clinical evaluation to identify non-ABPA triggers of the underlying airways disease and/or infective exacerbations of the underlying bronchiectasis which should be treated according to the existing relevant guidelines [10, 31]. Exacerbations caused by a flare of the underlying ABPA are defined by: (i) an increase in respiratory symptoms for > 2 weeks (increased shortness of breath and / or cough and / or mucous production usually associated with a fall in $FEV_1$ and peak flow) unexplained by other causes, and / or (ii) new ABPA-related radiological changes (focal consolidation, lobar collapse, new mucoceles), and (iii) a >50% rise in baseline total IgE level [13]. ABPA flares may also increase levels of *Aspergillus* serological markers or blood eosinophilia. ABPA flares generally require more intensive treatment than other causes of exacerbations as follows [32-34]:

(a) Oral prednisolone 0.5mg/kg (maximum dose 40mg) for up to two weeks, then weaning depending on the individual patient's need to the maintenance dose or to completely stop over 2 to 8 weeks. Higher doses of prednisolone do not provide greater clinical benefit but are associated with higher steroid side-effects. Other corticosteroid agents have less evidence to support their use.

(b) Triazole antifungal therapy (**Box 5**) should be considered in patients with a sub-optimal response to oral corticosteroids or at increased risk of corticosteroid-induced side effects (e.g. psychosis). Using azoles in combination with corticosteroids may increased the risk of adrenal insufficiency.

**Clinical Practice points for management of acute exacerbations of ABPA**

1. Use clinical assessment to determine if an acute exacerbation in a patient with ABPA is related to a flare of the underlying ABPA or an alternative cause.
2. Treat exacerbations caused by a flare of the ABPA with prednisolone 0.5mg/kg (ideal body weight) (maximum dose of 40mg) for up to two weeks, weaning to the maintenance dose or zero over 2 to 8 weeks tailored to the patient/clinical situation.
3. Consider temporary (no longer than 3 months) combined treatment with triazole therapy (**Box 5**) and prednisolone when weaning of oral corticosteroids leads to clinical deterioration.
4. Consider treatment with triazole therapy (**Box 5**) if systemic corticosteroids should be avoided, or fail to improve symptoms and restore lung function.

**Box 5: Treatment with antifungal agents for *Aspergillus*-related chronic lung disease**

Generalised advice on treatment for aspergillomas, ABPA and CPA with antifungal agents

1. Patients being considered for antifungal therapy should be discussed with a clinician with significant experience in caring for patients with *Aspergillus*-related chronic lung disease

2. The majority of patients will be treated with triazole therapies. However, the following situations are relative contraindications for initiating triazole therapy:
- clinically significant liver disease
- pregnancy
- concurrent treatment with rifampicin

3. Suggested triazole treatment depends on the type of *Aspergillus*-related chronic lung disease, speed of progression, degree of immunosuppression, and comorbidities as outlined below:

(i) Aspergilloma, ABPA and most forms of CPA:
First line: itraconazole 200mg BD:
Second line: voriconazole 200mg BD
Third line: posaconazole 300mg OD

(ii) Patients with more rapidly progressive CPA (e.g. SAIA or with >50% increase in radiological evidence of infection within 3 months), tracheobronchitis, large volume disease, with significant persisting immunosuppression, or co-existing cardiac disease:
First line: voriconazole 200mg BD
Second line: posaconazole 300mg OD

4. For all patients receiving triazole therapies:

(i) consider reducing the dose of inhaled corticosteroid therapy to reduce systemic side effects, depending on type of corticosteroid (a) fluticasone, budesonide, mometasone – initial 50% dose reduction (b) beclomethasone, ciclesonide – no dose adjustment needed; monitor for side effects (supplementary **Table 1**)
(ii) assess for other potential drug interactions and alter medications accordingly
(iii) request pre-treatment ECG and baseline bloods (LFTs, FBC and U&Es)
(iv) repeat LFTs and U&Es and request therapeutic drug measurements (TDM) 2 to 4 weeks after initiating therapy along with an ECG for patients with pre-treatment prolonged QTc or additional risk factors for a prolonged QTc (eg long term azithromycin)
(v) repeat LFTs, U&Es, and TDM at 3 months then 6 (itraconazole and voriconazole) or 12 (posaconazole) monthly, or after dose / formulation changes, or interacting medicines started or stopped
(vi) counsel patients about common and important side effects (see **Box 7**)
(vii) persist with one formulation of itraconazole and posaconazole, and if changing between capsules/tablets or the liquid formulation use TDM to ensure correct dosing.

(viii) consider testing for adrenal insufficiency (eg measuring a 9am cortisol, and if abnormal potentially performing a synacthen test) in patients also receiving either maintenance oral corticosteroids for >6 months, long term inhaled corticosteroids, or receiving two or more courses of oral corticosteroids in 6 months.

5. Assess treatment response 6 weeks to 3 months after initiating antifungal therapy depending on the individual patient and disease characteristics, and then every 3 to 6 months.

6. If there is no or only a minimal clinical response to therapy with a triazole after 3 months despite achieving therapeutic levels consider:

(i) sending respiratory samples for repeat culture and testing for triazole resistance of *Aspergillus* spp. Isolates

(ii) changing to second or third line agents

**Box 5 continued:**

7. For CPA, if itraconazole, voriconazole or posaconazole are not suitable agents due to the patient's comorbidities, side effects, failure to achieve therapeutic levels, or lack of clinical efficacy consider discussing with / or referral to a clinician with specific expertise in *Aspergillus*- related chronic lung disease about the potential use of:

(i) isavuconazole.

