Chapter 101
Approach to Candidemia in the ICU

101.1 Introduction

Candidemia is a significant bloodstream infection caused by *Candida* species, particularly affecting critically ill patients in the intensive care unit (ICU). The infection is associated with high morbidity and mortality, often due to delayed diagnosis and inappropriate treatment. Early identification and effective management are critical to improving outcomes.

Recent epidemiological trends have highlighted a rise in non-albicans species such as *Candida glabrata* and *Candida auris*, which often exhibit resistance to commonly used antifungals like fluconazole (azoles). Additionally, geographical variations in *Candida* species prevalence and resistance patterns necessitate region-specific management strategies. Understanding these patterns is essential for effective treatment and containment of the infection [1, 2] [Ref: Algorithm 101.1]

101.2 *Candida* Score and Colonization Index

1. *Candida* Score:

   The *Candida* Score is a clinical tool to identify ICU patients at high risk for invasive candidiasis (IC). It incorporates four parameters, with a total score of ≥3 suggesting a high risk for IC.

   Parameters

   1. Severe Sepsis: 2 points
   2. Total Parenteral Nutrition (TPN): 1 point
   3. Multifocal *Candida* Colonization: 1 point
   4. Surgery: 1 point

S. B. Mishra et al., *Mastering ICU Care*,
https://doi.org/10.1007/978-981-95-0179-3_101

Interpretation

- Score < 3: Low risk of invasive candidiasis
- Score ≥ 3: High risk of invasive candidiasis (sensitivity ~80%, specificity ~70%)

2. Colonization Index (CI):

The Colonization Index quantifies *Candida* colonization to predict the risk of IC. It is the ratio of the number of positive *Candida* culture sites to the total number of sites sampled.

Calculation

$$\text{Colonization Index}(\text{CI}) = \text{Number of positive } \textit{Candida} \text{ colonization sites} / \text{Total number of sites sampled}$$

- Threshold for Concern: CI ≥ 0.5 suggests significant colonization.
- Corrected Colonization Index (CCI): Adds weight to multifocal colonization.

$$\text{CCI} = \text{CI} \times 2(\text{if at least two sites are colonized})$$

Interpretation

- CI ≥ 0.5: Associated with increased risk of invasive candidiasis
- CCI ≥ 0.4–0.5: Stronger predictor of IC

Clinical Utility

- *Candida* Score and Colonization Index help in early identification of ICU patients who may benefit from empirical antifungal therapy.
- These tools complement clinical judgment and should be combined with other risk factors for optimal decision-making [3].

101.3 Monitor and Reassess Clinical Status Regularly

- Vigilance for candidemia is crucial for all ICU patients, especially those with risk factors such as recent surgery, central venous catheters (CVCs), hemodialysis, prolonged ICU stay, immunosuppression, or broad-spectrum antibiotic use. Immunocompromised patients, including neutropenic individuals, present unique challenges and may require tailored therapy.
- Candida Scoring Systems:
- Utilize validated tools like the *Candida* Score (≥3) or *Candida* Colonization Index (≥0.5) to evaluate the risk.
- These tools aid in the initiation of prophylactic or preemptive antifungal therapy.
- Implementing prophylactic or preemptive therapy in high-risk patients can reduce mortality but must be balanced against the potential for antifungal resistance due to unnecessary exposure.

- Advanced Diagnostic Modalities:
- Non-culture-Based Diagnostic Tools: Incorporate assays such as the beta-D-glucan test and PCR-based methods for early detection.
- Biomarkers in Preemptive Therapy: Monitor biomarkers to guide preemptive therapy strategies, aiming to initiate treatment before the onset of symptoms.
- Key Considerations:
- If the scoring criteria are not met and advanced diagnostics are negative, continue routine monitoring and reassess periodically.
- Prompt action is warranted when thresholds are crossed or if new risk factors emerge.

101.4 Initial Steps If Candidemia Is Suspected

- Removal of Central Venous Catheters (CVCs):
- If feasible, remove the CVC promptly, as it is often the source of candidemia.
- Early removal reduces fungal burden and prevents persistent infection.
- Blood Cultures:
- Obtain blood cultures from multiple sites to confirm the diagnosis and identify the *Candida* species and its susceptibility profile.
- Due to the rise of non-albicans species like *C. glabrata* and *C. auris*, which may be resistant to fluconazole, species identification is critical.
- Repeat cultures daily until clearance is documented.
- Additional Investigations:
- Transesophageal Echocardiography (TEE): Perform TEE to evaluate for *Candida*-associated endocarditis, a serious complication requiring prolonged therapy.
- Ophthalmologic Examination: Conduct regular ophthalmologic evaluations to rule out endophthalmitis.
- Infection Control Measures: Implement strict infection control practices to limit the spread of resistant species like *C. auris* within the ICU.
- These steps ensure the identification of infection sources and complications, guiding necessary adjustments in therapy and management strategies [4].

