Antifungal Prescribing Guidance in Respiratory Patients
Initiation by Respiratory Consultant Only

ALL PATIENTS SHOULD ALSO BE DISCUSSED AT COMPLEX RESPIRATORY 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 Subacute 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 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 Respiratory Infection MDT for discussion
• Standard bronchiectasis screen and discuss with Immunology if required
• Send sputum for MCS, Fungal Culture (specifying for azole resistance testing), and mycobacterial culture
• Consider bronchoscopy, prior to commencing antifungals in CPA, if not producing sputum
• Consider patient occupation and hobbies prior to treatment – note any where significant time spent outdoors for consideration of voriconazole therapy
• Full medication history and interaction check – ask Pharmacist for advice or use specialist antifungal websites and apps available: National Aspergillosis Centre/ Fungal Pharmacology
• FBC/LFTs/U&Es/Ca/Mg
• ECG – itraconazole/voriconazole/posaconazole all prolong QT interval (isavuconazole shortens QT interval)
• St Georges quality of life questionnaire

FOLLOW UP:
• Patient should be reviewed in clinic at 3 months then 3 monthly for 1 year then every 6 months
• LFTs 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
• St Georges quality of life questionnaire at 3 and 6 months
• Discussion at Complex Respiratory 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)
**Dispensing:** capsules (consistently low levels consider switch to liquid formulation for better bioavailability)

**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, H2RAs, antacids/calcium supplements, clarithromycin, anticoagulants

**Adverse Effects:** high rate of adverse reactions (40-50% of CPA patients) including GI upset, hair loss, peripheral neuropathy, 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
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 5.7mg/L
Younger patients often 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:** usually via hospital pharmacy (or prescribe on HBP pad for community pharmacy dispensing – discuss with pharmacist). Ensure at least 1-2 months supplied on initial script or on discharge.

**Monitoring:** LFTs 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
Many 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

**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

Other options for CPA: All require prior authorisation by ID/Micro or MDT
Isavuconazole oral/IV – no published data (oral 200mg tds for 2 days then 200mg od) d/w pharmacist re TDM
Caspofungin IV/Ambisome IV for 3 weeks in salvage therapy or severe cases at presentation. Refer to Antifungal Guideline for dosing advice

References:
IDSA Aspergillus guidelines 2016
ABPA ERS Review 2014
TDM of Posaconazole 2016
Fungal Pharmacology Website
ERS/ESCMID CPA Guidelines 2016
ESCMID Aspergillus guidelines 2018
NAC Manchester Guidance – adapted with kind permission

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