BTS Clinical statement on *Aspergillus*-related chronic lung disease

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Authors: Jeremy Brown (co-chair), Caroline Baxter (co-chair), Darius Armstrong-Jones, Jonathan Ayling Smith, Matthijs Backx, Meg Coleman, Dave Connell, Paddy Dennison, Damian Downey, Fiona Lynch, Wei Shen Lim, Jenny White

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Contact:
British Thoracic Society,
17 Doughty St, London WC1N 2PL
miguel.souto@brit-thoracic.org.uk

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Disclaimer A Clinical Statement reflects the expert views of a group of specialists who are well versed in the topic concerned, and who carefully examine the available evidence in relation to their own clinical practice. Clinical Statement does not involve a formal evidence review and is not developed in accordance with clinical practice guideline methodology. Clinical Statements are not intended as legal documents or a primary source of detailed technical information. Readers are encouraged to consider the information presented and reach their own conclusions.

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 using 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* IgG, 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 significant 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).

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 not.
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 treatment with triazole therapy (**Box 6**) for exacerbations caused by a flare of the ABPA if systemic corticosteroids should be avoided or fail to control 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. Titrate up inhaled corticosteroid and bronchodilator treatment to minimise symptoms and exacerbations, and maintain stable peak flow and/or spirometry recordings.
3. 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 6**)
   - or referral to severe asthma centre for evaluation for treatment with monoclonal antibodies
4. 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.
5. Consider testing for adrenal insufficiency 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 peri- and post-operative antifungal agents (triazole or echinocandin) for a duration of at least 4 weeks, maintaining therapy 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 continuing infection.
6. Consider antifungal therapy for cases of CPA not suitable for surgical resection, *Aspergillus* nodules with clinical or radiological evidence of persisting infection, and for *Aspergillus* bronchitis/bronchiolitis or tracheobronchitis. Suggested agents are described in box 6.
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, 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 depending 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.

Clinical practice points for use of antifungal therapy for chronic *Aspergillus*-related pulmonary 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 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 the 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 and 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* 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 in this clinical statement 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 ***June and July 2024***. The revised document was re-approved by the BTS SOCC in **XXXXXXXXXX** 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

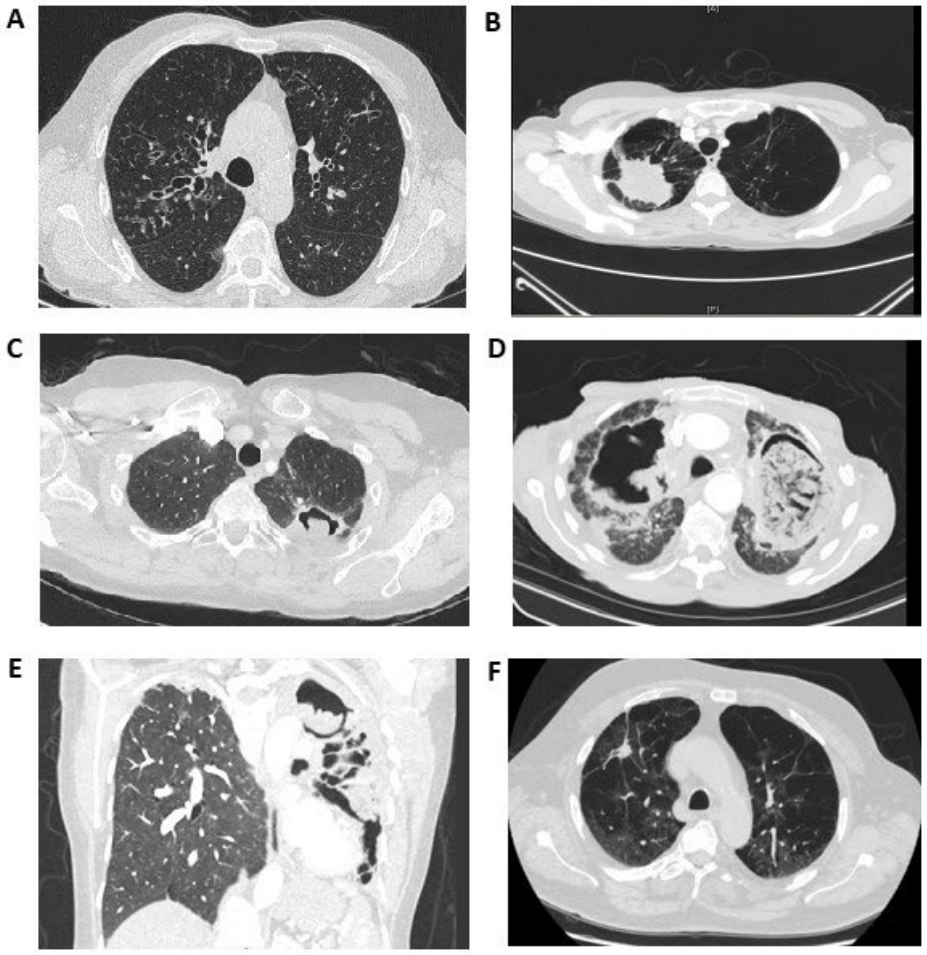
germinate to cause active lung infection, with the morphology and speed of progression of infection varying markedly depending on host immune function. Inhaled *Aspergillus* spp. can also generate an allergic response to fungal antigens resulting in inflammatory lung disease. Due to this dependence of 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 is recognised (e.g. aspergillomas evolving to more invasive forms of infection). Although *Aspergillus fumigatus* is the predominant species causing *Aspergillus*-related chronic pulmonary disease in the UK, other *Aspergillus* spp. (e.g. *A. niger*, *A. tereus*, and *A. flavus*) can also cause human lung 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 Complicated (e.g. haemoptysis)	Pre-existing cavities
Allergy	ABPA[1] SAFS[2]	Asthma, bronchiectasis, CF, COPD Asthma
Chronic infection	Forms of CPA[3]: (i) SAIA[4] (ii) CCPA[5] (iii) CFPA[6] Nodules Airways disease	 Immunosuppression Pre-existing lung disease Pre-existing lung disease Unclear Immunosuppression