101.5 Management

101.5.1 Empirical Antifungal Therapy

- When to consider: Critically ill patients with risk factors and no other known cause of fever. Assess the various risk factors and send surrogate markers. Start empirical therapy if the patient is in septic shock with positive above said factors.

- Examples: ICU patients persistently febrile, but without microbiological evidence, ICU patients with positive (1,3)-β-D-glucan test
- Initiation of Therapy:
- First-Line Agents: Initiate empirical antifungal therapy promptly with echinocandins (e.g., caspofungin—loading dose of 70 mg, then 50 mg daily; micafungin—100 mg daily; anidulafungin—loading dose of 200 mg, then 100 mg daily) due to their broad spectrum of activity and efficacy against most *Candida* species, including resistant non-albicans strains.
- Alternative Agents:
- Fluconazole, 800 mg (12 mg/kg) loading dose, then 400 mg (6 mg/kg) daily—no recent azole exposure and are not colonized with azole-resistant *Candida* species.
- For patients intolerant to echinocandins or with resistant species, consider liposomal amphotericin B (3–5 mg/kg daily) or voriconazole.
- Therapeutic Drug Monitoring (TDM): Implement TDM for antifungals like voriconazole to optimize efficacy and minimize toxicity.
- Clinical Considerations:
- Tailoring Therapy: Adjust antifungal therapy based on susceptibility results as soon as they are available.
- Recommended duration: 2 weeks if improvement noticed. Discontinue empiric therapy if no improvement after 4–5 days and negative evidence of invasive candidiasis or negative results for non-culture-based assays.
- Timelines: Early initiation of appropriate antifungal therapy significantly improves survival rates. Delays in therapy are associated with increased mortality [5].
- Ongoing Assessment: Continue clinical and microbiological assessments to ensure the effectiveness of therapy and to detect any potential complications early [6].

101.5.2 Prophylactic and Preemptive Therapy

- Definition:
  - Prophylactic antifungal therapy: treatment of a patient without signs or symptoms of fungal disease. It is usually used when the benefit to the patient outweighs the development of resistance and adverse effects.

For example, recent abdominal surgery AND recurrent gastrointestinal perforations or anastomotic leakages; critically ill surgical patients with an expected length of ICU stay ≥3 day, ventilated for 48 h and expected to be ventilated for another ≥72 h, ventilated, hospitalized for >3 day, received antibiotics, CVC, and ≥ 1 of: parenteral nutrition, dialysis, major surgery, pancreatitis, systemic steroids, immunosuppression, hematological malignancies (acute myeloid leukemia and myelodysplastic syndrome with neutropenia>10 days), transplant (stem cell, lung, liver and heart transplant on immunosuppressants), and inherited immune disorders.

– Preemptive antifungal therapy: Used in patients who have a laboratory assay positive for invasive fungal infections (galactomannan assays, beta-D-glucan assays). It is a therapy triggered by microbiological evidence of candidiasis without proof of invasive fungal infection.

- Risk-Based Prophylaxis:
- In patients with persistent risk factors or those who are highly colonized, consider initiating prophylactic or preemptive antifungal therapy based on scoring systems like the *Candida* Colonization Index.
- Balancing Risks: Weigh the benefits of preventing invasive candidiasis against the potential for antifungal resistance due to unnecessary exposure.
- Clinical Considerations:
- Tailored Approach: Customize prophylactic strategies based on individual patient risks, local epidemiology, and resistance patterns.
- In the ICU with incidence of invasive candidiasis >5%: Inj Fluconazole 800 mg (12 mg/kg) loading dose, then 400 mg (6 mg/kg) daily or with echinocandins (dose mentioned above).
- Daily chlorhexidine bath may be considered.
- Avoiding Resistance: Use antifungal agents judiciously to minimize the development of resistant strains [7].

101.5.3 Definitive Therapy

Nonneutropenic Patients:

– Initial Therapy: Echinocandin (caspofungin: loading dose 70 mg, then 50 mg daily; micafungin: 100 mg daily; anidulafungin: loading dose 200 mg, then 100 mg daily).
– Not critically ill and unlikely to have fluconazole resistance: Fluconazole, intravenous or oral, 800 mg (12 mg/kg) loading dose, then 400 mg (6 mg/kg) daily.
– Alternative: Lipid formulation amphotericin B (AmB) (3–5 mg/kg daily).
– *C. glabrata*: Higher-dose fluconazole 800 mg (12 mg/kg) daily or voriconazole 200–300 (3–4 mg/kg) twice daily if susceptible.
– Reassess Therapy After 5–7 Days

De-escalation: If the patient is clinically stable and the isolate is confirmed to be fluconazole-susceptible and has negative repeat blood cultures following initiation of antifungal therapy, consider transitioning to fluconazole for step-down therapy.

