Candida infection in ICU patients

Sara Abolghasemi
Infectious diseases specialist
Fellowship of infection in immunocompromised patients
Candida spp. infections are the most frequent fungal (78%) infections in the Intensive Care Unit (ICU), ranking the third most common isolated pathogen and the fourth most common cause of nosocomial bloodstream infection.
<table>
<thead>
<tr>
<th>Impaired immunity</th>
<th>Other medical conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncology</td>
<td>Hollow organ perforation</td>
</tr>
<tr>
<td>Haemato-oncology</td>
<td>Great abdominal surgery</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>Urologic intervention with parallel candiduria</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Polytrauma</td>
</tr>
<tr>
<td>HIV, AIDS</td>
<td>Malnutrition</td>
</tr>
<tr>
<td>Immunosuppressive therapy</td>
<td>Severe pancreatitis</td>
</tr>
<tr>
<td>Burn injury, where more than 50% of body surface is affected</td>
<td>ICU</td>
</tr>
</tbody>
</table>
Candida infections:

- Prolong the hospital stay,
- Increase costs,
- Are associated with high mortality.
• Non-albicans Candida species constitute approximately 50% of all relevant isolates (representing a steady trend in many regions throughout the world for more than a decade)
• There is geographic, center-to-center, and even unit-to-unit variability in the prevalence of pathogenic Candida species.
In an international surveillance study 1997-1998:

- **C. albicans**: 54%
- **C. parapsilosis**: 15%
- **C. glabrata**: 16%
- **C. tropicalis**: 8%
- **C. krusei**: 2%
- **Other Candida spp**: 5%


Since then increase in *Candida* spp. with higher incidence of fluconazole resistance.

For nearly 30 years, clinicians and researchers have tried to prevent and treat early IFI in critically ill patients.
Three antifungal strategies have been used in clinical practice for these purposes:

- **Prophylaxis**
- **Empiric treatment**
- **Pre-emptive treatment**
1) ‘Prophylaxis’ defined as the administration of antifungal agents in patients without proven or suspected fungal infections but with risk factors for its development (e.g. fungal colonization, central venous catheter, parenteral nutrition, dialysis, abdominal surgery, broad spectrum antibiotics);
2) ‘Empiric treatment’ defined as antifungals administration triggered by signs and symptoms of infection in patients at risk for IFI;
‘Pre-emptive treatment’ defined as treatment triggered by microbiological evidence of fungal infection, without definitive microbiological identification (e.g. positive biomarkers such as 1-3-beta-D-glucan, mannan-antimannan antibodies, procalcitonin).
• The common point of these strategies is that they are ‘untargeted treatments’ since they are not driven by an established diagnosis of IFI.

• In clinical practice, it is not always easy to clearly differentiate these strategies, which are used in patients with a different grade of probability of fungal infection.
Risk factors (+)
Biomarkers (-)
Clinical signs (-)
Mycology (-)

Prophylaxis*
Fluconazole

Risk factors (+)
Biomarkers (+)
Clinical signs (-)
Mycology (-)

Pre-emptive treatment

Risk factors (+)
Biomarkers (-)
Clinical signs (±)
Mycology (-)

Empirical treatment
What is the trigger for starting antifungal therapy?

- Prophylaxis
- Empiric (fever-driven)
- Pre-emptive (diagnostic-driven)
- Targeted
Prophylaxis and Invasive Candidiasis in the Intensive Care Unit Setting
Just because we can offer prophylaxis does not mean we have to do so
Prophylaxis: for or against?

Bias toward prophylaxis

- no
- yes
- no
- yes (low NNT)

Bias against prophylaxis

- yes
- no
- yes
- no (high NNT)

Could you easily treat the event you are trying to prevent if it happened?

Is it a "serious" event?

Does the prophylaxis have adverse effects?

Is the prophylaxis effective?

Balancing risks

FIP = Fear of Injuring the Patient

FIFI = Fear of Invasive Fungal Infection
• **Time to appropriate therapy** in candidemia appears to have a significant impact on the **outcome of patients** with this infection.

• However, **insensitivity and significant delays using culture techniques**, as well as limitations of rapid diagnostic tests, remain for this common cause of bloodstream infection among patients in the ICU.
The approach to prophylaxis has been either **broad**, in which all patients within the ICU setting are treated, or **selective**, in which only specific high-risk groups of patients are targeted for prophylaxis.
• Increased costs, toxicity and ecological pressure for antifungal resistance.

• Antifungal prophylaxis may be useful where there are risk factors or increased local incidence rates
For ICUs that show very high rates of invasive candidiasis, in excess of the expected rates of >5% of patients, antifungal prophylaxis may be warranted in selected patients who are at highest risk
• Fluconazole, 800-mg (12 mg/kg) loading dose, then 400 mg (6 mg/kg) daily, could be used in high-risk patients in adult ICUs with a high rate (>5%) of invasive candidiasis (weak recommendation; moderate-quality evidence).

