

Good Practice Recommendations on Use of Triazole Antifungal Agents in Chronic Respiratory Disease

Purpose of this guidance

The Scottish Antimicrobial Prescribing Group (SAPG) Antifungal Stewardship group have developed these recommendations through consultation with clinical specialists, to provide practical advice for Antimicrobial Management Teams and specialist clinicians for the appropriate and safe use of anti-fungal agents in chronic respiratory disease. The guidance adheres to the principles of Realistic Medicine:

- To minimise anti-fungal treatment associated harm and waste
- To minimise variation in prescribing practice across Scotland
- To promote shared decision making and individualised patient care.

They are intended to be used to inform/supplement local guidance for managing patients with Allergic bronchopulmonary aspergillosis (ABPA) and Chronic pulmonary aspergillosis (CPA). These recommendations do not replace clinical judgement, which should be influenced by individual patient risk factors. Clinicians should be mindful of the potential for harmful polypharmacy and increased risk to adverse drug reactions in patients with multiple co-morbidities or frailty.

Background

Chronic respiratory disease

Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity lung disease resulting from exposure to *Aspergillus fumigatus* and occurring primarily in people with asthma or with cystic fibrosis. Disease is characterized by a variety of clinical and immunologic responses to *A. fumigatus* antigens. Clinical manifestations include wheezing, pulmonary infiltrates (usually mucoid impaction), bronchiectasis and fibrosis.

Chronic pulmonary aspergillosis (CPA) is an uncommon and problematic pulmonary disease, complicating many other respiratory disorders. The most common form of CPA is chronic cavitary pulmonary aspergillosis (CCPA), which untreated may progress to chronic fibrosing pulmonary aspergillosis. The diagnosis of CPA requires a combination of characteristics: one or more cavities with or without a fungal ball present or nodules on thoracic imaging; direct evidence of *Aspergillus* infection (microscopy or culture from biopsy); an immunological response to *Aspergillus* spp. and exclusion of alternative diagnoses, all present for at least 3 months. *Aspergillus* IgG antibodies are elevated in over 90% of patients.

Current Practice

There are currently no UK guidelines specifically for management of chronic respiratory fungal disease. Clinicians in Scotland utilize European guidance and guidance on asthma, bronchiectasis and cystic fibrosis from the British Thoracic Society to inform patient management.

Various models of care have evolved with respiratory specialists in hospital and GP practices responsible for patient care often utilising a multi-disciplinary team (MDT) approach working with specialist pharmacists and specialist nurses. However, in some areas general medical consultants and GP Practice teams manage these patients following variable levels of advice from specialists. Shared care protocols to support effective joint hospital and primary care management of patients do not exist for ABPA or CPA.

Various models for providing prescriptions for antifungal medication are used with prescribing remaining hospital-based for some medicines due to their increased cost in the community.

Guidelines

International guidelines that provide useful advice on ABPA and CPA are listed below:

<https://www.cff.org/Care/Clinical-Care-Guidelines/Infection-Prevention-and-Control-Clinical-Care-Guidelines/Allergic-Bronchopulmonary-Aspergillosis-Clinical-Care-Guidelines/>

<https://erj.ersjournals.com/content/47/1/45>

Detailed advice on diagnosis and treatment of ABPA and CPA is provided in Appendices 1 and 2

Specialist Advice

Hospital respiratory consultants provide advice on ABPA and CPA to non-specialists and for complex cases; respiratory consultants seek peer support or contact the National Aspergillus Centre in Manchester. Work is underway to establish a Scottish network of specialist clinicians to provide a coordinated approach for peer discussion of complex cases.

Antifungal stewardship

Antimicrobial stewardship is essential to optimise antimicrobial use, minimise unnecessary use and to combat the emergence of resistance. In Scotland national and health board level programmes for antimicrobial stewardship have been established for over 10 years with work focused primarily on antibiotic use/ bacterial infections. Some health boards have established multidisciplinary antifungal stewardship teams to undertake ward rounds to optimise the management of patients in hospital on systemic antifungals.

