Antifungal Prescribing Guidance in Respiratory Patients

Initiation by Respiratory Consultant Only

NHS Tayside

ALL PATIENTS SHOULD ALSO BE DISCUSSED AT COMPLEX PULMONARY INFECTION MDT

NOTES:

- This guidance covers prescribing for Allergic Bronchopulmonary Aspergillosis (ABPA) and Chronic Pulmonary Aspergillosis (CPA). Some patients with Severe Asthma with Fungal Sensitisation may benefit from antifungals (SAFS)
- For guidance on treating Invasive Aspergillosis or Sub acute Invasive Aspergillosis (SAIA) see full Antifungal Guidance
- The aim of treatment for CPA, depending on type and severity, may be cure or to improve symptoms and quality of life
- CPA – minimum 3-6 months treatment but often long term maintenance is required to prevent relapse
- ABPA/SAFS – minimum 3 months initial treatment then review
- All the oral triazoles are active against *Aspergillus fumigatus* except fluconazole
- *Aspergillus niger* is resistant to itraconazole and isavuconazole
- Doses assume non pregnant adults with normal renal and hepatic function (unless otherwise stated)
- TDM samples should ideally be taken Monday to Thursday (to allow for transport to specialist lab) and state time of last dose on request
- TDM results – if out with range discuss with pharmacist for dose adjustment and when to recheck levels

BASELINE EVALUATION:

- Add to Complex Pulmonary Infection MDT for discussion
- Standard bronchiectasis screen (on ICE) and discuss with Immunology if required
- Send sputum for microscopy, bacterial culture and sensitivity, fungal culture (specifying for azole resistance testing), and mycobacterial culture
- Consider bronchoscopy, prior to commencing antifungals in CPA, if not producing sputum
- For voriconazole consider patient occupation and hobbies prior to treatment – note any where significant time spent outdoors
- Full medication history and interaction check – ask Pharmacist for advice or use specialist antifungal website available at: Antifungal Interactions Database
- FBC/LFTs/U&Es/Ca/Mg
- ECG – itraconazole/voriconazole/posaconazole all prolong QT interval (isavuconazole shortens QT interval)
- If considering voriconazole – CYP2C19 Genotyping (on ICE>genetics>pharmacogenomics>CYP2C19>respiratory/ID)

FOLLOW UP:

- Patient should be reviewed in clinic at 3 months then 3 monthly for 1 year then every 6 months
- LFTs/U&Es at 2 weeks and then at each clinic appointment (increase frequency if any concerns)
- TDM – as per specific guidance for each antifungal detailed below
- ECG at 2 weeks, repeated thereafter if new medicines which also prolong QT interval are prescribed
- For CPA - CXR at 3 months and CT and repeat immunology at 6 months
- Discussion at Complex Pulmonary Infection MDT at 6 months to confirm continuation of therapy

ITRACONAZOLE: Caution in patients with ventricular dysfunction or heart failure.

***Indications*:** First line treatment for CPA and second line for ABPA (after steroids)

Starting dose: 200mg twice daily (<50kg 2.5mg/kg bd d/w pharmacist)

Formulation: capsules (consistently low levels consider switch to liquid formulation for better bioavailability)

Dispensing: Initial 1-3 months can be prescribed by hospital or primary care (under direction of respiratory specialist). Prescribing can be continued in primary care. Changes in dosing or discontinuation will be notified to primary care.

Levels: random level after 2 weeks on treatment. Target range: 1-3mg/L (1-2mg/L if experiencing side effects)
If stable - no need to recheck level unless change in condition or interacting medicines.
Note: different brands of capsules have differing bioavailabilities which may affect levels

Interactions: CYP3A4 substrate and potent CYP3A4/P-gp inhibitor – check all medicines. In particular be aware of statins, fluticasone (safer to use beclometasone due to risk of Cushing syndrome), PPIs, H_2RAs, antacids/calcium supplements, clarithromycin, anticoagulants

Adverse Effects: high rate of adverse reactions (40-50% of CPA patients) including GI upset, hair loss, peripheral neuropathy, pseudohypoaldosteronism, hypertension, ankle oedema, hepatotoxicity, hypokalemia, cardiac failure, prolonged QT

Patient counselling: Take capsules with a meal and acidic drink e.g. cola/orange juice to increase absorption. Liquid should be taken on an empty stomach 1 hour before or 2 hours after food. Advise on signs of hepatotoxicity and Cushing's if on oral/inhaled steroids.