[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 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) Left 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 *Aspergillus* nodule in a patient with severe emphysema.



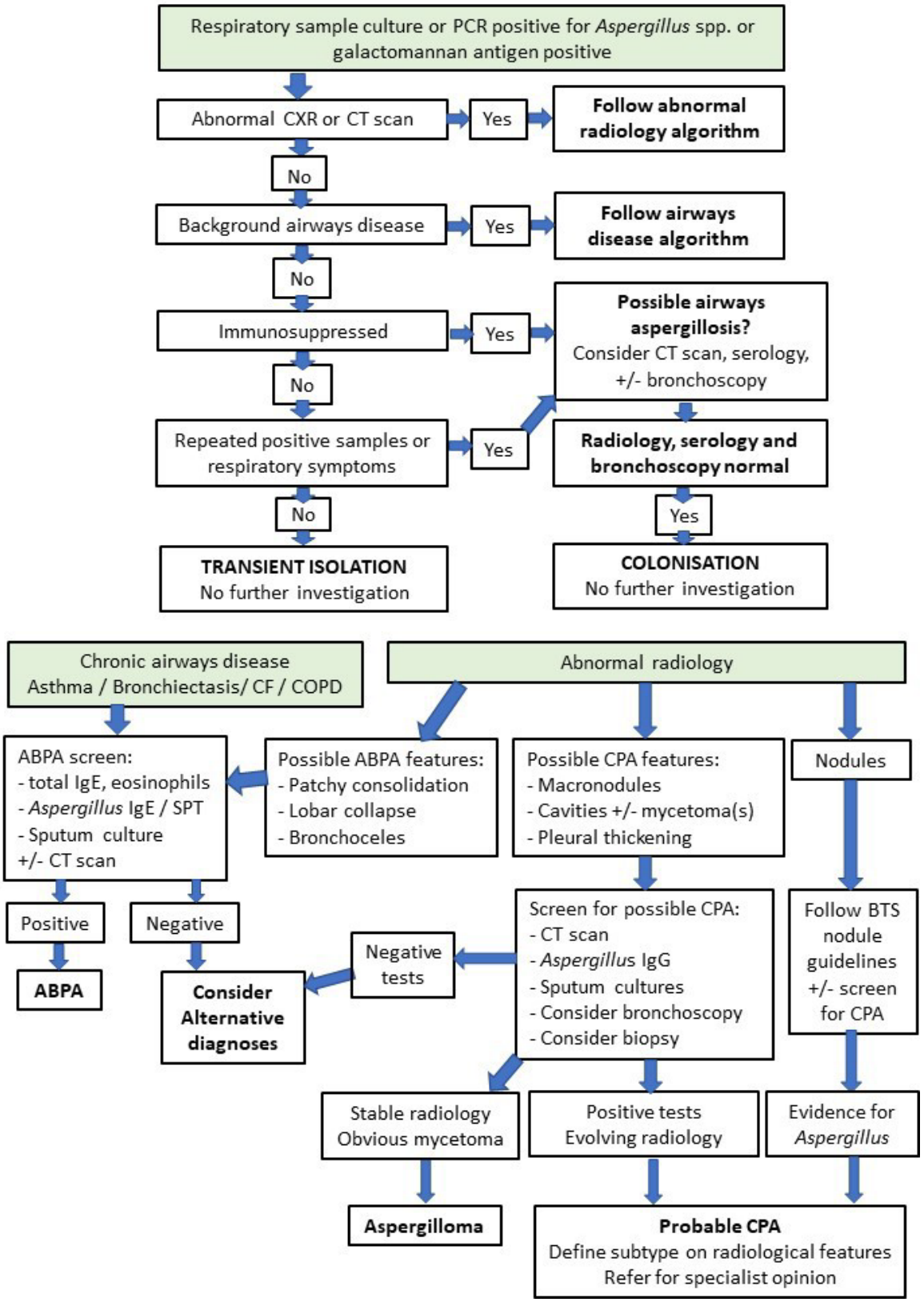
4. Classification and diagnostic criteria for sub-types of *Aspergillus*-related chronic lung disease