(ii) intravenous treatment with an echinocandin or liposomal amphotericin B

8. Discuss with a physician with specific expertise in *Aspergillus*-related chronic lung disease potential cases of antifungal resistance (e.g. disease progression with positive sputum cultures for *Aspergillus* spp. despite therapeutic triazole drug levels )

9. For severe cases of CPA (e.g. patients admitted to hospital) or patients unable to tolerate oral triazole therapy, consider initial intravenous therapy with an echinocandin or liposomal amphotericin B or voriconazole followed by maintenance oral triazole therapy

10. Consider treatment with nebulised amphotericin for patients with ABPA in which triazole therapies have failed due to side effects, failure to achieve therapeutic levels, drug resistance, or lack of clinical efficacy

Treatment duration and withdrawal – see clinical practice points for specific disease manifestations

## 6.2 Long term treatment of ABPA (Box 6)

### *6.2.1 General treatment*

Patients with ABPA will benefit from regular use of airway clearance techniques, treatments that improve mucociliary clearance, written treatment plans for the management of exacerbations and asthma, inhaler technique training, avoidance of smoking and other triggers, ensuring adherence to treatment, and pulmonary rehabilitation [10, 35]. In addition, patients with ABPA exposed to high *Aspergillus* spp. spore and hyphal fragment counts should be identified by taking an occupational and environmental history, and provided with advice on reducing their exposure. Potential at risk occupations include those that handle, disturb or process organic material (e.g. farmers, waste collectors, gardeners, or workers that handle grains or hay). Indoor environments associated with higher exposure to *Aspergillus* spp. include those with visible mould or damp, a history of water ingress, and those with air conditioning units, humidifiers or with poor ventilation.

*6.2.2 Bronchodilators, and inhaled and systemic corticosteroids*

Maintenance treatment for ABPA can follow the stepwise approach analogous to non-ABPA asthma described in **Box 6**. Underlying inhaled and/or oral asthma treatment should be optimised, as per the BTS/NICE/SIGN Asthma Guidelines [36]. Compared to other causes of asthma, patients with ABPA often require higher doses of inhaled corticosteroids. Although long term treatment with oral corticosteroids causes significant side effects and should be avoided when possible, in some patients with ABPA preventing exacerbations and maintaining lung function will require maintenance oral corticosteroids. Adrenal insufficiency is common, particularly in patients receiving maintenance long term corticosteroids, repeated oral corticosteroid courses, or corticosteroids combined with triazole therapy. Although it has not been tested specifically, analogous for other causes of asthma in ABPA a raised fractional exhaled nitric oxide (FeNO) level indicates poor adherence and/or a need to increase the inhaled steroid dose [33].

*6.2.3 Prophylactic antibiotics*

Prophylactic antibiotics have not been studied specifically for ABPA, but are likely to be beneficial for patients with recurrent infective exacerbations and should be used in accordance with existing bronchiectasis or asthma BTS guidelines [10, 35-37]. Both macrolides and most triazoles can cause prolongation of the QTc and caution is required if they are used in combination.

*6.2.4 Antifungals*

Treating ABPA with triazole antifungals can prevent exacerbations, maintain lung function, and/or reduce the requirement for treatment with systemic corticosteroids. Triazole treatment of ABPA is off-label and should be initiated only by clinicians with specific expertise in using antifungal therapies. Itraconazole is the most studied agent (including RCTs), and is considered the first line agent [38, 39]. Voriconazole and posaconazole have also been reported to have clinical benefits in ABPA and are alternative agents if itraconazole is poorly tolerated or fails to achieve therapeutic levels [40-44]. TDM of triazole therapy is important. Oral and inhaled corticosteroid dose will frequently need adjusting due to triazole-mediated inhibition of their metabolism (see Section 8 and **Supplementary Table 1**). The duration of triazole treatment for ABPA remains unclear; RCTs used treatment periods measured in months, but in practice deteriorations in ABPA control often occur when the triazole is withdrawn and long term treatment is frequently necessary. Nebulised amphotericin (fungizone) can be considered when there is intolerance or resistance to azole antifungals, but can cause acute and cumulative bronchospasm necessitating careful patient selection, a test dose challenge, and close clinical follow up including repeat lung function testing [43-45].

*6.2.5 Asthma monoclonal antibody treatments.*

The underlying pathology of ABPA indicates biological therapies should improve airways disease control for ABPA. However, ABPA was an exclusion criterion in many phase 3 trials of biological agents, and monoclonal antibody treatment of ABPA is only supported at present by a small randomised trial of omalizumab[46]. In addition, case-series and registry data suggest omalizumab [47-49], mepolizumab [50-56], benralizumab [57-59] and dupilumab [60-64] may reduce exacerbation frequency and improve overall asthma control in ABPA. Overall, patients with ABPA fulfilling the definition of difficult asthma (eg requiring maintenance oral

corticosteroids or >3 courses of prednisolone for exacerbations / year) should be discussed with a severe asthma centre to assess their eligibility for treatment with a monoclonal antibody.

**Clinical Practice points for the long term management of ABPA**

1. Optimise the general management of asthma and bronchiectasis according to BTS guidelines (including airway clearance, smoking cessation advice, avoiding other environmental triggers and exposure to *Aspergillus* spp.) and provide written action plans for treatment of exacerbations.
2. Monitor the response to treatment using clinical assessments supported by measuring total IgE and eosinophil counts, repeating the radiology (chest X-rays usually suffice, with CT scans as required), and monitoring lung function (peak flow and spirometry).
3. Titrate up inhaled corticosteroid and bronchodilator treatment to minimise symptoms and exacerbations, and maintain stable peak flow and/or spirometry recordings.
4. For patients with two or more exacerbations within 6 months requiring oral corticosteroids, failure to maintain stable $FEV_1$ / peak flows consider either:
   - long term oral prednisolone, with an initial dose 10mg/day weaning to 5mg/day after 3 months, and if disease control is maintained attempt weaning completely after 6 months
   - or trial of triazole therapy (**Box 5**)
   - or referral to severe asthma centre for evaluation for treatment with monoclonal antibodies
5. For patients with two or more exacerbations within 6 months requiring oral corticosteroids, or failure to maintain stable $FEV_1$ / peak flows despite monotherapy with maintenance prednisolone or antifungal therapy alone, consider combination treatment with oral prednisolone and an antifungal agent, or referral to severe asthma centre for evaluation for treatment with monoclonal antibodies.
6. Consider testing for adrenal insufficiency (eg measuring a 9am cortisol, and if abnormal perform a synacthen test) in patients either receiving two or more courses of oral corticosteroids in 6 months, or on maintenance oral corticosteroids for >6 months, or receiving long term (>6 months) triazole therapy in combination with inhaled corticosteroids.