– Continue antifungal therapy for at least 14 days after the first negative blood culture and resolution of symptoms.
– Extend treatment duration in cases involving endocarditis or endophthalmitis, following specialist recommendations.

- Neutropenic Patients:

- Recommended Drug: Echinocandin (caspofungin: loading dose 70 mg, then 50 mg daily; micafungin: 100 mg daily; anidulafungin: loading dose 200 mg, then 100 mg daily).
- Alternative: Lipid formulation amphotericin B (AmB) (3–5 mg/kg daily).
- Not Critically Ill and Unlikely to Have Fluconazole Resistance: Fluconazole, intravenous or oral, 800 mg (12 mg/kg) loading dose, then 400 mg (6 mg/kg) daily.
- Fluconazole Susceptible Isolates and Documented Bloodstream Clearance: Stepdown to fluconazole (400 mg (6 mg/kg) twice daily for 2 doses, then 200–300 mg (3–4 mg/kg) twice daily).
- *C. krusei* Infection: Echinocandin, lipid formulation amphotericin B, or voriconazole.
- Duration: 14 days after the first negative blood culture and resolution of symptoms.

- Abdominal Candidiasis:
  - Consider empiric therapy.
  - Source Control: Debridement with drain.
  - Drugs: Same as nonneutropenic patients.

- Cardiac:

  Native Valve Endocarditis:
  Lipid formulation AmB, 3–5 mg/kg daily, with or without flucytosine, 25 mg/kg four times daily, OR high-dose echinocandin (caspofungin 150 mg daily, micafungin 150 mg daily, or anidulafungin 200 mg daily).
  Similar step-down approach as mentioned in the above section.
  Voriconazole 200–300 mg (3–4 mg/kg) twice daily, or posaconazole tablets, 300 mg daily to be used if fluconazole resistant.
  Surgery: Valve replacement with 6 weeks of treatment after surgery.
  Prosthetic Valve Endocarditis.
  Same as native valve plus fluconazole 400–800 mg (6–12 mg/kg) daily for chronic suppression.

  Implantable Cardiac Device (ICD)

- Remove device.
- Drugs: Same as native valve endocarditis.
- Generator Pockets Infection: 4 weeks antifungal after device removal.
- ICD Wire: 6 weeks antifungal after wire removal.
- Candida Osteoarticular Infections
- Fluconazole, 400 mg (6 mg/kg) daily, for 6–12 months or an echinocandin (caspofungin 50–70 mg daily, micafungin 100 mg daily, or anidulafungin 100 mg daily) for at least 2 weeks followed by fluconazole, 400 mg (6 mg/kg) daily, for 6–12 months.
- Surgical debridement if necessary.
- Candida Septic Arthritis

- Same as osteoarticular infections.
- Mandatory surgical drainage and debridement.
- Candida Endophthalmitis
- All patients with candidemia should have a dilated retinal examination within the first week of therapy in nonneutropenic patients or after neutrophil count recovery in neutropenic patients.
- Consult ophthalmologist regarding treatment plan.
- Usual duration of antifungals (Fluconazole/Voriconazole/Liposomal Amphotericin B) is 4–6 weeks.
- Intravitreal injection of amphotericin B deoxycholate 5–10 μg/0.1 mL sterile water is used in macular involvement and in case of vitritis.
- Vitrectomy should be considered to decrease the organism burden and to allow the removal of fungal abscesses.
- CNS Candidiasis
- Liposomal AmB, 5 mg/kg daily, with or without oral flucytosine, 25 mg/kg four times daily.
- Stepdown: Fluconazole, 400–800 mg (6–12 mg/kg) daily after response to initial treatment.
- Duration: All signs and symptoms and CSF and radiological abnormalities have resolved.
- Urinary Tract Infection (UTI) with *Candida*
- Asymptomatic: Remove indwelling catheter; antifungals—oral fluconazole, 400 mg (6 mg/kg) daily, OR amphotericin B deoxycholate, 0.3–0.6 mg/kg daily if planning for urological procedures.
- Symptomatic:
  - Remove indwelling catheter.
  - Fluconazole-susceptible: Oral fluconazole 200 mg (3 mg/kg) daily for 2 weeks.
  - Fluconazole-resistant *C. glabrata*, *krusei*: Amphotericin B deoxycholate, 0.3–0.6 mg/kg daily for 1–7 days.
- Pyelonephritis:
- Fluconazole-susceptible: Oral fluconazole 200–400 mg (3–6 mg/kg) daily for 2 weeks.
- Fluconazole-resistant *C. glabrata*: AmB deoxycholate, 0.3–0.6 mg/kg daily for 1–7 days with or without oral flucytosine, 25 mg/kg four times daily.
- Fluconazole-resistant *C. krusei*: Amphotericin B deoxycholate, 0.3–0.6 mg/kg daily for 1–7 days.
- UTI with Fungal Balls: Surgical intervention plus antifungal therapy as in pyelonephritis. Amphotericin B deoxycholate irrigation (25–50 mg in 200–500 mL sterile water) if nephrostomy tube in situ.
- Moderate to Severe Oropharyngeal and Esophageal Candidiasis
- Oropharyngeal: Oral fluconazole, 100–200 mg daily, for 7–14 days (itraconazole—solution 200 mg daily/posaconazole suspension 400 mg twice daily for 3 days followed by 400 mg daily, for up to 28 days if refractory to fluconazole).