Triazole antifungals accounts for the majority of systemic antifungal use in Scottish hospitals and resistance in certain fungal species is increasing. It is important to ensure that antifungal agents are used appropriately and to reduce any unnecessary use (to minimise the risk of resistance) but also to reduce potential harm and redundancy/waste.

Patients receiving antifungal treatment for chronic respiratory conditions may require long duration of treatment and some aspects of their care will be undertaken in the community. Therefore, good communication with GP Practice staff and patients about goals of treatment, specific monitoring requirements and potential adverse effects is of utmost importance.

Detailed information about using antifungal agents in chronic respiratory conditions is provided in Appendix 3.

Key Recommendations for Antifungal Stewardship in Chronic Respiratory Disease

1. DIAGNOSIS	<p>A specialist with expertise in this area utilising the 2016 European Respiratory Society guidelines should establish the diagnosis of ABPA and CPA. Diagnosis should be made with a combination of clinical history, radiology findings, microbiology, immunology, and histology. Alternative diagnoses, particularly lung malignancy and tuberculosis, should be excluded where possible.</p> <p>GPs should not start antifungal treatment based on a single sputum culture but should seek specialist advice. Standardised interpretation of the significance of respiratory fungal isolates is under development by the Scottish Microbiology and Virology Network.</p>
2. GOALS OF THERAPY	<p>The goal of therapy for each patient should be defined at the outset of treatment.</p> <p>The aim of treatment for CPA should be to maximise quality of life taking into account the potential side effects from drugs; in some cases therapy may not be the best option.</p> <p>The aim of treatment in ABPA is usually to minimise requirement for long-term steroids.</p>
3. ROLE OF THE MULTIDISCIPLINARY TEAM (MDT)	<p>Initiation, monitoring and discontinuation of antifungal treatment for CPA should ideally be done as part of an MDT discussion. The MDT should include a specialist in respiratory medicine (with expertise in management of CPA), a specialist pharmacist, and ideally a clinical nurse specialist.</p>
4. CONSIDERATIONS BEFORE PRESCRIBING ANTIFUNGAL THERAPY	<p>Triazole drugs are the mainstay of therapy in CPA and the antifungal of choice in ABPA.</p> <p>Careful review of the patient's medications, consideration of potential drug-drug interactions should be performed ideally in conjunction with a specialist/clinical pharmacist.</p> <p>Review baseline ECG to ensure no QTc prolongation prior to commencement of triazoles.</p> <p>Highlight to GP Practice team the potential for other drug interactions due to triazoles increasing the plasma concentrations of medicines metabolised by CYP450 isoenzymes. All patients should receive counselling on azole treatment including the common and important side effects and action to take if they experience them.</p>
5. CHOICE OF TRIAZOLE DRUGS	<p>Choice of triazole drugs should take into account the patient's burden of disease, concurrent medications and diseases. Potential drug-drug interactions and risk of ECG QTc prolongation are significant with all triazole drugs and should be considered carefully prior to commencement. A diagnosis of heart failure may make Itraconazole a less good option, for example, and lifestyle, where risk of photosensitivity in patients who spend significant amounts of time outside, may make Voriconazole a less good option.</p> <p>Specific advice on Itraconazole capsules: Patients should be advised to take with food and an acidic drink to improve absorption. They should also be advised on signs of hepatotoxicity and steroid excess. See Appendix 3 for advice on liquid formulation.</p> <p>Specific advice on Voriconazole: Patients should be advised to take their medication 1-2 hours after a meal. They should be warned regarding visual disturbance and photosensitization, recommended to use Factor 50 sunscreen and advised to wear protective clothing when exposed to sunlight. All patients should be given a patient Alert Card, and have a treatment checklist https://www.medicines.org.uk/emc/rmm/1312/Document</p>
6. THERAPEUTIC DRUG MONITORING (TDM)	<p>TDM should be performed in patients on triazole drugs within the first 2-4 weeks of initiation of therapy. Repeated TDM should be considered in the context of treatment failure, concerns regarding malabsorption or in the case of potential drug- drug interactions.</p>
7. TOXICITY MONITORING	<p>Patients should have LFTs measured regularly after starting therapy with triazole drugs. An ECG should be performed 2 weeks after initiation, and after dose changes. Specialists should coordinate any monitoring requirements. Target serum level ranges should use guidance from specific lab used.</p>
8. EFFICACY MONITORING	<p>Patients should have decisions regarding long-term therapy made by a respiratory specialist 3-6 months after initiation. A number of factors (clinical, immunological, radiological) will help inform decision to continue, change, or stop triazole therapy. Patients who continue on triazole therapy should have a specialist review every 3-6 months until considered stable. Usually, they should have ongoing review in secondary care even when stable for long periods.</p>