**Box 6: Long term management of patients with a confirmed diagnosis of ABPA:**
Management takes a stepwise approach with progression to the next treatment step dependent on control of the clinical symptoms and airways obstruction

***Step 1:*** Regular inhaled corticosteroid and PRN short acting ß2 agonists

- provide smoking/vaping cessation advice
- define the treatment plan for infective exacerbations
- define the treatment plan for airways exacerbations
- maximise airway clearance, including appropriate use of airways clearance devices/adjuncts and mucolytics
- identify and advise on reduction in occupational or environmental exposure to *Aspergillus* spp.

Move to step 2 if persisting symptoms / variable PEFR / raised FeNO / two or more courses of oral corticosteroids within 6 months for exacerbations or required to maintain $FEV_1$

***Step 2:*** Optimise maximum inhaled therapy as per BTS guidance. Consider:

- high dose regular inhaled corticosteroids in combination with LABA
- adding a LAMA

If persisting regular symptoms / variable PEFR / raised FeNO / two or more courses of oral corticosteroids within 6 months for exacerbations or required to maintain $FEV_1$:
(i) refer to a respiratory physician with an interest in asthma/ABPA
(ii) move to step 3A, 3B or 3C depending on patient / physician preference, disease phenotype, comorbidities, and patient's drug intolerances or side effects

***Step 3***
(i) 3A: add in long term oral prednisolone: initial dose 10mg/day aiming to wean to 5mg/day after 2 to 3 months, and if disease control is maintained attempt weaning completely after 6 months
(ii) 3B: treatment trial of triazole antifungal agent(s)*
(iii) 3C: refer to a specialist asthma centre for consideration of biological therapies

Move to Step 4 if persisting regular symptoms / variable PEFR / raised FeNO / requirement for oral corticosteroid courses for exacerbations or to maintain $FEV_1$

***Step 4:*** consider more prolonged oral maintenance corticosteroid therapy, and / or monoclonal antibody therapy (if eligible)

*******consider trial of nebulised non-liposomal amphotericin 10mg twice daily when there is intolerance of triazole therapies or proven *Aspergillus* spp. resistance to triazole(s)

## 7. Management of chronic *Aspergillus* spp. Infections

### 7.1 Management of CCPA, CFPA, and SAIA (Figure 3)

*7.1.1 General management of CCPA, CFPA, and SAIA*

The clinical picture of CCPA, CFPA, and SAIA varies in severity and speed of progression, and affects individuals with different chronic respiratory diseases and varying levels of immune dysfunction. These factors all affect the decision whether and when to treat a patient and expert advice is crucial. The following factors indicate surgery (if appropriate) or antifungal treatment are likely to be necessary:

(i) Radiological progression clearly detectable on repeat imaging after three months
(ii) Significant systemic symptoms (fever, fatigue, night sweats, weight loss)
(iii) Ongoing minor haemoptysis or a single major haemoptysis
(iv) Progressive lung function decline (although this may be caused by the underlying respiratory condition(s) instead).
(v) Ongoing and/or future planned increases in immunosuppression.

Most patients have underlying lung conditions which could cause similar symptoms to CPA which will need appropriate investigation and management. In addition, underlying comorbidities can affect both patient suitability for antifungal treatment and the choice of agent used.

*7.1.2 Surgical resection of CCPA or SAIA*

For patients with localised CCPA or SAIA lesions and adequate lung function and performance status, resection (segmentectomy, lobectomy, or pneumonectomy) may be curative, and should be specifically considered in the following situations [65, 66]:

(i) when refractory to medical therapy
(ii) presenting with major haemoptysis
(iii) when the diagnosis is uncertain
(iv) if future increases in immunosuppression are planned

Surgery should be performed by a surgical team experienced in resection of CPA lesions. The clinical statement group consensus suggests adjunct antifungal therapy is needed in the peri-operative period to reduce the degree of active infection to make resection easier and limit the possibility of seeding and / or post- operative recurrence of *Aspergillus* infection. The extent of fibrosis in CFPA usually precludes surgery as a management option. The extent of fibrosis in CFPA usually precludes surgery as a management option.

*7.1.3 Antifungal treatment of CCPA, CFPA, or SAIA*

Several studies have evaluated antifungal treatment of CCPA, CFPA and SAIA. The key aims of antifungal treatment are:

(i) arrest radiological progression and, if possible, cause disease regression
(ii) improve systemic and respiratory symptoms, and overall health
(iii) maintain lung function
(iv) reduce the risk of haemoptysis [2, 65]

Based on the larger published dataset for its use, itraconazole remains the first line therapy for CCPA and CFPA [2, 65, 67, 68]. Voriconazole or posaconazole are reserved for use as second line therapies or for patients with SAIA or other more rapidly progressive or semi-invasive forms of disease who need effective treatment established rapidly (**Box 5**) [2, 69-71].

In the UK, at present isavuconazole is commissioned by nationally commissioned services for patients unable take other azoles. Published data suggest CCPA and CFPA patients treated for 12 months with triazole therapy reduces relapse rates compared to treatment for 6 months [68, 70, 72]. For some cases of SAIA shorter durations therapy of between 6 to 12 months may be appropriate depending on the balance between disease extent, immune status, comorbidities, and treatment efficacy. When triazole agents cannot be used due to side effects, poor response, or triazole- resistance, CPA can be treated with liposomal amphotericin B or an echinocandin (both have similar response rates), initially typically for 1 to 6 weeks and potentially cyclically thereafter [2, 71, 73, 74].

