Background

Candidaemia has a mortality rate of 20-49%, its incidence is increasing, and the at-risk population is expanding. European Society of Microbiology & Infectious Diseases (ESCMID)1 and Infectious Diseases Society of America (IDSA)2 Guidelines have been updated to reflect randomised controlled trial evidence. These guidelines have also emphasised the importance of excluding ongoing candidaemia and end-organ involvement when planning duration of treatment. A local retrospective audit demonstrated significant non-compliance with both ESCMID and IDSA Guidelines leading to the development of these local Guidelines.

Scope of Document

These Guidelines are intended for use by Microbiologists and Infectious Diseases Physicians working within all Trusts served by Liverpool Clinical Laboratories. They are intended to facilitate compliance with ESCMID and IDSA Guidelines by presenting the recommendations in the form of a “Candida Bundle”. They apply to non-neutropenic adults only. Section 1 of the document refers to patients with Yeast seen in Gram stain of positive blood culture. Section 2 of the document refers to patients at risk of invasive candida infection in whom the clinician is considering empirical antifungal treatment.

The Guidelines are a composite of ESCMID and IDSA updated Guidelines and are intended as a guide only. They do not account for individual variation amongst patients, and are not intended to supplant clinical judgment.
SECTION 1: MANAGEMENT OF CANDIDAEMIA IN ADULT NON-NEUTROPENIC PATIENTS

BUNDLE 1: Initial Management of Yeast seen in Blood culture Gram stain

Key Components:
- Initial treatment with an echinocandin at the appropriate dose
- Removal of indwelling intravascular catheter where appropriate
- Repeat blood cultures at initiation of treatment and every 48 hours thereafter until a negative blood culture is obtained following 72 hours of incubation

1. The initial advice to the clinical team should include:
   - **Commence IV echinocandin at the appropriate dose** (see Appendix, Table 1 and Table 2 for contra-indications, pharmacokinetic/pharmacodynamics, resistance profiles and alternative agents).
   - **Remove indwelling intravascular catheters where appropriate**
   - **Repeat blood cultures at initiation of treatment and every 48 hours thereafter until a negative blood culture is obtained following 72 hours of incubation**

All advice given to the clinical team should be documented on Telepath using the Candidaemia Bundle (See Appendix, Figure 3), and the clinical notes.

2. The Medical Microbiologist / Infectious Diseases Physician communicating the result should refer the patient to the respective Medical Microbiology / Infectious Diseases Consults Service for patients at Royal, Aintree and Walton Centre. For patients at other sites the Microbiology Consultant responsible for that site should be informed (Liverpool Women’s = Tim Neal, Liverpool Heart and Chest = Toong Chin or Carlos Nistal de Paz).

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1. IDSA and ESCMID recommend daily blood cultures. For local purposes it is felt that alternate days would facilitate compliance in practice.
BUNDLE 2: Clinical Review

Key Components:

- All patients should be clinically reviewed by a member of the Infection Service within 48 hours or at the earliest opportunity.
- The duration of the antifungal agent should be at least 14 days from the date of the first negative blood culture AND/OR clinical resolution (whichever occurs later).
- Trans-thoracic echo (TTE) followed by discussion (and documentation of discussion) with Cardiology regarding requirement for trans-esophageal echo (TOE).
- Dilated fundoscopy performed by Ophthalmologist (pending discussion at Ophthalmology Audit/Governance meeting).
- Rationalisation of antifungal agent when full identification and sensitivities available.

1. All patients should be physically reviewed by a member of the Infection service within 48 hours of the initial report Monday-Friday, or at the earliest opportunity Saturday-Sunday.

2. The initial clinical ward review should include:

- Request a transthoracic echocardiography to assess for endocarditis. Aintree and Walton Centre patients should be referred to the I.E. MDT.
- Request inpatient Ophthalmology review for dilated fundoscopy.
- Repeat blood cultures should be performed on alternate days until a set has been negative after 72 hours incubation.
- Clinical assessment including inflammatory markers, NEWS, presence of indwelling devices, and possible sources of Candidaemia (i.e. intra-abdominal, urinary etc.). For Walton Centre patients consider sampling CSF if blood brain barrier breached (and refer to Appendix Table 3, and Walton Centre Guidelines regarding management of CNS infection).
- Review of prescribing system to ensure patient is on the correct antifungal at the correct dose (see Appendix, Table 1).

