Fungal infection in Intensive Care Unit patients

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Background

• Two basic forms
  – Yeasts
    • Unicellular, small rounded form
    • E.g. Candida, Cryptococcus, Trichosporon, Rhodotorula
  – Molds
    • Filamentous forms known as hyphae
    • E.g. Aspergillus, Penicillium
Background

• Fungal infections
  – An increasingly important infection
  – Associated with increased mortality and morbidity, longer duration of hospital stay, and increased costs

• International study (the EPIC II study)
  – demonstrated fungi accounted for 20.9% of microorganisms recovered from positive cultures from ICU patients in Western Europe [1]

• Yeasts, particularly Candida species
  – 18.5% of all microorganisms from positive culture
  – ranked fourth in the most commonly isolated microorganisms after Staphylococcus aureus, Pseudomonas spp. and Escherichia coli

Background

• Invasive Candida (IC) infections, particularly candidemia, represent the most common invasive fungal infection (IFI) in critically ill patients [1]

• In recent years, Invasive aspergillosis has gained importance in the ICU setting, although its frequency is very low compared to IC [2]

• IFIs caused by other filamentous or yeast-like fungi have rarely been encountered in ICUs unless patients are immunocompromised

Candida infection
Candida infection

• Candida albicans and other candida species
  – Harmless inhabitants of skin
  – Normal flora in the gastrointestinal and genitourinary tracts of humans
  – Normal immune system keeps candida on body surfaces
• Endogenous opportunistic infection
• A wide spectrum of conditions
  – From local overgrowth of cutaneous or mucous membrane to invasive candidiasis (invasive focal infections, disseminated, hematogenous)
Main Defense Mechanisms

- Skin and mucous membranes integrity
- Presence of normal bacterial flora
- Presence of an intact immune system

INVASIVE CANDIDIASIS
Risk factors

- Patients in ICU and those who are immunocompromised are most at risk for the development of candidemia
- Among ICU patients, risk factors include [1, 2]:
  - Central venous catheters
  - Total parenteral nutrition
  - Broad-spectrum antibiotics
  - High APACHE scores
  - Acute renal failure, particularly if requiring hemodialysis
  - Prior surgery, particularly abdominal surgery
  - Gastrointestinal tract perforations and anastomotic leaks

Invasive candidiasis - Epidemiology

- Candida albicans
  - the most common cause of candidemia
- In a multicenter surveillance study in the United States between 2004 and 2008, in 2019 bloodstream isolates [1]

Epidemiology

- Distribution – influenced by age, study designs, geographical locations
- C. glabrata
  - Ranked 2nd in north America
  - More common in the aged
- C. parapsilosis
  - Ranked 2nd in European candidemia surveys
  - the second most common species isolated from the pediatric population [1]
  - More related to CVC line infection

Epidemiology

• In another prospective multicenter study of 300 ICU patients in France with proven invasive candidiasis [1]
  – C. albicans 57%,
  – C. glabrata 17%,
  – C. parapsilosis 8% 
  – C. krusei 5% 
  – C. tropicalis 5%

• The case fatality ratio 45.9%

Diagnosis

• Gram stain and blood culture isolation
  – Gold standard for diagnosis
  – Relatively insensitive
    • positive in only approximately 50 percent of patients who were found to have disseminated candidiasis at autopsy [1,2]
  – At least days are required for growth and identification of the organism

Diagnosis

• Other definitive diagnostic methods
  – Positive culture of other body fluid e.g. CSF or peritoneal fluid
  – Directed biopsy of organ involved
Diagnosis

• Beta-D-glucan antigen (BG)
  – A cell wall component of many fungi
  – In one multicenter study in US [1]
    • At a cutoff of 60 pg/mL, sensitivity 69.9% and specificity 87.1%
    • At a cutoff of 80 pg/mL, the sensitivity 64.4% and specificity 92.4%
  – Could be of low level in cryptococcosis and zygomycosis [2]
  – False positive
    • Hemodialysis with cellulose membranes, those treated with immunoglobulin, albumin or blood products filtered through cellulose depth filters which contain BG
    • Serosal exposure to glucan-containing gauze
    • Bacteremia, hemolysed sample, glucan contaminated sample

Diagnosis

• Polymerase chain reaction (PCR)
  – Can identify Candida to the species level
  – to date, there is no commercially available approved PCR test to detect Candida species
Treatment: Antifungal agents

• Three main classes
  – Azoles
  – Echinocandins
  – Polyenes
Azole

• E.g. Fluconazole, Voriconazole, Itraconazole
• Inhibits the cytochrome P450-dependent enzyme lanosterol 14-alpha-demethylase
Azole

• **Fluconazole**
  - **Coverage**
    • General good coverage for candida species
    • except some C. glabrata isolates and all C. krusei
  - **Administration**
    • Available in intravenous and oral formulations (highly bioavailable)
    • Recommended dose for candidiasis, 800mg loading then 400mg daily
  - **Metabolism and excretion**
    • partly by liver, excreted through urine, renal adjustment needed
  - **Side effect**
    • Liver derrangement
    • Inhibited hepatic CYP2C9 (potent); CYP3A4 (moderate)
    • Cases of QTc prolongation and torsade de pointes have been reported
Azole

• Voriconazole
  – Activity against candida is superior to fluconazole
  – Greater in vitro activity against C. Krusei isolates
  – Yet, cross- resistance between fluconazole and voriconazole is frequent especially with C. glabrata
Echinocandins

• Noncompetitive inhibitors of the synthesis of 1,3-beta-D-glucan
  – an integral component of the fungal cell wall
Echinocandins