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 generally should 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**.

Table 2: Interpretation of diagnostic tests

Disease form	Relevant diagnostic tests
Colonisation	Positive sputum/BAL culture for *Aspergillus* spp. or BAL GM Total IgE and *Aspergillus* IgE normal *Aspergillus* IgG may be raised No radiological changes suggestive of *Aspergillus* lung disease.
ABPA	Total IgE at least >500 IU/ml Positive *Aspergillus* spp. specific IgE or skin prick test Eosinophil count often raised >0.5x10^9/L *Aspergillus* spp. specific IgG often raised Sputum/BAL culture for *Aspergillus* or BAL GM often positive Typical radiological changes are common (see Box 3)
Aspergilloma	Mycetoma visible on chest X ray or CT scan *Aspergillus* spp. specific IgG usually raised May have positive sputum/BAL culture or BAL GM
CPA	Radiological changes of progressive cavitary and fibrotic parenchymal disease with or without concurrent aspergilloma *Aspergillus* spp. specific IgG almost always raised and may be used to monitor response to treatment Sputum/BAL culture for *Aspergillus* spp. or BAL GM often positive Confirmed by histological demonstration of *Aspergillus* hyphae in lung parenchyma from CT-guided, bronchoscopic or surgical biopsy Total IgE and specific *Aspergillus* IgE may or may not be raised Serum GM usually negative
Sub-acute invasive aspergillosis	Radiology demonstrates rapidly expanding macro-nodules. Sputum/BAL culture for *Aspergillus* spp. or BAL GM usually positive Serum GM may be positive *Aspergillus* spp. specific IgG usually raised Confirmed by histological demonstration of *Aspergillus* hyphae in lung parenchyma from CT-guided, bronchoscopic or surgical biopsy
Aspergillus nodules	Usually detected by CT scan and requires exclusion of malignancy. Diagnosis confirmed by histology (CT guided or surgical biopsy) *Aspergillus* spp. specific IgG may be elevated or normal
Airways infection	CT changes of airway inflammation +/- nodules usually present Sputum/BAL culture for *Aspergillus* or BAL GM usually positive, often recurrently *Aspergillus* spp. specific IgG usually raised Confirmed by endobronchial biopsy

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



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 to a positive *Aspergillus* spp. culture for 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 a fungal ball 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 radiological appearances of an intracavitary body (a mycetoma) 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 an aspergilloma cavity over time, the diagnosis is chronic pulmonary aspergillosis (CPA) (section 4.4). A change in size of the aspergilloma alone does not indicate evolution to CPA.

Box 2: Diagnostic criteria for conditions with *Aspergillus* spp. colonisation and Aspergilloma

Non-pathological *Aspergillus* spp. colonisation:

(a) Repeated positive culture 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 lesion 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, galactomannan, 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. 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]. Patients with poor asthma control and a positive serological IgE response but do not fulfil the other ABPA diagnostic criteria, SAFS should be considered (not discussed further).