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2 Sensitivity of blood cultures estimated approx. 50%, thus negative blood culture cannot exclude ongoing candidaemia and clinical correlation required.

3 ESCMID recommends TOE whereas IDSA make no recommendation. Prevalence of IE ranges from 5.9-8% in Candidaemia, with all cases identified by TOE (Eur J Clin Microbiol Infect Dis (2015) 34:1543–1549).

4 The optimal timing of fundoscopy is unclear. Early review is advocated to commence appropriate treatment. There is some evidence to suggest fundoscopy at 2 weeks allows identification of a further 13% of cases (Eye (2000) 14, 30-3).
3. The patient should be reviewed with identification and sensitivity results. This review should include:
   1. Rationalisation of antifungal agent when full identification and sensitivities available.
      o In cases of fluconazole sensitive *Candida albicans* the echinocandin should be changed to fluconazole provided there are no contra-indications (see Appendix, Table 1).
      o Antifungal choice for non-albicans species should be based on susceptibility profile (NB: Remember to check the MICs in the word processor on Telepath\(^5\) and refer to breakpoint data in Appendix, Table 4)
   2. Features of antifungal toxicity i.e. hypersensitivity, liver and renal function
   3. Transthoracic echocardiography results
   4. Where transthoracic echocardiography is negative or inconclusive, the requirement for trans-eosophageal echocardiography should be discussed with Cardiology and documented in the clinical notes and on Telepath.

   The duration of the antifungal agent should be at least 14 days from the date of the first negative blood culture AND/OR clinical resolution (whichever occurs later\(^6\)). Oral step down can be considered from Day 10 onwards. The advice should be documented in the clinical notes and Telepath using the Candida 2 Bundle (Appendix, Figure 4).

   For advice regarding management of end organ or complex disease refer to ESCMID and IDSA Guidelines and see Appendix, Table 3.

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\(^5\) Note: All MICs given for *C. albicans* – take particular care with non-albicans species.

\(^6\) Sensitivity of blood cultures estimated approx. 50%, thus negative blood culture cannot exclude ongoing candidaemia and therefore clinical correlation is required.
SECTION 2: PROPHYLAXIS AND EMPIRICAL/PRE-EMPTIVE AND TREATMENT OF CANDIDAEMIA

Prophylaxis: The evidence for use of fluconazole as prophylaxis in ICU settings is inconclusive. The number needed to treat to prevent one episode of candidaemia varies from 8-188. Given the relatively low prevalence of candidaemia locally fluconazole prophylaxis is not recommended in non-neutropenic adult ICU patients. Exceptions to this include patients with variceal bleeds, mediastinitis, and oesophageal perforation or on the advice of Birmingham Liver Transplant Unit.

Empirical: Retrospective trials have demonstrated improved survival in high risk groups on ICU receiving empirical therapy, but this has not been confirmed in prospective trials. High risk groups include:

- Abdominal surgery, particularly recurrent anastomotic leaks or perforations
- Acute necrotising pancreatitis
- Haematological malignancy
- Solid organ transplant
- Solid organ tumour
- Total parenteral nutrition
- Haemodialysis
- Steroid use
- Chemotherapy
- Candida colonisation at non-sterile sites
- Central venous catheter
- Broad spectrum antibiotic use

In adult non neutropenic patients empirical antifungal therapy should ONLY be given to patients with unexplained clinical features of infection (such as fever, increasing or raised WCC, hemodynamic instability etc.) AND presence of at least two risk factors (above). The preferred antifungal choice is:

- ICU patients: Micafungin 100mg once daily for 14 days
- Non ICU patients: Fluconazole 400mg once daily UNLESS the patient has been exposed to azoles in the recent past, is colonised with azole-resistant candida species or been admitted to ICU, in which case micafungin should be used.