The response to antifungal therapy in CPA is monitored primarily by assessing changes in the radiological appearances (discussed below) along with respiratory and systemic symptoms (preferably assessed using a symptom score scale e.g. St George's quality of life questionnaire) [75]. Radiological changes suggesting treatment response are:

(i) regression in size of macronodules or cavities, or reduction in the extent of consolidation
(ii) new cavitation in a previous solid macronodule or area of consolidation
(iii) reduced cavity wall thickness
(iv) reduction in parenchymal disease associated with cavities
(v) improved definition of lesion margins

Reductions in blood markers (e.g. *Aspergillus* IgG levels, ESR, and CRP), increases in serum albumin and body weight, and negative repeat respiratory sample cultures provide further support for a response to treatment.

For SAIA, associated with some degree of immunosuppression, complete resolution of the lesions is often possible and should be the goal of therapy. In contrast, CCPA and CFPA usually do not regress completely with antifungal therapy and the goal of medical treatment is clinical and radiological stabilization. Major haemoptysis can be controlled acutely with bronchial artery embolization and tranexamic acid [2]. Patients with CCPA, CFPA and SAIA often have severe underlying lung disease and are at risk of other complications such as lung cancer and infection with respiratory bacterial pathogens (e.g. *Pseudomonas aeruginosa*, *Haemophilus influenzae*, and less commonly *Nocardia* spp. and mycobacteria). Whether active fungal disease is the primary cause of new clinical changes or an alternative diagnosis requires careful ongoing assessment.

### 7.2 Management of *Aspergillus* nodules

The natural history of *Aspergillus* nodules is unclear and there are only very limited published data on their management. In patients with adequate lung function and performance status, single *Aspergillus* nodules can be cured by surgical resection. Progressive multiple nodules should be treated with antifungal agents as described for CCPA, CFPA and SAIA **(Box 5)**; treatment response is assessed by reduction in nodule size. Antifungal therapy may not be necessary for patients with stable *Aspergillus* nodules unless they are undergoing increased immunosuppression.

### 7.3 Management of airways-based *Aspergillus* infection

Tracheobronchitis should be treated aggressively with antifungal agents as described for SAIA, monitoring response by repeat bronchoscopy and CT scanning. *Aspergillus* bronchitis/bronchiolitis infections are generally more indolent than tracheobronchitis, but

may require treatment with triazole antifungal agents (**Box 5)** to prevent radiological progression and/or to control symptoms. Duration of treatment should be determined according to clinical response.

**Clinical practice points for management of chronic *Aspergillus* spp. infections**

1. Optimise the management of underlying lung disease and other comorbidities (e.g. diabetes) and if relevant consider whether immunosuppressive therapy can be modified.
2. Patients being considered for surgical intervention or long-term treatment with antifungal agents should be discussed with clinicians with significant expertise in *Aspergillus*-related chronic lung diseases.
3. Consider surgical resection for CPA lesions in patients with low operative risk and adequate lung function, particularly in patients with a poor response to antifungal therapy or previous life-threatening haemoptysis.
4. Treat patients undergoing surgical resection of CPA with antifungal agents (triazole or echinocandin) for a duration of at least 2 weeks pre-operatively and 2 weeks post-operatively, extending therapy (eg for three months) if persisting infection is suspected.
5. Do not routinely offer antifungal therapy to patients with *Aspergillus* nodules identified by surgical excision or biopsy (e.g. to exclude suspected lung cancer) with no clinical or radiological evidence of progressive infection.
6. Consider antifungal therapy for cases of CPA not suitable for surgical resection, *Aspergillus* nodules with clinical or radiological evidence of progressive infection, and for *Aspergillus* bronchitis/bronchiolitis or tracheobronchitis. Suggested agents are described in **Box 5**.
7. Assess antifungal treatment response 6 weeks to 3 months after initiating antifungal therapy depending on the individual patient and disease characteristics, and then every 3 to 6 months using:
   (i) clinical assessment (e.g. weight change, malaise, cough, sputum, haemoptysis, and preferably a validated QoL score such as the St George's Questionnaire [71])
   (ii) TDM for patients receiving itraconazole, voriconazole, or posaconazole
   (iii) radiology (see point 10)
   (iv) additional tests according to clinical need, including sputum cultures, CRP, FBC, U&Es, serum *Aspergillus* IgG, ECG, lung function tests and/or 6-minute walk tests.
8. In most instances, continue antifungal therapy for CPA for at least 12 months. Further treatment will depend on the clinical and radiological response, recurrence after stopping therapy, and other clinical factors (e.g. level of immunosuppression, side effects caused by antifungal agents and, background comorbidities). Treatment duration for SAIA could be shorter if there is rapid clinical improvement.
9. The duration of antifungal treatment for *Aspergillus* nodules, bronchitis/bronchiolitis or tracheobronchitis will vary depending on the clinical presentation, response to antifungal treatment, and whether relapses occur when stopping antifungals.
10. Consider repeat CT scans at 3 to 6 months after initiating antifungal therapy, at key management decision points, then annually whilst on antifungal therapy.
11. Monitor for disease relapse 3 months after stopping antifungal therapy then 3 to 6 monthly thereafter for a minimum of 12 months.
12. Consider further discussions with clinicians with significant expertise in *Aspergillus*-related chronic lung diseases for patients with poor response to first or second line antifungal therapy.