Early detection and management of ABPA can prevent progression and 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)**
- bronchial casts or visible mucoid impaction on bronchoscopy
- a positive respiratory culture for *Aspergillus* spp.
- raised total serum IgE and/or serological markers or a positive skin prick test to *Aspergillus* spp.

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 positive skin prick responses (**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 in driving 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

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 / 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 occurs most commonly 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 and sweats, haemoptysis (which can be life-threatening), cough, and progressive breathlessness. A diagnosis of CPA requires radiological appearances consistent of CPA and microbiological, serological, and/or histological evidence of *Aspergillus* spp. infection (**Box 4**). CPA can be separated into the following subsets largely based on radiological appearances **(Figure 1)** and rate of progression:

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. macronodule(s), but in SAIA these enlarge over weeks to months rather than days to weeks. Due to the faster speed of progression 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.

4.4.3 Chronic fibrosing pulmonary aspergillosis (CFPA): CFPA is best considered a subset of CCPA with a stronger 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 progressive 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 nodule(s) +/- surrounding ground glass opacity ('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 +/- 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, galactomannan, or PCR 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), +/- nodules <1cm that may cavitate
(c) **And** negative biochemical markers for ABPA (total IgE, *Aspergillus* spp. specific IgE)
(d) Supportive criteria are underlying immunosuppression +/- chronic lung disease

Aspergillus tracheobronchitis:

(a) Suggestive macroscopic appearances of the trachea +/- major bronchi on bronchoscopy (erythematous plaques, ulceration, pseudomembrane formation)

(e) **And** positive culture +/- histological evidence of *Aspergillus* spp. infection in bronchial biopsies
(b) A supportive criterium is a significant degree of background immunosuppression

Aspergillus spp. nodules:
(a) Well defined single or multiple pulmonary nodules
(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 some degree of immunosuppression can develop infection of the medium and small airways with *Aspergillus* spp. which we term *Aspergillus* bronchitis/bronchiolitis. This can cause cough, chronic sputum production, 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. The patients have normal total IgE and generally negative *Aspergillus* spp. specific IgE, although serum *Aspergillus* spp. specific IgG is often positive [17]. 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 also affect less severely immunosuppressed patients and lung transplant recipients (often occurring at 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 culture 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 unreliable. The mortality is high unless effective treatment is started rapidly.

4.5.3 Aspergillus nodules: Localised indolent infection with *Aspergillus* spp. can cause single or multiple parenchymal lung nodules (sometimes termed intrapulmonary aspergillomas) that are usually asymptomatic. The nodules are usually well-defined, predominantly affect the upper lobes (>60%), have a diameter (mean 21 mm) significantly smaller than SAIA macronodules, and frequently diagnosed at resection or biopsy when investigated as suspected lung cancer [18]. The natural history of *Aspergillus* spp. nodules if untreated can vary; many cases are non-progressive, but some patients represent an early SAIA or CCPA lesion and close follow-up is necessary. The patients usually have underlying lung disease rather than significant immunosuppression. The diagnosis is based on radiological appearances and histology of nodule biopsies. *Aspergillus* IgG is positive in 40-70% cases. [18, 19]

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 one of these categories and with the evolution of immunosuppressive therapies less common presentations may become more frequent. Diagnosis requires an accurate assessment of the radiology combined with clinical,

microbiological and serological data (**Box 4**), and is often difficult. Subspecialty input from physicians and radiologists with specific experience in *Aspergillus*-related chronic lung disease is often necessary. 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), and these conditions need to be actively considered and excluded.