The duration is the same as that for candidaemia (14 days). These patients do not require TTE or fundoscopy unless end organ disease is suspected clinically.
SECTION 3: AUDIT STANDARDS

Bundle 1: Initiation of Treatment
- Initial treatment with an echinocandin at an appropriate dose
- Removal of indwelling intravascular catheter where appropriate
- Repeat blood cultures should be performed on alternate days until a set has been negative after 72 hours incubation

Bundle 2: Follow up
- The duration of the antifungal agent should be at least 14 days from the date of the first negative blood culture AND/OR clinical resolution (whichever occurs later).
- Trans-thoracic echo (TTE) followed by discussion (and documentation of discussion) with Cardiology regarding requirement for trans-esophageal echo (TOE)
- Dilated fundoscopy performed by an Ophthalmologist
- All patients should be clinically reviewed by a member of the Infection service within 48 hours or at the earliest opportunity

Prophylaxis and Empirical Treatment
- Antifungal prophylaxis is not recommended in non-neutropenic ICU patients \(\text{Exceptions = variceal bleeds, mediastinitis, and oesophageal perforation or on the advice of Birmingham Liver Transplant Unit}\).
- In adult non neutropenic patients empirical antifungal therapy should ONLY be given to patients with unexplained clinical features of infection AND presence of at least two risk factors.

REFERENCES

## APPENDIX

Table 1: Antifungal Agents Adapted from J Antimicrob Chemother 2015; 70: 587–593

<table>
<thead>
<tr>
<th>Antifungal</th>
<th>Dose</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micafungin</td>
<td>100mg once daily (can be increased up to 200mg once daily in patients &gt;40kg with poor clinical response)</td>
<td>Poor penetration into intra-ocular fluid and urine Animal studies describe development of liver tumours with long term use. Use with caution for prolonged periods in patients with diseases known to represent pre-neoplastic conditions (such as cirrhosis).</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>Loading dose 70mg then 50mg once daily (In patients weighing more than 80 kg, after the initial 70 mg loading dose, caspofungin 70 mg daily is recommended)</td>
<td>Poor penetration into intra-ocular fluid and urine Echinocandin of choice in Haemato-oncology patients</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Loading dose 800mg then 400mg daily (Larger doses may be required in obese patients)</td>
<td>Avoid if recent azole exposure C. glabrata and kruseii are considered resistant Increased risk of miscarriage reported</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>IV: 6mg/kg 12-hourly for two doses then 3-4mg/kg 12 hourly (Dose using IBW and adjust following TDM, refer to BNF for oral dose)</td>
<td>TDM recommended Intravenous formulation associated with renal toxicity Poor penetration in urine Increased risk of skin cancer in lung transplant patients, and potentially in other patients groups</td>
</tr>
<tr>
<td>Liposomal Amphotericin B</td>
<td>Test dose = 1mg then 1-5mg/kg daily</td>
<td>May be agent of choice in C. glabrata, C. krusei and C. guillermondii No activity against C. lusitaniae</td>
</tr>
<tr>
<td>5 Flucytoscine</td>
<td>25mg/kg 6-hourly</td>
<td>Use in combination with other antifungal agents TDM recommended</td>
</tr>
</tbody>
</table>

Table 2: Antifungal Spectrum: Adapted from Sanford Guide

<table>
<thead>
<tr>
<th>Candida Species</th>
<th>Echinocandin</th>
<th>Fluconazole</th>
<th>Voriconazole</th>
<th>Amphotericin</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. albicans</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>C. dubliensis</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>C. glabrata</td>
<td>++</td>
<td>+/-</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>C. krusie</td>
<td>++</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>C. guillermondii</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>C. lusitaniae</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+/-</td>
</tr>
</tbody>
</table>
### Guidelines for the Management of Candidaemia

<table>
<thead>
<tr>
<th>Candida species</th>
<th>+/-</th>
<th>++</th>
<th>+</th>
<th>++</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>C. parapsilosis</em></td>
<td>+/-</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td><em>C. tropicalis</em></td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td><em>C. auris</em></td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
</tbody>
</table>

++ = Likely to be clinically effective; +/- = Variable activity; - = Likely to be ineffective