– Esophageal: Oral fluconazole, 200–400 mg (3–6 mg/kg) daily, for 14–21 days. IV fluconazole or 400 mg (6 mg/kg) daily, or an echinocandin (micafungin, 150 mg daily, caspofungin, 70 mg loading dose, then 50 mg daily, or anidulafungin, 200 mg daily) can also be given if oral therapy is not tolerated or cannot be given. Itraconazole solution, 200 mg daily, OR voriconazole, 200 mg (3 mg/kg) twice daily either intravenous or oral, for 14–21 days if disease is refractory to fluconazole.

101.6 Management of Complications

- Early Detection and Intervention:
- Regular Evaluations: Emphasize the importance of regular TEE and ophthalmologic examinations to detect complications such as endocarditis and endophthalmitis early.
- Specialist Involvement: Involve infectious disease specialists and other relevant consultants to manage complex cases effectively.
- Treatment Strategies:
- Extended Therapy: Implement prolonged antifungal therapy for patients with confirmed complications, following evidence-based guidelines.
- Surgical Intervention: Consider surgical management when indicated, such as valve replacement in endocarditis.

101.7 Multimodal Interventions

- Bundled Care Approaches:
- Infectious Disease Consultations: Engage infectious disease specialists early to optimize antifungal therapy and management plans.
- Central Venous Catheter Management: Implement protocols for the timely removal or replacement of CVCs and strict adherence to catheter care practices.
- Infection Control Practices:
- Preventing Spread: Apply rigorous infection control measures to prevent the transmission of resistant species like *C. auris* within the ICU.
- Education and Training: Provide ongoing staff education on hand hygiene, equipment disinfection, and isolation precautions.

101.8 Special Populations and Comorbidities

- Immunocompromised Patients:
- Tailored Therapy: Adjust antifungal regimens for immunocompromised patients, including those with neutropenia, to address their specific needs and risks.

- Close Monitoring: Intensify monitoring for signs of infection and response to therapy, given their higher risk for complications.
- Comorbid Conditions:
- Holistic Management: Consider the impact of comorbidities on treatment choices and patient outcomes, adjusting therapy as necessary.