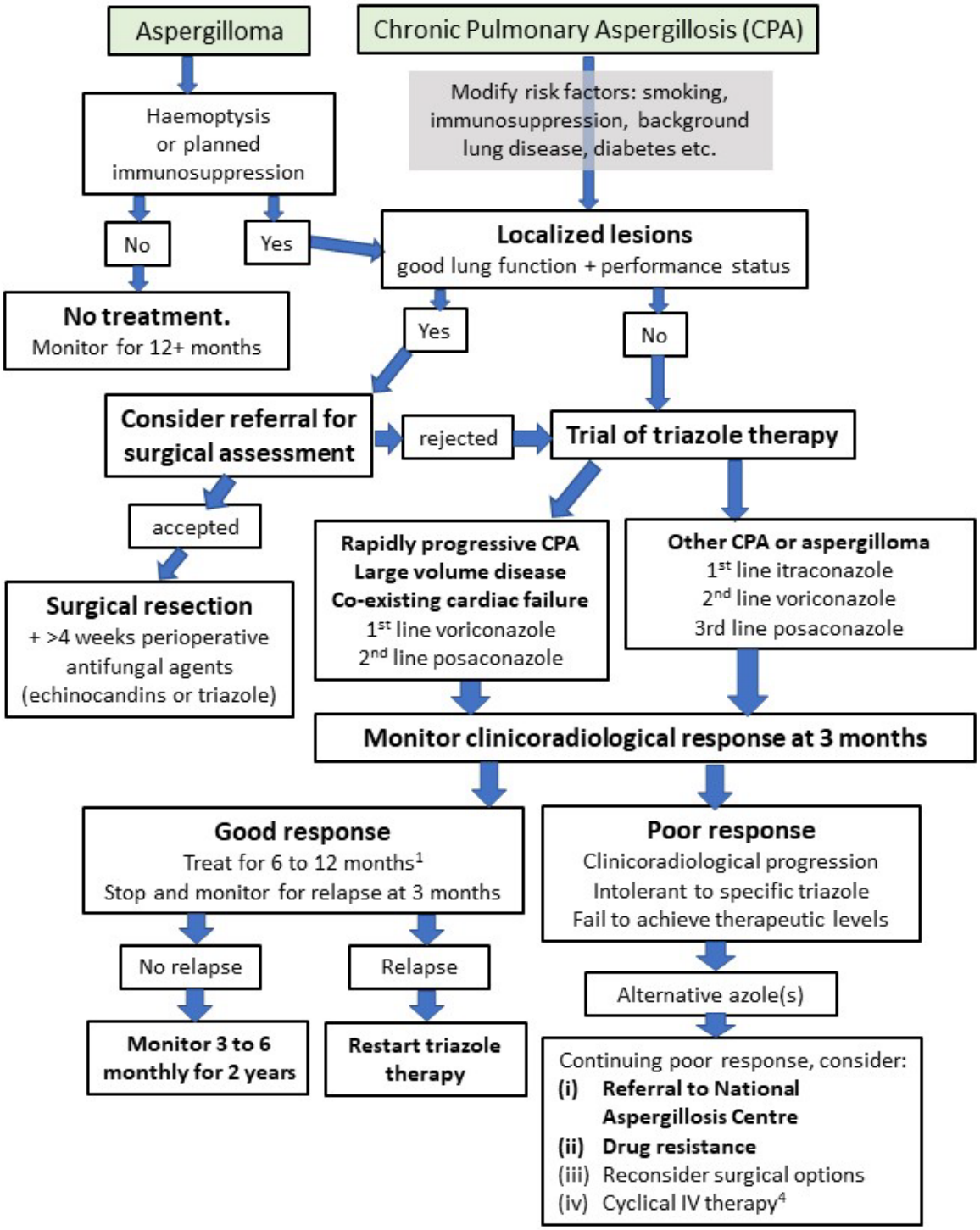
Clinical practice points for diagnosis of *Aspergillus*-related chronic lung disease (Figure 2)

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 using 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* IgG, 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 [20, 21]. For patients with complicated aspergillomas associated with major haemoptysis or repeated minor haemoptysis treatment with antifungals is first- line therapy, with the most published evidence for oral itraconazole [20, 22, 23]. The evidence base for either percutaneous or transbronchial instillation of antifungal agents is limited [24]. Single aspergillomas (or aspergillomas limited to one lobe) in patients with adequate lung function and performance status can be cured by surgical resection [21, 25, 26]. 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 [27]. Hence the decision to offer surgical resection is complex, and in general should be reserved for patients with a history of recurrent major haemoptysis or in patients with new or increased immunosuppression (due to the potential for progression to CPA).

Figure 3: Management of aspergilloma and CPA



Notes:
[1]Duration of treatment: usually initially 6 months for SAIA and 12 months for CCPA or CFPA; aspergilloma varies with clinical situation and treatment response

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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 significant 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 (Box 5)

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.

Box 5: 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 how well controlled are 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.

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 move to step 2

Step 2:

Optimise maximum inhaled therapy with:

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

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 weaning to 5mg/day after 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

If persisting regular symptoms / variable PEFR / raised FeNO / requirement for oral corticosteroid courses for exacerbations or to maintain FEV_1 move to Step 4.