### Table 3: Management of End Organ Disease (also refer to ESCMID and IDSA Guidelines)

<table>
<thead>
<tr>
<th>System</th>
<th>Antifungal</th>
<th>Duration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intra-abdominal</td>
<td>As Candidaemia</td>
<td>Minimum 14 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Duration determined by source control and clinical response</td>
<td></td>
</tr>
<tr>
<td>Endocarditis</td>
<td>Amphotericin B +/- 5-Flucytoscine OR High dose echinocandin</td>
<td>Minimum 6 weeks post valve replacement Consider long term suppression if valve replacement inappropriate</td>
<td>Valve replacement recommended</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>Fluconazole OR echinocandin for 14 days followed by fluconazole for 6-12 months</td>
<td>6-12 months</td>
<td>Consider surgical debridement</td>
</tr>
<tr>
<td>Septic Arthritis</td>
<td>Fluconazole OR echinocandin for 14 days followed by 4 weeks fluconazole</td>
<td>6 weeks</td>
<td>Surgical drainage indicated Prosthetic material should be removed. If prosthetic material cannot be removed long term suppression should be considered</td>
</tr>
<tr>
<td>Choreoretinitis</td>
<td>WITHOUT VITRITIS: Fluconazole daily OR Voriconazole WITH VITRITIS: As choreoretinitis without vitritis PLUS intravitreal Amphotericin B</td>
<td>4-6 weeks</td>
<td>With macular involvement intra-vitreal amphotericin B or voriconazole recommended Consider vitrectomy</td>
</tr>
<tr>
<td>Central Nervous System</td>
<td>ENDOGENOUS: Amphotericin B +/- 5-Flucytoscine</td>
<td>Until signs, symptoms, CSF and</td>
<td>Consider TDM within CSF</td>
</tr>
</tbody>
</table>
**Guidelines for the Management of Candidaemia**

**EXOGENOUS:** Fluconazole or voriconazole +/- 5-flucytosine

**radiological changes have resolved**

| **Pyelonephritis** | **Fluconazole OR Amphotericin B** | **14 days** | Remove obstructing nephropathy |

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Table 4: Breakpoints (copied from: Drug Resistance Updates 16 (2013) 81–95)

<table>
<thead>
<tr>
<th>Antifungal agent</th>
<th>MIC breakpoint (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C. albicans</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>EUCAST</td>
</tr>
<tr>
<td></td>
<td>S ≥ 1</td>
</tr>
<tr>
<td>Amisulofungin</td>
<td>EUCAST</td>
</tr>
<tr>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>EUCAST</td>
</tr>
<tr>
<td></td>
<td>0.25</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>EUCAST</td>
</tr>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Flucytosine</td>
<td>EUCAST</td>
</tr>
<tr>
<td></td>
<td>ND</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>EUCAST</td>
</tr>
<tr>
<td></td>
<td>0.016</td>
</tr>
<tr>
<td></td>
<td>0.25</td>
</tr>
<tr>
<td>Micafungin</td>
<td>EUCAST</td>
</tr>
<tr>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>0.12</td>
</tr>
</tbody>
</table>

**Notes:**
- **ND:** not done; **IP:** in preparation; **IE:** insufficient evidence.
- 1. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for organisms that do not have specific breakpoints.
- 2. The ECOFFs for these species are in general higher than for **C. albicans**.
- 3. Due to significant inter-laboratory variation in MIC ranges for caspofungin, **EUCAST** breakpoints have not yet been established.
- 4. MICS for **C. tropicalis** are 1–2 two-fold dilution steps higher than for **C. albicans** and **C. glabrata**. In the clinical study, successful outcome was numerically slightly lower for **C. tropicalis** than for **C. albicans** at both doses 100 and 150 mg daily. However, the difference was not significant and whether it translates into a relevant clinical difference is unknown. MICS for **C. krusei** are approximately three two-fold dilution steps higher than for **C. albicans** and, similarly, those for **C. guilliermondii** are approximately eight two-fold dilution steps higher. In addition, only a small number of cases involved these species in the clinical trials. This means there is insufficient evidence to indicate whether the wild-type population of these pathogens can be considered susceptible to micafungin.
- 5. Strains with MIC values above the S/I breakpoint are not or are not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint (in italics) they should be reported resistant.
Figure 1: Local Epidemiology LCL, all clinical areas, 2005-2015
Technical Aspects of Telepath – to insert into the patient notepad on a template.
Figure 4: Candida Bundle 2 Checklist

Note pad for:

SPECIMEN NUMBER: #
CLINICAL PROGRESS: #
LIKELY SOURCE: #
DATE OF FIRST NEG BC: #
ANTIFUNGAL: #
DOSE: #
TTE?: #
TOE?: #
FUNDOSCOPY?: #
PLANNED STOP DATE: #
RATIONALE FOR NON-COMPLIANCE: #

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