13. Patients and their carers with chronic aspergillus infections can benefit from patient support groups, details of which should be provided by their local specialist clinician

## 8. Antifungal therapies

### 8.1 Overview

Currently there are three classes of antifungal therapeutics available for the treatment of *Aspergillus* spp. [76]. The mainstay of therapy are oral triazoles. Rarely, patients may need intravenous treatment with either echinocandins or liposomal amphotericin B (both of which can be administered in an outpatient setting). *Aspergillus*-related chronic lung disease often requires prolonged antifungal therapy and has high rates of drug intolerance or toxicity.

### 8.2 Triazoles (Supplementary Table 1)

Triazoles inhibit the synthesis 14-α-sterol demethylase, a cytochrome P-450 enzyme involved in the synthesis of ergosterol, which impairs *Aspergillus* spp. membrane integrity [76]. At present there are four triazoles active against *Aspergillus* spp. in clinical use - itraconazole, voriconazole, posaconazole and isavuconazole. Additional triazole therapies are likely to be available in the future, but their potential role in the management of *Aspergillus*-related chronic lung disease has yet to be defined. *Aspergillus* spp. are intrinsically resistant to fluconazole [76]. Triazoles have a wide range of side-effects and toxicities, and patients receiving triazole therapies generally require pre-treatment blood tests (LFTs, FBC and U&Es) which need repeating 2 to 4 weeks after commencing treatment and intermittently thereafter. The most important side effects and toxicities are listed in **Table 3.** Dosing recommendations, pharmacokinetics, adverse effects, and interactions for each agent are summarised in **Supplementary Table 1.** Triazoles have narrow therapeutic windows, with low levels potentially associated with the development of resistance and high levels may lead to toxicity. Both itraconazole and voriconazole exhibit non-linear pharmacokinetics. Itraconazole absorption is poor and heavily influenced by food and gastric pH; the liquid formulation improves bioavailability but has greater gastrointestinal side effects. There is large interpatient variability in the metabolism of voriconazole due to differences in CYP2C19 activity.

Itraconazole and voriconazole drug levels should be monitored closely, especially in patients with previous high levels, toxicity with another triazole, poor clinical response, side effects, hepatic impairment, extremes of body weight, and when altering other medications [1, 77]. Posaconazole exhibits linear kinetics and the tablets are well-absorbed, and drug levels can be monitored less frequently. Isavuconazole has predictable pharmacokinetics and absorption and the need for TDM is less well established but is often used when there is poor clinical response or potential drug interactions [77-81]. Triazoles both inhibit and are substrates for drug metabolising enzymes, and additional interactions occur due to altered absorption or additive toxicity [78]. This results in many clinically significant interactions, including with anticoagulants, systemic and inhaled corticosteroids, statins, immunosuppressive therapies, proton pump inhibitors, and enzyme inhibitors (eg ritonavir) or inducers (eg rifampicin) (**Supplementary Table 1**; see also https://antifungalinteractions.org/). General advice for patients receiving triazole therapy is provided in **Box 7**.

**Table 3: Common and important side effects of triazole therapies**

| Side effect | Notes |
|---|---|
| Gastrointestinal | Nausea, vomiting and diarrhoea common with all triazoles<br>Associated with raised levels, usually self-limiting |
| Hepatotoxicity | Approximately 25% of patients usually in the first 4 weeks<br>Associated with raised drug levels, prolonged treatment, risk factors for other causes of hepatotoxicity<br>Discontinue if severe or not reversed by dose reduction<br>Generally reversible, and can cautiously trial use of a different triazole |
| Peripheral neuropathy | Up to 10% of patients (especially on prolonged treatment)<br>Requires dose reductions or cessation of therapy<br>Generally slowly reversible, and can cautiously trial use of a different triazole |
| Prolonged QTc | Prolonged by itraconazole, voriconazole and posaconazole<br>Torsades de pointe is rare without other risk factors<br>Monitor ECG, and avoid other QTc prolonging medications if possible |
| Adrenal insufficiency | On withdrawal of itraconazole, voriconazole or posaconazole if on concurrent high dose inhaled or systemic corticosteroids |
| Pseudohyperaldosteronism | Rare; due to posaconazole or itraconazole inhibition of CYP11B1 and 11β-HSD2. |
| Fluid retention / oedema | Common with itraconazole: need to exclude congestive heart failure<br>Change to an alternative triazole, or if mild treat with small doses of furosemide |
| Congestive heart failure | Itraconazole and to a lesser extent posaconazole are negative inotropes; avoid in patients with risk factors for heart failure |
| Alopecia | Usually partial hair loss only, not always reversible |
| Voriconazole specific | (i) Phototoxicity and squamous cell carcinoma of the skin (mainly in patients with solid organ or stem cell transplants). Avoid sunlight and use high factor sunscreen. If phototoxicity occurs stop voriconazole, consider dermatology referral<br>(ii) Transient visual disturbance (blurred vision, photophobia, altered light / colour perception) occurs in 45% of patients soon after taking voriconazole. Usually decreases in intensity over time and is fully reversible<br>(iii) Neurotoxicity (altered mental status, visual/auditory hallucinations), especially with toxic voriconazole levels. Stop voriconazole |

**Box 7: Key counselling points for patients receiving triazole therapy**

**(i) General**

- Drug doses are often altered depending on the blood test results
- Treatment should not be stopped or reduced without guidance from your specialist
- Triazoles interact with many medications, and you should seek medical/pharmacist advice when commencing a new medication
- Gastrointestinal side effects (e.g. altered bowel habits) are common: if severe or lasting over 2 weeks you should contact your specialist team
- Rarely the drugs can cause liver or nerve damage
- Women of childbearing potential should contact their clinical team if planning a pregnancy

**(ii) Itraconazole specific**

- The capsules should be taken with food and an acidic drink e.g. orange juice, cola
- The liquid form should be taken on an empty stomach an hour before or two hours after food
- Antacids should be taken at a separate time to the capsules
- Ankle swelling (oedema) is not uncommon but rarely itraconazole can cause heart failure

