ADULT ANTIFUNGAL GUIDANCE

NHS Tayside

ALWAYS DISCUSS WITH ID OR MICROBIOLOGY PRIOR TO PRESCRIBING IV ANTIFUNGALS

- These guidelines apply to invasive infections in non pregnant adults only. See separate guidelines for oncology and haematology patients.
- Invasive fungal infections are mostly seen in non-neutropenic intensive care patients and in patients with neutropenia or significant immunosuppression.
- Voriconazole offers no advantage over fluconazole for isolates that are sensitive to both of these azole antifungals.
- Refer to voriconazole professional checklist and patient alert card here
- Always check for antifungal interactions in SPC or consult pharmacist or specialist website - https://antifungalinteractions.org/

INFECTION	PATIENT	ANTIFUNGAL	ALTERNATIVE	DURATION	COMMENTS
PROVEN OR PRESUMED CANDIDAEMIA Empiric treatment prior to identification of species	Clinically stable patients + Non neutropenic + No recent (within 4 weeks) azole exposure or fluconazole treatment failure + No previous positive blood culture/invasive infection due to azole resistant isolate + No prolonged exposure to azoles + No current colonization with fluconazole resistant Candida species + No intolerance of/contraindication (e.g. drug interaction) to fluconazole	FLUCONAZOLE IV 800mg loading dose then 400mg daily maintenance dose Check drug interactions For patients with BMI ≥ 30kg/m^2 use 12mg/kg loading dose and 6mg/kg maintenance dose (usual maximum 1200mg loading dose and 600mg maintenance dose) If CrCl <50ml/min dose needs adjusted – refer to renal drug database or seek advice from pharmacist Maintenance dose may be increased to 800mg daily (12mg/kg) on advice of ID/Micro if *Candida glabrata* identified with dose-dependent sensitivity If IVOST criteria are met oral fluconazole can be used to complete course. Bioavailability of oral fluconazole is >90%.	Change to ANIDULAFUNGIN or CASPOFUNGIN as per guidance below if clinical deterioration	2 weeks after first negative blood culture and resolution of symptoms ***If patient was neutropenic:*** 2 weeks after first negative blood culture and resolution of symptoms and resolution of neutropenia ***If patient was culture negative:*** For patients who have no clinical response to empiric antifungal therapy at 4–5 days and who do not have subsequent evidence of invasive candidiasis after the start of empiric therapy or have a negative non-culture-based diagnostic assay with a high negative predictive value, consideration should be given to stopping antifungal therapy	Blood cultures should be repeated every second day until negative Central line removal/replacement is recommended as it can act as a reservoir. Remove any implicated prosthetic material unless absolutely contra-indicated. If eye symptoms, consider dilated fundoscopy to exclude endophthalmitis and investigations to rule out infective endocarditis FLUCONAZOLE/ CASPOFUNGIN – always check for drug interactions Fluconazole IV is significantly less expensive than anidulafungin and caspofungin
	ALL OTHER PATIENTS (except oncology and haematology patients – see links in red box above)	**Neutropenic or Non-neutropenic:** ANIDULAFUNGIN IV 200mg loading dose then 100mg daily maintenance dose OR CASPOFUNGIN IV 70mg loading dose then 50mg daily (≤80kg) 70mg daily (>80kg) 105mg daily (>110kg) Check drug interactions Do not use Caspofungin in severe liver impairment (Child Pugh score>9) Alter dose if Child Pugh score 7-9 unless score driven by hypoalbuminaemia. All patients: change to Fluconazole if *Candida albicans* isolated and patient clinically stable	✧Amphotericin B **liposomal** 3mg/kg/day (can be increased up to 5mg/kg/day) Prescribe by full generic name and brand/supplier e.g. Amphotericin B liposomal (Ambisome or Tillomed brand)		