Step 4: consider combined antifungal and maintenance oral 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)

6.1 Treatment of acute exacerbations of ABPA

Patients with ABPA who present with worsening respiratory symptoms 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, 28]. Exacerbations caused by a flare of the underlying ABPA are defined by: (i) an increase in respiratory symptoms (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 (ii) associated with a >50% rise in total IgE level or new ABPA-related radiological changes (focal consolidation, lobar collapse, new mucoceles) [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 [29-31]:

(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 6**) 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.

Box 6 Treatment with antifungal agents for *Aspergillus*-related chronic lung disease Generalised advice on treatment with antifungal treatment when required for aspergillomas, ABPA and CPA cases

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

2. 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

3. 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 but monitor for side effects (see Box 1 and supplementary Table 1 for details)
(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 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.

4. 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.

5. 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

6. 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 AMB

7. 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 effective triazole drug levels)

8. For severe cases (e.g. patients admitted to hospital) or patients unable to tolerate oral triazole therapy consider initial intravenous therapy with an echinocandin or AMB or voriconazole followed by maintenance oral triazole therapy

9. 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

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 not.
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 treatment with triazole therapy (**Box 6**) for exacerbations caused by a flare of the ABPA if systemic corticosteroids should be avoided or fail to control symptoms and restore lung function.

6.2 Maintenance treatment

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, 32]. In addition, ABPA patients 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 5**. Underlying inhaled and/or oral asthma treatment should be optimised, as per the BTS Asthma Guidelines [40]. Compared to other causes of asthma, ABPA patients often require higher doses of inhaled corticosteroids. Although maintenance oral corticosteroids cause significant side effects and should be avoided when possible, preventing exacerbations and maintaining lung function for some ABPA patients will require maintenance oral corticosteroids. Adrenal insufficiency is common, particularly in patients receiving maintenance long term corticosteroids, repeated oral corticosteroid courses, or oral corticosteroids combined with triazole therapy. Although it has not been tested specifically ABPA, analogous for other causes of asthma 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 following existing bronchiectasis or asthma BTS guidelines [10, 32]. Both macrolides and most triazoles can cause prolongation of the QTc and need to be used in combination cautiously.

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 [34, 35]. 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 [36-38]. TDM of triazole therapy is important. Oral and inhaled corticosteroid dose may 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 lung function testing [39-41].

6.2.5 Asthma monoclonal antibody treatments.

The underlying pathology of ABPA indicates biological therapies should improve airways disease control for ABPA patients with. 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 to a small randomised trial of Omalizumab[42]. In addition, case-series and registry data suggest omalizumab [43-45], mepolizumab [46-52], benralizumab [53-55] and dupilumab [56-60] 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 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. Titrate up inhaled corticosteroid and bronchodilator treatment to minimise symptoms and exacerbations, and maintain stable peak flow and/or spirometry recordings.
3. 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 6**)
   - or referral to severe asthma centre for evaluation for treatment with monoclonal

antibodies

4. 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.
5. Consider testing for adrenal insufficiency 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.

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 haemoptyses or a single major haemoptysis
(iv) Progressive lung function decline (may be caused by the underlying respiratory condition(s)).
(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 off 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 [61, 62]:

(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

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.

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, 61]

Based on the larger published dataset for its use, itraconazole remains the first line therapy for CCPA and CFPA [2, 61, 63, 64]. 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 6**) [2, 65-67]. In the UK, isavuconazole is commissioned for use by the National Aspergillosis Centre for patients unable take other azoles. Published data suggest CCPA patients treated for 12 months with triazole therapy reduces relapse rates compared to treatment for 6 months [64, 66, 68]. When triazole agents cannot be used due to side effects, poor response, or triazole-resistance, CPA can be treated with intravenous ambisome (AMB) or an echinocandin (both have similar response rates), initially typically for 1 to 6 weeks and potentially cyclically thereafter [2, 67, 69, 70].

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) [2]. Radiological changes suggesting treatment response are:
(i) regression in size of macronodules, sometimes developing cavitation
(ii) reduced cavity wall thickness
(iii) reduction in parenchymal disease associated with cavities
(iv) improved definition of lesion margins
Reductions in blood markers (e.g. *Aspergillus* IgG levels, ESR, and CRP serum), increases in serum albumin, 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, infection with respiratory bacterial pathogens (e.g. *Pseudomonas aeruginosa*, *Haemophilus influenzae*, and less commonly *Nocardia* and mycobacteria). Hence, whether active fungal disease is the primary cause of new clinical changes or an alternative diagnosis requires careful re-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 6)**; treatment response is assessed by reduction in nodule size. Stable *Aspergillus* nodules can potentially just be observed unless the patient is 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 are still likely to require treatment with triazole antifungal agents (**Box 6)** to prevent radiological progression and/or to control symptoms.