**(iii) Voriconazole specific**

- Should be taken every 12 hours, 1 hour before or 2 hours after food
- Avoid direct sunlight and wear sun cream SPF 50 if spending prolonged periods outdoors as there is an increased risk of developing skin cancers (squamous cell carcinoma).
- Skin rashes are common; if persistent contact your specialist team.
- Visual disturbances (vivid colours, floating lights) and nightmares are common in the first 2 weeks but should resolve and have no permanent effects
- If you become confused or have hallucinations stop voriconazole immediately and speak to a doctor

**(iv) Posaconazole specific**

- Capsules can be taken with or without food
- Liquid formulation needs to be taken with a high fat meal

### 8.3 Echinocandins (Supplementary Table 2)

Echinocandins inhibit 1,3-β-D-glucan synthase, impairing fungal cell wall synthesis. Echinocandins are better tolerated and have lower potential for interactions than other antifungal agents but are only available as intravenous preparations (administered over one hour to avoid histamine-release infusion reactions) [76]. They can cause elevated liver function tests, hypocalcaemia, hypomagnesaemia, and hypophosphatemia [83, 84]. Liver function, urea and electrolytes, and bone profile should be monitored 2-3 days after starting therapy and weekly thereafter. Caspofungin levels are reduced by rifampicin and potentially other enzyme inducers [85].

### 8.4 Amphotericin B (Supplementary Table 2)

Amphotericin B (AMB) disrupts ergosterol in the fungal cell membrane leading to leakage of intracellular contents. AMB is only currently available as intravenous preparations, which can be used off-label as nebulised therapy (e.g. for ABPA); this can cause bronchospasm [43-45, 86]. AMB causes dose related nephrotoxicity (hypokalaemia, hyponatraemia, hypomagnesemia, increased creatinine, more likely with prolonged treatment or in combination with other renal risk factors), idiosyncratic hepatotoxicity, and infusion reactions (fever, rigors, headache, arthralgia, nausea and vomiting and hypotension, rarely anaphylaxis) [87-90]. Lipid (Abelcet®) and liposomal (AmBisome®) formulations reduce the risk of

nephrotoxicity, as does adequate hydration [76, 91]. Patients receiving liposomal AMB should be monitored during the infusion as it can cause a type 1 hypersensitivity reaction presenting with chest, abdominal, flank, and/or leg pain, hypoxia, dyspnoea, flushing and urticaria, usually within 5 minutes of administration [87]. AMB has a low risk of drug-drug interactions other than with nephrotoxic medicines.

### 8.5 Antifungal resistance

Antifungal resistance may be intrinsic e.g. *A. terreus* resistance to AMB, or acquired e.g. *A. fumigatus* resistance to triazoles caused by reduced binding affinity to the target site, overexpression of the target enzyme, or efflux pumps. Acquired antifungal resistance is increasing, with resistance to posaconazole often combined with itraconazole and some reports of pan-azole resistance [92-94]. Sensitivity testing is advisable for the pre-treatment *Aspergillus* isolate and when there is a poor response to antifungal therapy, but is only available at a limited number of microbiological laboratories. Molecular methods are also available to predict triazole sensitivity [95-97]. Sub-optimal exposure to triazoles can increase the probability of resistance, accentuating the importance of maintaining therapeutic drug levels [98]. Within an aspergilloma / focus of CPA there can be a mixture of resistant and susceptible isolates [94, 99]*., Aspergillus* spp. resistance to AMB is uncommon except for the intrinsic resistance of *A. terreus* [100-102]. Raised minimum effective concentrations (MEC) to echinocandins due to mutations of 1,3-β-D- glucan synthase or modifications to the lipid membrane have been reported [103-105]. Patients with identified resistance to their antifungal agent should be monitored closely for treatment failure and their therapy adjusted accordingly.

**Clinical practice points for use of antifungal therapy for chronic *Aspergillus*-related lung disease:**

1. Take a thorough drug history from all patients to inform on the choice of antifungal prescribed.
2. Consider altering existing medications to avoid potential drug interactions.
3. For patients starting a triazole consider reducing the dose of inhaled corticosteroid therapy to reduce systemic side effects, depending on type of corticosteroid: (a) fluticasone, budesonide, mometasone – initial 50% dose reduction; (b) beclomethasone, ciclesonide – no dose adjustment needed but monitor for side effects.
4. Consider testing for adrenal insufficiency (eg measuring a 9am cortisol, and if abnormal perform a synacthen test) in patients receiving triazole therapy and either maintenance oral corticosteroids for >6 months, long term inhaled corticosteroids, or receiving two or more courses of oral corticosteroids in 6 months for exacerbations of airways diseases.
5. For patients receiving triazole therapies, request pre-treatment ECG and baseline bloods (LFTs, FBC and U&Es). Repeat the LFTs and request therapeutic drug levels after 2 to 4 weeks along with an ECG for patients with pre-treatment prolonged QTc or additional risk factors for a prolonged QTc (e.g. long term azithromycin). Repeat LFTs / U&Es and TDM at 3 months then 6 (itraconazole and voriconazole) or 12 (posaconazole) monthly, or after dose / formulation changes, or interacting medicines are started or stopped.
6. Counsel patients receiving antifungal agents about common and important side

effects, and what to do if a potential side effect occurs (**Box 7** and **Table 3**).

7. Persist with one formulation of itraconazole or posaconazole, and if changing between capsules/tablets or the liquid formulation use TDM to ensure correct dosing.