• An alternative is to give an echinocandin (caspofungin: 70-mg loading dose, then 50 mg daily; anidulafungin: 200-mg loading dose and then 100 mg daily; or micafungin: 100 mg daily) (weak recommendation; low-quality evidence).
The major challenge is to select individual patients or subgroups that will benefit most from prophylaxis in order to limit the number needed to treat and to avoid the problem of selective pressure that leads to the emergence of resistance.
At this time, antifungal prophylaxis should be limited to patients in whom it has proved to be beneficial:

- Patients with **gastrointestinal anastomotic leakage**
- Patients undergoing transplantation of the **pancreas or the small bowel**
- Selected patients undergoing **liver transplantation** who are at high risk for candidiasis (renal insufficiency, long operative time, significant intra-abdominal bleeding)
- Extremely low-birth-weight neonates in settings with a high incidence of neonatal candidiasis.
Empiric Treatment and Suspected Invasive Candidiasis in the Intensive Care Unit Setting
Risk factors for development of invasive candidiasis include:

- Candida colonization,
- severity of illness,
- exposure to broad spectrum antibiotics,
- recent major surgery, particularly abdominal surgery,
- necrotizing pancreatitis,
- dialysis,
- parenteral nutrition,
- corticosteroids,
- and the use of CVCs
Empiric antifungal therapy should be started as soon as possible in patients who have the above risk factors and who have clinical signs of septic shock (strong recommendation; moderate-quality evidence).
• In those patients who have septic shock due to Candida species and who do not have adequate source control or antifungal therapy begun within 24 hours, the mortality approaches 100%

• Prompt initiation of appropriate antifungal therapy has been associated with as much as a 50% reduction in mortality
IDSA

- criteria for starting empirical antifungal therapy in ICU patients are poorly defined and recent IDSA guidelines suggesting that “empirical antifungal therapy should be considered in
- critically ill patients with risk factors for invasive candidiasis and no other known cause of fever”
- could lead to an overuse of antifungal agents.
In 2006, a Spanish group, using the database of the Estudio de Prevalencia de CANdidiasis project, identified four predictors of proven invasive Candida infection.

Based on these predictors, a score named “Candida score” was built.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multifocal Candida colonization</td>
<td>1</td>
</tr>
<tr>
<td>Surgery</td>
<td>1</td>
</tr>
<tr>
<td>Receipt of TPN</td>
<td>1</td>
</tr>
<tr>
<td>Clinical signs of severe sepsis</td>
<td>2</td>
</tr>
</tbody>
</table>

A “Candida Score” of > 2.5 was associated with a >7 - fold increase in the likelihood of documented Candida infection.
• there are many concerns about these rules: high specificity but low sensitivity, no prospective validation, and complicated use.
Ostrosky-Zeichner:

Any systemic antibiotic (days 1–3) OR
CVC (days 1–3) AND
at least TWO of the following:
TPN (days 1–3), any dialysis (days 1–3), any major surgery (days 7–0), pancreatitis (days 7–0), steroid use (days -7–3).
other immunosuppressive drug (days 7–0)
IDSA: Pre-emptive

• Empiric antifungal therapy should be considered in critically ill patients with risk factors for invasive candidiasis and no other known cause of fever and should be based on clinical assessment of risk factors, surrogate markers for invasive candidiasis, and/or culture data from nonsterile sites (strong recommendation; moderate-quality evidence).
Strategies for initiating empiric antifungal therapy include an evaluation of risk factors and use of surrogate markers.
Surrogate markers that have been evaluated in the ICU setting include:

- β-D-glucan,
- mannan-antimannan antibodies,
- PCR testing.
**β-D-glucan**

- cell wall constituent of *Candida species*, *Aspergillus species*, *Pneumocystis jiroveci*, and several other fungi.
- Approved by the FDA as an adjunct to cultures for the diagnosis of invasive fungal infections (Fungitell; Associates of Cape Cod, East Falmouth, Massachusetts)
- the pooled sensitivity and specificity for diagnosing invasive candidiasis were 75%–80% and 80%, respectively.
• True-positive results are not specific for invasive candidiasis, but rather suggest the possibility of an invasive fungal infection.