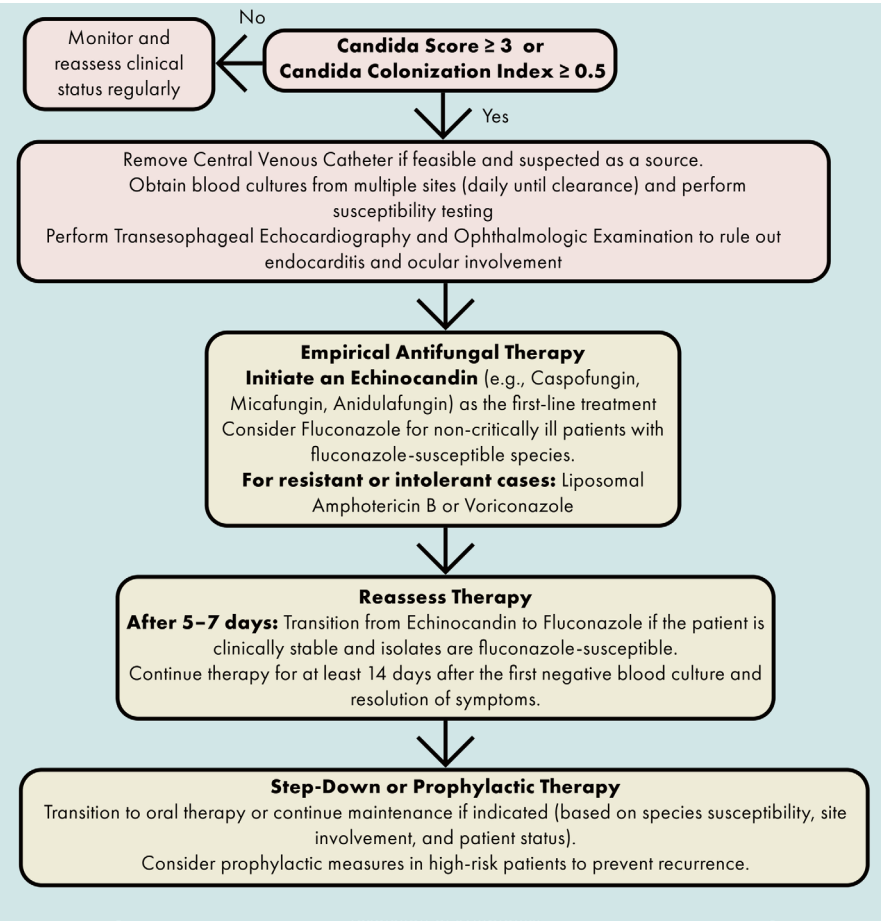
101.9 Outcomes and Prognostic Indicators

- Mortality Rates:
- Species-Specific Outcomes: Recognize that ICU mortality rates associated with candidemia vary by *Candida* species, with higher mortality observed in infections caused by non-albicans species like *C. glabrata* and *C. auris*.
- Treatment Delays: Understand that delays in initiating appropriate antifungal therapy are linked to worse outcomes, reinforcing the need for rapid diagnosis and treatment.
- Recent Studies:
- Timeliness of Therapy: Incorporate findings from recent research highlighting that early antifungal therapy significantly reduces mortality rates.
- Prognostic Indicators: Utilize prognostic indicators to identify high-risk patients who may benefit from more aggressive interventions.

101.10 Conclusion

The management of candidemia in the ICU requires a comprehensive and systematic approach that incorporates early risk assessment, advanced diagnostic modalities, prompt initiation of appropriate antifungal therapy, and careful monitoring to guide treatment adjustments. Recognizing the rise of resistant non-albicans *Candida* species and geographical variations in prevalence and resistance patterns is essential for effective management. Removal of central venous catheters and thorough diagnostic evaluations are critical first steps. Echinocandins remain the preferred first-line agents in most cases, with transitions to alternative therapies based on susceptibility results and patient stability. Multimodal interventions, including bundled care approaches and infection control practices, play a vital role in improving outcomes. Special attention to immunocompromised patients and timely initiation of therapy are paramount. Adherence to these guidelines ensures optimal patient outcomes while minimizing complications and the development of antifungal resistance.

Algorithm 101.1: Approach to candidemia in the ICU



Bibliography

1. Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Clinical practice guideline for the Management of Candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;62(4):e1–50.
2. Azim A, Ahmed A. Diagnosis and management of invasive fungal diseases in non-neutropenic ICU patients, with focus on candidiasis and aspergillosis: a comprehensive review. Front Cell Infect Microbiol. 2024;14:1256158.

3. Keighley C, Cooley L, Morris AJ, Ritchie D, Clark JE, Boan P, et al. Consensus guidelines for the diagnosis and management of invasive candidiasis in haematology, oncology and intensive care settings, 2021. Intern Med J. 2021;51(Suppl 7):89–117.
4. Hankovszky P, Tarsy D, Oveges N, Molnar Z. Invasive Candida infections in the ICU: diagnosis and therapy. J Crit Care Med (Targu Mures). 2015;1(4):129–39.
5. Cornely OA, Bassetti M, Calandra T, Garbino J, Kullberg BJ, Lortholary O, et al. ESCMID* guideline for the diagnosis and management of Candida diseases 2012: non-neutropenic adult patients. Clin Microbiol Infect. 2012;18(Suppl 7):19–37.
6. Martin-Loeches I, Antonelli M, Cuenca-Estrella M, Dimopoulos G, Einav S, De Waele JJ, et al. ESICM/ESCMID task force on practical management of invasive candidiasis in critically ill patients. Intensive Care Med. 2019;45(6):789–805.
7. Nascimento T, Inacio J, Guerreiro D, Patricio P, Proenca L, Toscano C, et al. Insights into Candida colonization in intensive care unit patients: a prospective multicenter study. J Fungi (Basel). 2024;10(6)