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**Supplementary table 1: Pharmacology, common side effects and interactions for triazole antifungal agents with activity against *Aspergillus* spp.**

| | Itraconazole | Voriconazole | Posaconazole | Isavuconazole |
|---|---|---|---|---|
| **Formulations** | Capsules 100mg<br>Solution 50mg/5ml | Tablets 200mg and 50mg<br>Suspension 40mg/ml<br>Injection 200mg | Tablets 100mg<br>Suspension 40mg/ml<br>Injection 300mg | Capsules 100mg<br>Injection 200mg concentrate |
| **Dose**[a] | Oral 200mg BD<br><50kg consider 100mg BD | >50kg 200mg BD; 40-50kg 150mg BD<br><40kg 100mg BD<br>IV: 6mg/kg BD 2 doses 4mg/kg BD | Oral /IV: 300mg OD<br><50kg consider 200mg OD | Oral/IV: 200mg OD |
| **Absorption** | Capsule: poor absorption, take with food or acidic drink[b]<br>Liquid: better absorption, take on an empty stomach<br>Peak levels at 2.5 hours | 96% bioavailability<br>Take on an empty stomach<br>Peak levels at 1-2 hours, | Tablets: take with or without food, peak levels at 4-5 hours;<br>Liquid: poor absorption, peak levels at 3 hours, take with high fat food | 98% bioavailable<br>Not affected by food<br>Peak levels at 2-3 hours |
| **Route of elimination** | Hepatic via CYP3A4 | Hepatic via CYP2C19, CYP2C9 and CYP3A4 | Hepatic via uridine diphosphate-glucuronosyltransferases | Hepatic via CYP3A4, CYP3A5 and uridine diphosphate-glucuronosyltransferases |
| **Half life** | 40 hours<br>Non-linear pharmacokinetics | 6 hours<br>Non-linear pharmacokinetics | 29 hours<br>Linear kinetics | 110 hours<br>Linear kinetics |
| **Main adverse effects** | Gastrointestinal symptoms<br>Oedema<br>Heart failure<br>Hypertension<br>Prolonged QTc<br>Peripheral neuropathy<br>Hepatotoxicity<br>Adrenal suppression<br>Pseudo hyperaldosteronism | Gastrointestinal symptoms<br>Phototoxicity<br>Visual disturbance<br>Hallucinations<br>Hepatotoxicity<br>Peripheral neuropathy<br>Prolonged QTc<br>Hyponatraemia<br>Hypokalaemia | Gastrointestinal symptoms<br>Oedema<br>Heart failure<br>Hypertension<br>Prolonged QTc<br>Peripheral neuropathy<br>Hepatotoxicity<br>Adrenal suppression<br>Pseudo hyperaldosteronism | Gastrointestinal symptoms<br>Peripheral neuropathy<br>Shortened QTc<br>Hepatotoxicity<br>Hypokalaemia |
| **Therapeutic drug level monitoring** | | | | |
| **Therapeutic level** | Depends on test used | 1 – 5.5mg/L | 1 - 3.75mg/L | Aim >1mg/L, preferably 2-4mg/L |
| **Timing of levels** | Trough preferable but random level acceptable | Trough | Trough preferable but random level acceptable | Trough preferable but random level acceptable |
| **Frequency** | 2 to 4 weeks after starting therapy, then 3 months, then minimum 6 monthly (12 monthly for posaconazole)<br>Plus after dose or formulation changes, or interacting medicines started or stopped | | | Not routinely recommended |
| **Maximum dose** | Titrate up to 300mg BD[c]. | Titrate up to 350mg BD[c] | Titrate up to 400mg/day (tablets)[c,d]. Daily dose >300mg can use 2 divided doses | 200mg OD[e] |
| **Adverse effects monitoring regimen** | | | | |
| **LFTs, U+Es** | Baseline; then 2 to 4 weeks after starting or an increase in dose; then minimum annually; more frequently if high-risk of hepatotoxicity | | | |

| | | | | |
|---|---|---|---|---|
| **ECG** | Baseline; then repeat at 2 to 4 weeks after starting if baseline ECG has prolonged QTc or taking another QTc prolonging medication or other risk factors | | | Baseline<br>On starting medication that shortens QTc |
| **Skin assessment** | Not necessary | Each clinic visit (phototoxicity, SCCs) | Not necessary | Not necessary |
| **Blood pressure** | Clinic visits | Not necessary | Clinic visits | Not necessary |
| **Cortisol** | Annually, particularly for patients on long term inhaled or oral corticosteroids or taking multiple courses of oral corticosteroids | | | |
| **Interactions** | | | | |
| **Liver enzyme effects** | Potent CYP3A4 inhibitor<br>p-glycoprotein inhibitor | Potent CYP3A4, CYP2C19, CYP2C9 inhibitor | Potent CYP3A4 inhibitor | Moderate CYP3A4/5 inhibitor |
| **Statins** | Switch to pravastatin or rosuvastatin (not metabolised by CYP enzymes) | | | No significant interactions |
| **Antacids / gastric acid suppression medication** | Avoid if possible, or separate timing of administration | Halve the dose of omeprazole if taking 40+mg | Avoid if possible or monitor levels closely if on liquid form<br>Tablets not affected | No significant interactions |
| **Drugs affecting QTc** | Monitor ECG if starting medication that can prolong QTc (eg macrolides, quinolones, citalopram) | | | Monitor ECG if on medication that can shorten QTc<br>(eg nicorandil, rufinamide) |
| **Corticosteroids** | • Consider 50% dose reductions for - fluticasone, budesonide, ciclesonide, mometasone, dexamethasone, methylprednisolone, triamcinolone<br>• No dose adjustment needed but monitor for side effects – beclomethasone, prednisolone, hydrocortisone | | | Clinical relevance unknown. |
| **Immunosuppressives** | Ciclosporin, tacrolimus, sirolimus and everolimus need close therapeutic monitoring (metabolised by CYP3A4) | | | |
| **CFTR modulators** | Consider dose adjustments according to manufacturers guidance for Ivacaftor, tezacaftor and elexacaftor | | | |
| **Other** | Drug metabolising enzymes inhibitors (eg ritonavir) or inducers (eg rifampicin, carbamazepine) require close monitoring of triazole levels | | | |
| **Anticoagulants** | | | | |
| **Warfarin** | Inhibit warfarin metabolism, monitor INR closely | | | |
| **Rivaroxaban, Apixaban** | Contraindicated - levels increased | | | Use with caution |
| **Edoxaban** | Reduce to 30mg | No interaction | No dose reduction, monitor for increased bleeding risk | No dose reduction, monitor for increased bleeding risk |
| **Dabigatran** | Contraindicated | No interaction | No dose reduction, monitor for increased bleeding risk | No dose reduction, monitor for increased bleeding risk |
| **Special populations (for all monitor drug levels closely)** | | | | |
| **Hepatic impairment** | Use with caution | Mild-moderate: use half dose<br>Severe: avoid and seek expert hepatology advice | Use with caution | Severe: use with caution |
| **Renal impairment** | No dose adjustments, monitor levels closely | | | |
| **Pregnancy** | Avoid. Reproductive toxicity in animals and humans | Reproductive toxicity in animals, generally avoid (discuss with patient and obstetricians) | | |
| **Breastfeeding** | Excreted in breast milk. Weigh benefits versus risk | No data<br>Breast-feeding contra-indicated | Excreted into rat breast milk<br>Breast-feeding contra-indicated | Excreted into animal breast milk<br>Breast-feeding contra-indicated |
| **Obesity** | Limited data | Oral: no dose adjustment<br>IV: dose adjusted to weight | Limited data | Limited data |