• \( \beta-D \)-glucan detection can identify cases of invasive candidiasis days to weeks prior to positive blood cultures, and shorten the time to initiation of antifungal therapy.
On the one hand, antifungal agents may reduce diagnostic sensitivity, but decreasing β-D-glucan levels may also correlate with responses to antifungal therapy.
Causes of false positivity include:
- other systemic infections, such as gram-positive and gram-negative bacteremia,
- certain antibiotics, such as intravenous amoxicillin-clavulanate,
- hemodialysis,
- fungal colonization,
- receipt of albumin or immunoglobulin,
- use of surgical gauze or other material containing glucan,
- and mucositis or other disruptions of gastrointestinal mucosa
• The specificity of β-Dglucan can be improved by requiring consecutive positive results rather than a single result, but false positivity remains a significant limitation if the above-listed factors are common.
• Therefore, the test will be most useful if targeted to subgroups of patients whose clinical course or risk factors are particularly suggestive of invasive candidiasis or other fungal infection.
combined mannan/antimannan antibody assay

- Approved for use in Europe but not the United States (Platelia Candida Ag and Ab; Bio-Rad)
- The sensitivity/specificity for the diagnosis of invasive candidiasis of mannann and antimannan IgG individually were 58%/93% and 59%/83%, respectively. Values for the combined assay were 83% and 86%, with best performances for C. albicans, C. glabrata, and C. tropicalis infections.
- This assay is not used widely in the United States, and its role in the diagnosis and management of invasive candidiasis is unclear.
PCR

- The pooled sensitivity and specificity were 95% and 92%, respectively.
- The impact of antifungal agents on diagnostic sensitivity was unclear.
- Data among patients colonized with Candida were surprisingly limited, but there was a trend toward lower specificity.
• A major limitation of PCR studies is the lack of standardized methodologies and multicenter validation of assay performance.

• FDA approved assay: detects Candida DNA by PCR and T2 magnetic resonance (T2 Biosystems, Lexington, Massachusetts).

• In Europe: a whole-blood, multiplex real-time PCR assay (SeptiFast, Roche) that detects 19 bacteria and 6 fungi (C. albicans, C. glabrata, C. parapsilosis, C. tropicalis, C. krusei, and Aspergillus fumigatus).
PCR has potential advantages over β-D-glucan or antigen-antibody assays, including the capacity for species identification, detection of molecular markers for drug resistance, and multiplex formatting.
• β-D-glucan appears to be more sensitive than Candida colonization scores or indices, but appears to have low positive predictive value. False-positive results are a problem, as noted in the Background section. The optimal timing and number of samples is unknown.

• In a recent prophylaxis trial of high-risk ICU patients, β-D-glucan testing performed twice weekly identified 87% of patients with proven candidiasis.

• Small studies basing preemptive therapy on β-D-glucan testing suggest that the high negative predictive value of this test could be useful in excluding invasive candidiasis in the ICU setting.
Treatment

- Antifungal drugs for the treatment of candidiasis include:
  - Polyenes (amphotericin B deoxycholate, liposomal amphotericin B),
  - Triazoles (fluconazole, itraconazole, voriconazole, posaconazole),
  - Echinocandins (caspofungin, anidulafungin, micafungin)
  - Flucytosine (administered mostly by oral formulation)
Preferred empiric therapy for suspected candidiasis in nonneutropenic patients in the ICU is:

- **Echinocandin** (caspofungin: loading dose of 70 mg, then 50 mg daily; micafungin: 100 mg daily; anidulafungin: loading dose of 200 mg, then 100 mg daily)

- #

- **Fluconazole**, 800-mg (12 mg/kg) loading dose, then 400 mg (6 mg/kg) daily, is an acceptable alternative for patients who have had no recent azole exposure and are not colonized with azole-resistant Candida species.

- **Lipid formulation AmB**, 3–5 mg/kg daily, is an alternative if there is intolerance to other antifungal agents (strong recommendation; low-quality evidence).
• Preference should be given to an **echinocandin** in hemodynamically unstable patients, those previously exposed to an azole, and in those colonized with azole-resistant Candida species.

• **Fluconazole** may be considered in hemodynamically stable patients who are colonized with azole-susceptible Candida species or who have no prior exposure to azoles.
Documented *Candida* infection (positive blood culture or positive biopsy)

Immediate treatment start

Change of CVC, funduscopic examination

Is the patient haemodynamically stable?

- **YES**
  - Fluconazole if:
    - no recent fluconazole use
    - no NAS suspected
    - no intolerance to azoles
    - known local epidemiology

- **NO**
  - Echinocandins
    - AmB or LipAmB
  - Patient improving
  - Isolate susceptible
  - De - escalation to fluconazole
C. albicans  C. glabrata  C. krusei  C. parapsilosis

Haemodynamically OK? Neutropenic?, Septic?

No  Yes

Fluconazole 400–800 mg/day iv

Echinocandin Caspofungin: first 70 mg iv, 50 mg/day iv or LipAmB*: 3–5 mg/kg/day

LipAmB* or fluconazole (avoid echinocandins)

*LipAmB, liposomal amphotericin B.
duration of empiric therapy

- for suspected invasive candidiasis in those patients who improve is 2 weeks, the same as for treatment of documented candidemia (weak recommendation; low-quality evidence).

- 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 (strong recommendation; low-quality evidence).
THANK YOU