CANDIDAEMIA **targeted treatment following identification of species**	*Candida nakaseomyces* isolated *(previously known as Candida glabrata*) OR *Candida pichiakudriavzevii* isolated *(previously known as Candida krusei*)	ANIDULAFUNGIN IV 200mg loading dose then 100mg daily maintenance dose OR CASPOFUNGIN IV 70mg loading dose then 50mg daily (≤80kg) 70mg daily (>80kg) 105mg daily (>110kg) Check drug interactions Do not use Caspofungin in severe liver impairment (Child Pugh score>9) Alter dose if Child Pugh score 7-9 unless score driven by hypoalbuminaemia. All patients: change to fluconazole only if susceptibility confirmed. Maintenance dose maybe increased to 800mg daily (12mg/kg) on advice of ID/Micro if *Candida glabrata* identified with dose-dependent sensitivity	✧Amphotericin B **liposomal** 3mg/kg/day (can be increased up to 5mg/kg/day) Prescribe by full generic name and brand/supplier e.g. Amphotericin B liposomal (Ambisome or Tillomed brand)	As above	As above
	Candida albicans isolated	FLUCONAZOLE IV (dosing as above)	CASPOFUNGIN IV or ANIDULAFUNGIN IV		
	Candida parapsilosis isolated	FLUCONAZOLE IV (dosing as above)	✧Amphotericin B **liposomal** 3mg/kg/day (can be increased up to 5mg/kg/day) Prescribe by full generic name and brand/supplier e.g. Amphotericin B liposomal (Ambisome or Tillomed brand)		*Candida parapsilosis* usually has higher MICs to echinocandins (caspofungin/ anidulafungin)
CANDIDA in <u>urine</u> **DO NOT TREAT** if asymptomatic and not at high risk of dissemination	**Check sensitivities and consult with ID/Microbiology before initiating treatment.** Treat high risk patients including neutropenic or those undergoing urologic manipulation/instrumentation	FLUCONAZOLE IV (dosing as above) High concentrations in urine	IV Conventional or NON-LIPID Amphotericin B FUNGIZONE brand Prescribe by full generic name and brand name. Dosing as per p5 below. DO NOT USE	Review at 7 days	Amphotericin B liposomal (Ambisome or Tillomed brands), other azoles and echinocandins CANNOT be used as they do not reach adequate levels in urine. Consider removal of prosthetic material

			liposomal Amphotericin B Consider adding FLUCYTOSINE PO 25mg/kg qds if available (unlicensed product)		(catheter/nephrostomy etc) if possible. Flucytosine – see cryptococcal section below re levels

Invasive ASPERGILLOSIS or Subacute Invasive ASPERGILLOSIS (SAIA)	VORICONAZOLE IV 6mg/kg every 12 hours for 2 doses then 4mg/kg every 12 hours (for obese patients use adjusted body weight) Consider early switch to oral if patient clinically responding, able to tolerate and absorb oral medication. Bioavailability of oral voriconazole is 96%.	If patient is intolerant of IV voriconazole use ✧Amphotericin B **liposomal** 3mg/kg/day (can be increased up to 5mg/kg/day) Prescribe by full generic name and brand/supplier e.g. Amphotericin B liposomal (Ambisome or Tillomed brand or IV ISAVUCONAZOLE 200mg tds for 2 days then 200mg od Oral POSACONAZOLE* or oral ISAVUCONAZOLE may be an alternative switch in patients unable to tolerate voriconazole	Minimum of 6-12 weeks	Always check for drug interactions with VORICONAZOLE, ISAVUCONZAOLE and POSACONAZOLE* Therapeutic drug monitoring within 3-5 days if loading dose given. Pre dose voriconazole (1.3 -5.5mg/L) or posaconazole (1-3.75mg/L) Ensure patient has voriconazole alert card *Posaconazole liquid and tablets are not interchangeable – always specify formulation on prescription and check dosage.
HAEMATOLOGY/ ONCOLOGY PATIENTS	See separate guidance			
RESPIRATORY PATIENTS Chronic Pulmonary Aspergillosis (CPA), Allergic Bronchopulmonary Pulmonary Aspergillosis (ABPA), Severe Asthma with Fungal Sensitisation (SAFS)	See separate guidance			