| | | | | |
|---|---|---|---|---|
| **Low body weight** | Reduced dose | Reduce dose | Consider starting at lower dose | Monitor levels |
| **Elderly** | No dose adjustment<br>Consider co-morbidities | No dose adjustment.<br>Consider co-morbidities<br>Visual side effects increase falls risk | No dose adjustment<br>Consider co-morbidities | No dose adjustment<br>Consider co-morbidities |

[a]Loading doses are given in invasive disease, this is not essential for chronic disease where rapid achievement of therapeutic levels is not needed
[b]e.g. orange juice or coca cola
[c] Maximum doses stated in this clinical statement are off- label. Specialists advise from tertiary care or experienced clinicians within this area and antifungals should be consulted. Therapeutic drug monitoring is strongly recommended in these cases.
[d] Co-administration with strong enzyme inducers can influence further dose increase and therefore specialist advise is recommended in these patients. Tablet and liquid formulation of posaconazole are not interchangeable and therefore the maximum dose for liquid formulation should be in line with summary product characteristics.
[e] Currently there is insufficient data for maximum off-label doses in isavuconazole.

**Supplementary Table 2: Pharmacology, and common side effects and interactions for intravenous antifungal agents active against *Aspergillus* spp.**

| | **Liposomal Amphotericin B** | **Micafungin*** | **Caspofungin*** |
|---|---|---|---|
| **Dose** | 3mg/kg OD or 5mg/kg x3 / week | >40kg 150mg OD<br><40kg max 4mg/kg OD | 70mg loading dose<br>Maintenance dose <80kg 50mg , >80kg 70mg OD |
| **Main adverse effects** | Infusion reactions<br>Nephrotoxicity<br>Electrolyte disturbance (hypokalaemia, hyponatraemia, hypomagnesemia)<br>Hepatotoxicity | Electrolyte disturbance (hypomagnesemia, hypophosphatemia, hypocalcaemia)<br>Risk of hepatocellular tumours in rats | Electrolyte disturbance (hypomagnesemia, hypophosphatemia, hypocalcaemia) |
| **Formulations** | Liposomal 50mg powder for infusion<br>Must be reconstituted with 5% glucose | 50mg and 100mg powder for infusion | 50mg and 70mg concentrate for infusion |
| **Elimination route** | Unknown | Hepatic metabolism, not CYP mediated | Spontaneous degradation |
| **Half life** | 7 hours; antifungal effect lasts 12 hours | 10-17 hours | Polyphasic half-life over 45 hours |
| **Monitoring** | Minimum twice weekly U+Es, magnesium, LFTs | Minimum weekly LFTs, phosphate, calcium, magnesium, U+Es | Minimum weekly liver function, calcium, magnesium, U+Es |
| **Interactions** | Caution with nephrotoxic medicines | Nil significant | Concentration decreased by CYP3A4 inducers<br>Effective dose increased by ciclosporin |
| **Special populations** | | | |
| **Hepatic impairment** | Limited data | Mild-moderate; no dose adjustment<br>Severe; caution needed | Mild; no dose reduction<br>Moderate; Childs Pugh 7-9 reduce dose to 35mg (following 70mg loading dose)<br>Severe; avoid |
| **Renal impairment** | No dose adjustment; use with caution | No dose adjustment | No dose adjustment |
| **Pregnancy** | Safety not established<br>No harmful effects in animals | Avoid; reproductive toxicity in animals | Avoid; reproductive toxicity in animals |

| | | | |
|---|---|---|---|
| **Breastfeeding** | Unknown whether excreted in breast milk. Consider risks vs benefits | Excreted in animal breast milk<br>Advise not to breastfeed | Excreted in animal breast milk<br>Advise not to breastfeed |
| **Obesity** | Dose based on adjusted body weight<br>Close monitoring for nephrotoxicity | If weight >115kg consider 200mg dose | Increase volume of distribution and clearance in obesity, clinical relevance unknown |
| **Low body weight** | Dose based on actual body weight<br>Monitor renal function closely | If weight <40kg reduce to 4mg/kg | Limited information |
| **Elderly** | No dose adjustment needed<br>Consider nephrotoxic risk | No difference in PK in elderly patients | AUC increased by 30% in elderly patients<br>No dose adjustment needed |

*Additional echinocandins therapies are likely to be available in the future (eg rezafungin)