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 peri- and post-operative antifungal agents (triazole or echinocandin) for a duration of at least 4 weeks, maintaining therapy 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 continuing infection.
6. Consider antifungal therapy for cases of CPA not suitable for surgical resection, *Aspergillus* nodules with clinical or radiological evidence of persisting infection, and for *Aspergillus* bronchitis/bronchiolitis or tracheobronchitis. Suggested agents are described in box 6.
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, 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 depending 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.

8. Antifungal therapies

8.1 Overview

Currently there are three classes of antifungal therapeutics available for the treatment of *Aspergillus* spp. [72]. The mainstay of therapy are oral triazoles. Rarely, patients may need intravenous treatment with either echinocandins or 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

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 [72]. At present there are four triazoles active against *Aspergillus* spp. in clinical use - itraconazole, voriconazole, posaconazole and isavuconazole. *Aspergillus* spp. are intrinsically resistant to fluconazole [72]. Triazoles have a wide range of side-effects and toxicities, the most important of which 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. 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, 73]. 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 in the UK [73-77]. 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, corticosteroids, statins, immunosuppressive therapies, proton pump inhibitors, and enzyme inhibitors (eg ritonavir) or inducers (eg rifampicin) (**Supplementary Table 2**; see also https://antifungalinteractions.org/). General advice for patients receiving triazole therapy is listed 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 Associated with raised levels, usually self-limiting
Hepatotoxicity	Approximately 25% of patients usually in the first 4 weeks Associated with raised drug levels, prolonged treatment, risk factors for other causes of hepatotoxicity Discontinue if severe or not reversed by dose reduction Generally reversible, and can cautiously trial use of a different triazole
Peripheral neuropathy	Up to 10% of patients (especially on prolonged treatment) Requires dose reductions or cessation of therapy Generally slowly reversible, and can cautiously trial use of a different triazole
Prolonged QTc	Prolonged by itraconazole, voriconazole and posaconazole Torsade's de pointe is rare without other risk factors Monitor ECG, and avoid other QTc prolonging medications if possible
Adrenal insufficiency	On withdrawal of itraconazole, voriconazole or posaconazole.
Pseudohyperaldosteronism retention / oedema	Rare; due to posaconazole or itraconazole inhibition of CYP11B1 and 11β-HSD2. Fluid Common with itraconazole Need to exclude the presence of congestive heart failure 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 and stem cell transplants). Avoid sunlight and use high factor sunscreen. If phototoxicity occurs stop voriconazole, consider dermatology referral (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 (iii) Neurotoxicity (altered mental status, visual/auditory hallucinations), especially with toxic voriconazole levels. Stop voriconazole

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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 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
- 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)

The 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) [72]. They can cause elevated liver function tests, hypocalcaemia, hypomagnesaemia, and hypophosphatemia [79, 80]. 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 [81].

8.4 Amphotericin B (Supplementary Table 2)

Amphotericin B (AMB) binds to ergosterol in the fungal cell membrane leading to leakage of intracellular contents. AMB is only available as intravenous preparations, which can be used off-label as nebulised therapy (e.g. for ABPA); this can cause bronchospasm [39-41, 82]. AMB causes dose related nephrotoxicity (hypokalaemia, hyponatraemia, hypomagnesemia, increased creatinine, more likely with prolonged treatment or in combination with other renal risk factors and prevented by adequate hydration), idiosyncratic hepatotoxicity, and infusion reactions (fever, rigors, headache, arthralgia, nausea and vomiting and hypotension, rarely anaphylaxis) [83-86]. Lipid (Abelcet®) and liposomal (AmBisome®) formulations reduce the risk of nephrotoxicity, as does adequate hydration [72, 87]. Test doses of AmBisome should be given 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 [83]. AMB has a low risk of drug-drug interactions other than nephrotoxic medicines.