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VORICONAZOLE: **Requires prior authorisation by ID/Micro or MDT**

Pharmacogenomic Testing – CYP2C19 genotyping ideally prior to treatment if feasible – discuss result with pharmacist

Consider occupation and hobbies prior to prescribing - if significant time outdoors other azoles may be more suitable

Indications: Second line CPA if itraconazole not tolerated, inadequate response (or first line if SAIA, large fungal burden/fungal ball or poor performance status)

Starting dose: 200mg twice daily (no loading dose required unless treating SAIA or large fungal burden)
If <50kg or mild/moderate cirrhosis check dosing with pharmacist

Formulation: tablets (liquid is available but should be discussed with pharmacist prior to prescribing)

Dispensing: Currently due to cost differences all dispensing should be done via hospital pharmacy. Ensure at least 1-2 months supplied on initial script or on discharge.

Monitoring: LFTs/U&Es/FBC (amylase/lipase if risk factors for acute pancreatitis) at 2 weeks then at each clinic appointment. Increase frequency if any concerns and if LFTs >3x ULN discuss with MDT

Levels: pre dose level 2 weeks after starting Target: 1.3 to 5.5mg/L
Some patients may require increase to 250-300mg twice daily

Interactions: CYP2C9/3A4/2C19 inhibitor – check all medicines. In particular beware of PPIs, opiates, NSAIDs, statins

Adverse Effects: more common than with itraconazole and include visual disturbances (usually transient and reversible normally resolving within 60 minutes but some reports of prolonged visual adverse effects), hepatotoxicity, photosensitivity, squamous cell carcinoma, peripheral neuropathy, prolonged QT

Patient counselling/warnings: Use Risk Materials including check list when initiating treatment, issue all patients with Alert Card, avoid intense or prolonged exposure to direct sunlight during treatment and wear protective clothing and factor 50 sunscreen. Also warn patient re visual disturbances.
Take tablets one hour before or two hours after a meal (food reduces absorption).

POSACONAZOLE: **Requires prior authorisation by ID/Micro or MDT**

Indications: Third line treatment for CPA due to previous antifungal intolerance, toxicity, clinical failure or resistance

Starting dose: 300mg daily (no loading dose required unless being used for SAIA or large fungal burden)

Formulation: 100mg gastro resistant tablets
DO NOT prescribe liquid unless discussed with a pharmacist: different dosing

Dispensing: Currently due to cost differences all dispensing should be done via hospital pharmacy. Ensure at least 1-2 months supplied on initial script or on discharge.

Monitoring: LFTs/U&Es at 2 weeks then at each clinic appointment (increase frequency if any concerns)

Levels: random level 2 weeks after starting Target: >1 to <3.75mg/L
Some patients reach adequate levels on 200mg daily

Adverse effects: less common than with voriconazole and include peripheral neuropathy, prolonged QT, hepatotoxicity, hypertension, GI upset, paresthesia, taste disturbance, pseudohypoaldosteronism.
Increased risk of photosensitivity added to SPC October 2024.

Interactions: CYP3A4 inhibitor and affected by P-gp enzyme inducers - check all medicines. In particular be aware of statins, digoxin, calcium channel blockers

Patient counselling: Swallow tablets whole with or without food. Advise on signs of hepatotoxicity. Advise patient to avoid intense or prolonged exposure to direct sunlight during treatment and wear protective clothing and factor 50 sunscreen

Other options for CPA: **All require prior authorisation by ID/Micro or MDT**

Isavuconazole oral/IV – oral 200mg tds for 2 days then 200mg od d/w pharmacist re TDM

Caspofungin IV/Amphoteracin B Liposomal IV (Ambisome or Tillomed brand) for 3 -4 weeks in salvage therapy or severe cases at presentation. Refer to Antifungal Guideline for dosing advice

References: Magharabi F, Denning D. The Management of CPA Curr Fungal Infect Rep (2017) 11:242-251
IDSA Aspergillosis guidelines 2016 ABPA ERS Review 2014 DTB 2022
ERS/ESCMID CPA Guidelines 2016 ESCMID Aspergillus guidelines 2018
SAPG ABPA/CPA Guidance 2020 TDM of Posaconazole 2016
NAC Manchester Guidance – adapted with kind permission

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