• Efficacy in non neutropenic patients with IC
  – as effective as and better tolerated than amphotericin B [1]
  – more effective than fluconazole [2]
• Preferred over azoles if C. glabrata or C. krusei is identified or suspected [3]
• Yet the MIC for C. parapsilosis with all the echinocandins are higher than for other Candida species
  – Clinical implication unclear

Echinocandins

– Less drug-drug interaction
  • Not primarily metabolized by cytochrome P450, nor are they substrates or inhibitors of P-glycoprotein pumps

– Anidulafungin, Micafungin, Caspofungin
  • Share similar spectrum of activity and mechanism of action
  • Only available in intravenous formulations
  • non-dialyzable, minimally excreted via urinary tract, no renal dosing adjustment needed
Echinocandins

- Caspofungin
  - Dose adjustment for severe hepatic insufficiency
- Micafungin
  - Also partially metabolised hepatically, elimination pharmacokinetics in advanced hepatic insufficiency are not well defined
- Anidulafungin:
  - No dose adjustment for hepatic insufficiency
Polyenes

- Binds to ergosterol altering cell membrane permeability and causing leakage of cell components with subsequent cell death
Polyenes

• Amphotericin B
  – rapidly cidal in vitro activity against most species of Candida
  – Side effects
    • Significant nephrotoxicity
    • Anaphylaxis, infusion reaction, thrombopheblitis
    • Electrolyte disturbance e.g. hypoK, hypoMg
  – New development of various lipid-based derivatives e.g. liposomal amphotericin B
    • improved side effect profile
General patterns of susceptibility of commonest Candida species

<table>
<thead>
<tr>
<th>Species</th>
<th>Fluconazole</th>
<th>Voriconazole</th>
<th>Echinocandins</th>
<th>Amphotericin B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida albicans</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Candida glabrata</td>
<td>S-DD to R</td>
<td>S to R</td>
<td>S</td>
<td>S to I</td>
</tr>
<tr>
<td>Candida parapsilosis</td>
<td>S</td>
<td>S</td>
<td>S-DD to R</td>
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<tr>
<td>Candida tropicalis</td>
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<td>S</td>
</tr>
<tr>
<td>Candida krusei</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S to I</td>
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</tbody>
</table>

S: susceptible, R: resistant, I: intermediately susceptible
S-DD: susceptible dose-dependent
Treatment

• Fluconazole: usually the first line prophylactic or empirical antifungal agent
• Increased isolation of non-albicans species of candida namely C. glabrata, C. parasilosis, C. tropicalis and C. krusei.
• Some C. glabrata isolates: resistant to fluconazole
• All C. Krusei isolates: resistance to fluconazole
Invasive Aspergillosis (IA)
Aspergillosis

- Aspergillus species
  - Ubiquitous in nature, living in soil and on plants
  - They have small conidia forming aerosols, inhalation of which is frequent
• Aspergillosis
  – Illness due to allergy, airway or lung invasion, cutaneous infection, or extrapulmonary dissemination caused by species of Aspergillus

• Main defense mechanism
  – phagocytosis specifically in airway epithelial cells and alveolar macrophages

• Tissue invasion
  – uncommon
  – occurs most frequently in immunosuppression associated with therapy for hematologic malignancies, hematopoietic cell transplantation, or solid organ transplantation
Aspergillosis

• In recent years, IA has become more important in critically ill patients

• Predisposing conditions in ICU patients for developing IA includes [1,2]
  – chronic obstructive pulmonary disease (COPD)
  – Prolong High dose corticosteroid use
  – Severe hepatic failure

• Crude mortality rate for IA is higher (97% among patients with proven IA in one survey) [1]

Diagnosis of aspergillosis

• Often referred to within a scale of certainty
  – possible, probable, or proven

• Proven
  – Demonstration of hyphal elements invading tissues (from biopsy of any affected site, such as the lung or skin)
  – Culture from a normally sterile site
• Possible or probable diagnosis of IA and decision on treatment depends on
  – Isolating the organism (or markers of the organism most commonly galactomannan)
  – AND the probability that it is the cause of disease
Diagnosis of aspergillosis: Culture

• Culture
  – both microscopic examination and culture are insensitive

• In multicenter surveillance studies
  – only 25 to 50 percent of hematopoietic cell transplant recipients who met criteria for invasive aspergillosis based upon galactomannan antigen results had positive cultures [1,2]

Galactomannan antigen detection

• Galactomannan
  – a polysaccharide that is a major constituent of Aspergillus cell walls

• The galactomannan antigen assay
  – Approved by FDA for serum and BAL fluid
  – An optical density index of $\geq 0.5$ regards as positive, for both serum and BAL fluid
Galactomannan antigen detection

• A meta-analysis included 27 studies with a total of 4000 patients, for serum specimen: [1]
  – the sensitivity and specificity: 61% and 93% respectively

• Another retrospective study, for BAL fluid:[2]
  – the sensitivity and specificity: 61% and 93% respectively (with an OD index threshold ≥0.5)

Treatment of IA

• Azoles – Voriconazole
• Polyenes – Amphotericin B
• Echinocandins – limited role in initial treatment
Treatment of IA

- For established diagnosis of invasive aspergillosis
  - Voriconazole
  - Amphotericin B (lipid formulation) if intolerant to voriconazole

- For suspected invasive mold infection
  - Started with lipid formulation of amphotericin B (to cover possible mucormycosis)
  - Once diagnosis of aspergillosis is established -> switch back to voriconazole

- For those intolerance or resistant to standard treatment
  - Caspofungin, approved by FDA, often in combination with another antifungal agent if it is used for salvage therapy
Other fungal infections in ICU

- Invasive fungal infections caused by other filamentous or yeast-like fungi have rarely been encountered in ICUs
- In Immunocompromised in need ICU support
  - Cryptococciosis, Fusariosis, zygomycosis, mucormycosis and Trichosporon spp. should be considered
The End