Appendix 1

Management of Allergic bronchopulmonary aspergillosis (ABPA)

Use of steroid therapy

If a patient has suspected ABPA together with asthma, treatment should usually be initiated using a high dose inhaled corticosteroid (HDICS) such as Fluticasone at 1000 Mcg-2000 mcg or Beclomethasone 400 mcg. The ICS may be combined with a long-acting beta-agonist (LABA).

If ABPA is not controlled by the HDICS alone, the patient can be treated with oral Prednisolone (40-60mg daily – 0.5mg/kg). This should be gradually reduced after the first month to the lowest dose (7.5-10mg) for maintenance control with careful monitoring.

Choice of antifungal agent

Itraconazole should be prescribed as a first line antifungal agent at the initiation of treatment to limit the need for steroid medication, or if the patient's symptoms do not respond to or cannot be controlled on HDICs or HDICs plus oral steroid treatment.

Treatment can be switched to Voriconazole if the patient is unable to tolerate Itraconazole.

An antifungal agent can also be given if there is evidence of saprophytic infection. Radiological features may guide this, or if there is a particular high Aspergillus IgG indicative of a significant burden of disease.

Occasionally other antifungal agents may be used on the advice of Microbiology e.g. Caspofungin, Anidulafungin or Amphotericin, and would be given in hospital or via an outpatient antibiotic therapy (OPAT) service if available.

Starting antifungals

Starting antifungal therapy should be informed by a history of asthma, chest x-ray/CT scan and clinical assessment. Serology should include the following, with interpretation guided by a physician with experience of diagnosis of ABPA:

- Total IgE
- Aspergillus IgE
- Aspergillus IgG
- Eosinophil count

Discontinuing antifungals

Antifungal treatment is for 3-6 months initially.

If symptoms significantly reduce with improvement in Total IgE, Aspergillus IgE, Aspergillus IgG and eosinophil count, clinicians may consider stopping antifungal therapy.

A chest x-ray/CT scan may be performed to inform decision-making.

Patients should be followed up regularly by a respiratory physician to review the ongoing need for antifungal treatment.

Appendix 2

Management of Chronic Pulmonary Aspergillosis (CPA)

Starting antifungals

Commencing antifungal therapy for CPA should be informed by chest x-ray/CT scan, exclusion of other conditions such as mycobacterial infection and malignancy, and perceived benefit of treatment. Serology should include the following, with interpretation guided by a physician with experience of diagnosis of CPA:

- Total IgE
- Aspergillus IgE
- Aspergillus IgG
- Eosinophil count

Choice of antifungal agent

First line treatment should usually be with Itraconazole. Voriconazole should be reserved for patients with a significant burden of disease. Second line treatment should be with Voriconazole or Posaconazole, where disease is not controlled, or unacceptable side effects are experienced.

Occasionally other antifungal agents may be used on the advice of Microbiology e.g. Caspofungin, Anidulafungin or Amphotericin, and would be given in hospital or via an outpatient antibiotic therapy (OPAT) service.

Discontinuing antifungals

Depending on clinical response, radiological and serological improvement, a patient may be on antifungal treatment for CPA for 6-12 months or long-term/indefinitely if there are no drug side effects with persisting radiological changes, symptoms, and immunological markers.

If there is an improvement in a patient's weight and inflammatory markers and symptoms significantly reduce with reduction in Aspergillus IgG, then clinicians may consider stopping antifungal therapy. A chest x-ray/CT scan may also be performed to inform decision-making.