MUCORMYCOSIS	Consult ID/Microbiology, start ✧Amphotericin B **liposomal** (Ambisome or Tillomed) brand IV 5mg/kg/day (brain involvement or solid organ transplant or refractory disease use 10mg/kg /day) Prescribe by full generic name and brand/supplier name. Consider IV isavuconazole 200mg tds for 2 days then 200mg od as alternative in renal disease, progressive disease or toxicity with Amphotericin B liposomal. In stable disease or partial response switch to oral isavuconazole or posaconazole tablets. TDM required for posaconazole (pre dose 1-3.75 mg/L) and should be considered for isavuconazole (pre dose 1-4mg/L) in some clinical situations such as suspected treatment failure, drug interactions, suspected toxicity or intolerance, obesity, or after switching from IV to oral therapy in a patient with documented mucormycosis. If rhino-orbital disease seek urgent surgical opinion for consideration of debridement. Echinocandins (caspofungin/andidulafungin) and Voriconazole are not active against this infection.				
CRYPTOCOCCAL MENINGITIS	HIV patients	See separate guidance for Treatment of Opportunistic Infections			Echinocandins (caspofungin/ anidulafungin) do not have activity against *Cryptococcus* spp. IV Flucytosine has been discontinued in the UK PO Flucytosine is not licensed for use in the UK d/w pharmacist to obtain supply Haematological/hepatic toxicities are are associated with high blood levels - flucytosine levels (pre dose and 2 hour post dose) should be done 3-5 days after starting therapy and after any changes in renal function).
	Transplant patients/ Non HIV patients	Induction: ✧IV Amphotericin B **liposomal** (AMBISOME or Tillomed brand) 10mg/kg day 1 only + FLUCYTOSINE PO 25mg/kg/every 6 hours + FLUCONAZOLE 1200mg daily (if oral route not available use fluconazole IV 800mg daily) OR ✧ IV Amphotericin B **liposomal** (AMBISOME or Tillomed brand) 4mg/kg daily + FLUCYTOSINE PO 25mg/kg/every 6 hours (if oral route not available use fluconazole IV 800mg daily) Consolidation: FLUCONAZOLE PO 400-800mg/day Maintenance: FLUCONAZOLE PO 2OOmg/day	Seek advice	Induction: 2- 4 weeks Consolidation: 8 weeks Maintenance: 12 months	

✧ IV Amphotericin B **liposomal** (AMBISOME or Tillomed brand) - Initial test dose of 1mg should be given over 10 minutes, stop infusion and observe patient for at least 30 mins, continue if no anaphylactoid/allergic reactions. Test dose has to be repeated at beginning of each new course of treatment. Always prescribe by full generic name and brand/supplier name. Avoid slow escalation of doses. Use adjusted body weight in obese patients.

References:

1. IDSA Candidiasis Guidelines 2016
2. Global guideline for the diagnosis and management of cryptococcosis 2024
3. IDSA Treatment of Aspergillosis Guidelines 2016
4. ESCMID Candida Guidelines 2012
5. British Society for Medical Mycology Invasive Fungal Infections 2003
6. JA Roberts et al; Drug Dosing in Obesity; published 2017
7. Wurtz et al; Antibiotic Dosing in Obese Patients; Clin Inf Dis; 1997
8. Mourad et al; Tolerability profile of the current antifungal armoury; JAC; 2018
9. Pea et al; Overview of antifungal dosing in invasive candidiasis; JAC; 2018
10. Dosing antifungals in Obesity: a Literature Review; Current Fungal Infection Reports (2019)
11. SAPG Candidaemia Guidance 2019
12. Global guideline for the diagnosis and management of mucormycosis 2019

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NON-LIPID AMPHOTERICIN - FUNGIZONE® Infusion Information Sheet

(amphotericin B deoxycholate)

(also known previously as conventional or non lipid based or non liposomal amphotericin)

MUST BE PRESCRIBED BY COMPLETE GENERIC NAME AND BRAND NAME

MHRA July 2018: Risk of potential fatalities if IV amphotericin formulations confused. Verify product name and dose before administration.