8.5 Antifungal resistance

Antifungal resistance may be intrinsic e.g. *A. tereus* 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 [88-90]. 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 [91, 92]. Sub-optimal exposure to triazoles can increase the probability of resistance, accentuating the importance of maintaining therapeutic drug levels [93]. Within an aspergilloma / focus of CPA there can be a mixture of resistant and susceptible isolates [90, 94]. *Aspergillus* spp. resistance to AMB is uncommon [95-97]. 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 [98-100]. 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 pulmonary 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 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 the 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 and 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 Solution 50mg/5ml	Tablets 200mg and 50mg Suspension 40mg/ml Injection 200mg	Tablets 100mg Suspension 40mg/ml Injection 300mg	Capsules 100mg Injection 200mg concentrate
Dose[a]	Oral 200mg BD <50kg consider 100mg BD	>50kg 200mg BD; 40-50kg 150mg BD <40kg 100mg BD IV: 6mg/kg BD 2 doses 4mg/kg BD	Oral /IV: 300mg OD <50kg consider 200mg OD	Oral/IV: 200mg OD
Absorption	Capsule: poor absorption, take with food or acidic drink[b] Liquid: better absorption, take on an empty stomach Peak levels at 2.5 hours	96% bioavailability Take on an empty stomach Peak levels at 1-2 hours,	Tablets: take with or without food, peak levels at 4-5 hours; Liquid: poor absorption, peak levels at 3 hours, take with high fat food	98% bioavailable Not affected by food 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 Non-linear pharmacokinetics	6 hours Non-linear pharmacokinetics	29 hours Linear kinetics	110 hours Linear kinetics
Main adverse effects	Gastrointestinal symptoms Oedema Heart failure Hypertension Prolonged QTc Peripheral neuropathy Hepatotoxicity Adrenal suppression Pseudo hyperaldosteronism	Gastrointestinal symptoms Phototoxicity Visual disturbance Hallucinations Hepatotoxicity Peripheral neuropathy Prolonged QTc Hyponatraemia Hypokalaemia	Gastrointestinal symptoms Oedema Heart failure Hypertension Prolonged QTc Peripheral neuropathy Hepatotoxicity Adrenal suppression Pseudo hyperaldosteronism	Gastrointestinal symptoms Peripheral neuropathy Shortened QTc Hepatotoxicity 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) 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 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 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 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 (eg nicorandil, rufinamide)
Corticosteroids	• Consider 50% dose reductions for - fluticasone, budesonide, ciclesonide, mometasone, dexamethasone, methylprednisolone, triamcinolone • 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)			
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 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 Breast-feeding contra-indicated	Excreted into rat breast milk Breast-feeding contra-indicated	Excreted into animal breast milk Breast-feeding contra-indicated
Obesity	Limited data	Oral: no dose adjustment 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 Consider co-morbidities	No dose adjustment. Consider co-morbidities Visual side effects increase falls risk	No dose adjustment Consider co-morbidities	No dose adjustment 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.

	AmBisome	Micafungin	Caspofungin
Dose	1mg test dose, observe for 30 minutes 3mg/kg OD or 5mg/kg x3 / week	>40kg 150mg OD <40kg max 4mg/kg OD	70mg loading dose Maintenance dose <80kg 50mg >80kg 70mg OD
Main adverse effects	Infusion reactions Nephrotoxicity Electrolyte disturbance (hypokalaemia, hyponatraemia, hypomagnesemia) Hepatotoxicity	Electrolyte disturbance (hypomagnesemia, hypophosphatemia, hypocalcaemia) Risk of hepatocellular tumours in rats	Electrolyte disturbance (hypomagnesemia, hypophosphatemia, hypocalcaemia)
Formulations	Liposomal 50mg powder for infusion 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 Effective dose increased by ciclosporin
Special populations			
Hepatic impairment	Limited data	Mild-moderate; no dose adjustment Severe; caution needed	Mild; no dose reduction Moderate; Childs Pugh 7-9 reduce dose to 35mg (following 70mg loading dose) Severe; avoid
Renal impairment	No dose adjustment; use with caution	No dose adjustment	No dose adjustment
Pregnancy	Safety not established 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 Advise not to breastfeed	Excreted in animal breast milk Advise not to breastfeed
Obesity	Dose based on adjusted body weight 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 Monitor renal function closely	If weight <40kg reduce to 4mg/kg	Limited information
Elderly	No dose adjustment needed Consider nephrotoxic risk	No difference in PK in elderly patients	AUC increased by 30% in elderly patients No dose adjustment needed