Risks of stopping including subsequent worsening of symptoms should be fully explored with the patient.

Appendix 3

Use of antifungal agents

Pre-treatment checks

Clinicians should routinely check the British National Formulary (BNF) for potential drug interactions that could reduce efficacy or drug toxicity before commencing a patient on antifungal therapy. Decision-making on choice of treatment should be in collaboration with the multidisciplinary team with consideration of cautions around heart failure and QTc interval. An ECG should be done before starting antifungal treatment to provide a baseline then repeated after starting an azole. This is particularly important if patients are on other QT prolonging medicines or at risk of QT prolongation. Prescribers should seek pharmacy or cardiology advice if they have any questions about a prolonged QTc interval. Checks undertaken for clinical decision-making should be explicitly documented in the patient's notes.

Interactions with other medicines

Triazoles (Voriconazole & Itraconazole) are metabolised by, and inhibits the activity of, cytochrome P450 isoenzymes, Medicines that are inhibitors or inducers of these isoenzymes may increase or decrease triazole plasma concentrations, respectively, and there is potential to increase the plasma concentrations of medicines metabolised by these isoenzymes.

Triazoles should be administered with caution in patients with concomitant medication that is known to prolong QTc interval.

For Itraconazole it is recommended that proton pump inhibitors (PPI) and other acid suppression agents should be discontinued if possible. Reduced dosage can be considered if necessary.

For Itraconazole there is also a potential interaction with inhaled /oral steroids that can in rare cases result in Cushing's syndrome.

Always consult the relevant section of the [BNF](#) for full details of interactions.

Counselling Patients

Patients who are receiving antifungal therapy should be provided with appropriate counselling. This will include information about when to take medication, what to do if they experience adverse effects and how to avoid them.

Patients taking Voriconazole should be advised of the important identified risks connected with liver disease, photosensitivity, skin cancer and serious visual disturbance and to be alert to signs of these reactions and how to avoid them. The manufacturer of Voriconazole provides a patient warning card about skin cancer risk and this should be given to patient when they start treatment.

Useful resources to support discussions with patients being treated with Voriconazole are available <https://www.medicines.org.uk/emc/product/7981/rmms>

Monitoring liver function tests (LFTs)

Baseline LFTs should be undertaken before antifungal therapy starts. The [BNF](#) recommends following this up with weekly checks for the first month and then monthly during treatment. This may not be practical and a suggested compromise is after 2 weeks on treatment then at each follow-up clinic visit. If there are concerns about LFTs the patient's GP can be asked to carry out more frequent checks. Hospitals should ensure they have a robust process in place to ensure that the patient's GP or outpatient clinic is aware of the need for continued monthly monitoring of LFTs. Patients and their carers should also be advised of the need to arrange ongoing LFT testing.

Therapeutic drug monitoring

Therapeutic drug monitoring (TDM) is recommended for all patients to ensure effective treatment and is particularly helpful when patients are prescribed antifungal therapy where there is a known drug interaction. Check random levels at 14 days for Itraconazole, and a trough level at 14 days for Voriconazole. Earlier checks should be performed if Voriconazole has been given parenterally, as is sometimes done in very extensive disease.

Note that target serum level ranges vary between laboratories so it is important to use guidance from the specific laboratory used.

For some patients use of a liquid formulation may be useful if TDM suggests there are problems with absorption of solid oral dose forms.

To maximise absorption of Itraconazole capsules should be taken with or after food. Other suggested actions include stopping PPI or other acid lowering treatments where possible, taking the capsules with a cola drink or other acidic beverage, switching from capsules to liquid formulation. The liquid formulation should be taken on an empty stomach 1 hour before or 2 hours after food. Voriconazole is more reliably absorbed so consider switching to this if Itraconazole levels remain sub-therapeutic despite the above measures.

Adverse effects

Healthcare professionals are urged to report suspected adverse drug reactions with antifungal medicines directly to the Medicines and Healthcare products Regulatory Agency (MHRA) through the Yellow Card Scheme using the electronic form at www.mhra.gov.uk/yellowcard