General:

- **Clinical Use:**
  - Fungal urinary tract infections where fluconazole is not suitable
  - Other indications based on recommendation of Infectious Diseases or Microbiology only
  - This document refers to IV administration, for administration via bladder instillation see SmPC and references

- **Dosing:**
  - Use lean body weight in obese patients
  - Recommended dosing for urinary tract infections is 0.3-0.6mg/kg/day
  - Usual starting dose is 0.25mg/kg/day. In critically ill patients, with good cardiopulmonary function, consider starting with 0.3mg/kg/day
  - Doses may be gradually increased by 5-10mg/day
  - For other infections the dose can be increased gradually to 1mg/kg daily
  - Maximum dose of 1.5mg/kg/day should **NEVER BE EXCEEDED**
  - If stopped for >7 days therapy should be initiated at starting dose above
  - No dose adjustments are required for existing renal impairment

- **Preparation of Infusion:**
  - Check with Pharmacy staff if Fungizone is prepared at ward level or by aseptic pharmacy department, may vary depending on NHS Scotland Board
  - Refer to Medusa NHS Injectable Medicines Guide website for instructions on reconstitution
  - Incompatible with sodium chloride 0.9%, dilute only with glucose 5%
  - Fungizone vials of powder for reconstitution are kept in the fridge
  - Fungizone will precipitate from solution at pH <4.2. If no buffer is available check pH of glucose batch with pharmacy aseptic unit, if agreed local practice, or Baxter Medicines Information Department (medinfo_uki@baxter.com; phone 01635 206345). If pH ≥ 4.2 then buffer not required. Local Medicines Information Department will be able to provide contact details for other fluid manufacturers if needed. Approximately 1ml of phosphate buffer will adjust the pH of every 250ml of glucose 5% to adequate pH. Buffer may be available via pharmacy department (product supplied by NHSS Pharmaceutical Specials Service as a 2ml vial)
  - Fungizone infusion should be a maximum concentration of 1mg/10ml. See advice in Medusa NHS Injectable Medicines Guide website if considering more concentrated infusion
- **Administration of Infusion:**
  - Infusions should be used promptly after preparation

- Flush line/cannula before and after each dose, with 5% glucose as Fungizone is incompatible with sodium chloride 0.9%
- Nephrotoxicity may be reduced by giving an IV infusion of 250ml to 500ml of suitable fluid over 30-45 minutes (according to patient's age and clinical status) immediately **prior** to each dose of Fungizone
    - A 1mg test dose **must** be administered at the beginning of each new course of treatment
        - **For test dose** - infuse 1mg over 20-30 minutes using an infusion pump, stop infusion and observe patient for further 30 minutes. If no severe anaphylactic or allergic reaction
        - Infuse the rest of the bag over 2-4 hours using an infusion pump. Flush the administration set before it is disconnected with sufficient glucose 5% to ensure the total dose is given

- **Adverse Reactions/Monitoring:**
    - If patient develops 'flu like' symptoms or other acute infusion related adverse effects decrease the rate of the infusion and administer over up to 6 hours if necessary
    - Severity of reactions can be reduced by giving antipyretics, antihistamines or anti-emetics. See Medusa website for further advice
    - Daily monitoring of electrolytes (especially Mg and K), renal function, FBC, LFTs is recommended. Mg and K supplementation is often routinely required and local guidelines should be followed.
    - Extravasation may cause chemical irritation or tissue damage - if extravasation occurs refer to local treatment policies
    - For full information on adverse reactions refer to Electronic Medicines Compendium or BNF

References:

Medusa NHS Injectable Medicines Guide. Accessed 28/08/2023
Electronic Medicines Compendium. Accessed 28/08/2023
Medicines Complete. Accessed 28/08/2023
Renal Drug Database. Accessed 28/08/2023
John Hopkins Antibiotic Guide. Accessed 28/08/2023
IDSA Candidiasis Guidelines (2016). Accessed 03/10/2023
Antifungal dosing in Obesity: A Review of the Literature. Curr Fungal Infect Rep (2011) 5:83-91

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