Fungal infection in Intensive Care Unit patients

14/3/2014

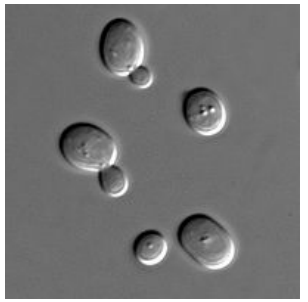
Presenter: Joanne Chan
Supervisor: Dr. KC Chan

Content

1. Background
2. Invasive Candidemia
    1. Epidemiology
    2. Risk factors
    3. Diagnosis
    4. Treatment
3. Invasive aspergillosis
4. Other fungal infections in immunocompromised patients require ICU support

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

1. Vincent J-L, Rello J, Marshal J, Silva E, Anzueto A, Martin CD *et al.* International study of the prevalence and outcomes of infection in intensive care units. JAMA 2009;302:2323- 9.

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

1. Trick, WE, Fridkin SK, Edwards JR, Hajjeh RA, Gaynes RP. Secular trend of hospital-acquired candidemia among intensive care unit patients in the United States during 1989–1999. Clin Infect Dis 2002;35:627−30.
2. 6. Meersserman W, van Wijngaerden E. Invasive aspergillosis in the ICU:an emerging disease. Intensive Care Med 2007;33:1679-81.

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

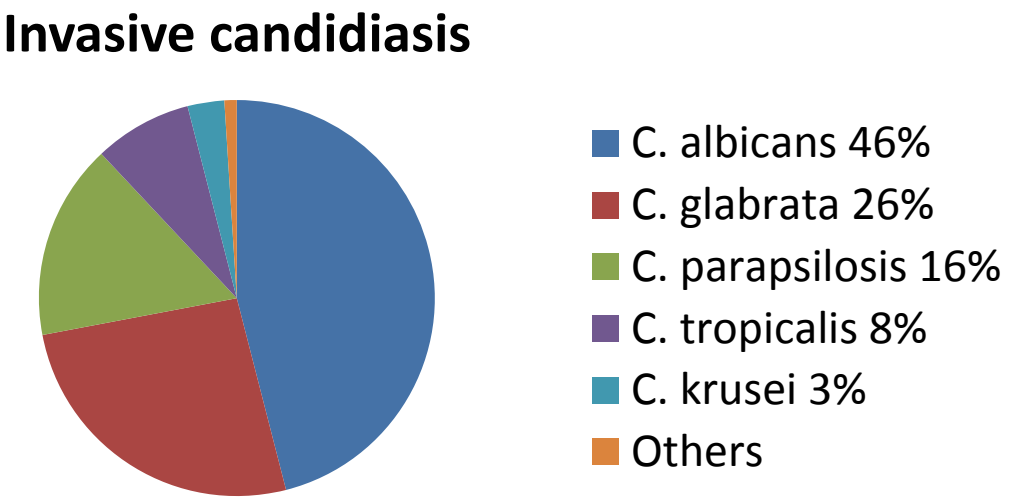
Risk factors

- 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

1. Jarvis WR. Epidemiology of nosocomial fungal infections, with emphasis on Candida species. Clin Infect Dis 1995; 20:1526.
2. Blumberg HM, Jarvis WR, Soucie JM, et al. Risk factors for candidal bloodstream infections in surgical intensive care unit patients: the NEMIS prospective multicenter study. The National Epidemiology of Mycosis Survey. Clin Infect Dis 2001; 33:177.

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]



1. Horn DL, Neofytos D, Anaissie EJ, et al. Epidemiology and outcomes of candidemia in 2019 patients: data from the prospective antifungal therapy alliance registry. Clin Infect Dis 2009; 48:1695.

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

1. Singhi S, Deep A. Invasive candidiasis in pediatric intensive care units. Ind J Ped 2009;76:1033-44.

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%

1. Leroy O, Gangneux JP, Montravers P, et al. Epidemiology, management, and risk factors for death of invasive Candida infections in critical care: a multicenter, prospective, observational study in France (2005-2006). Crit Care Med 2009; 37:1612.

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

1. Bodey GP. Fungal infections complicating acute leukemia. J Chronic Dis 1966; 19:667.
2. Hart PD, Russell E Jr, Remington JS. The compromised host and infection. II. Deep fungal infection. J Infect Dis 1969; 120:169.

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

1. Ostrosky-Zeichner L, Alexander BD, Kett DH, et al. Multicenter clinical evaluation of the (1-->3) beta-D-glucan assay as an aid to diagnosis of fungal infections in humans. Clin Infect Dis 2005; 41:654.
2. Shea YR. Algorithms for detection and identification of fungi. In: Murray PR, editor. Manual of clinical microbiology. 9th edition. Washington C:American Society for Microbiology Press, 2007:1745-61..

Diagnosis

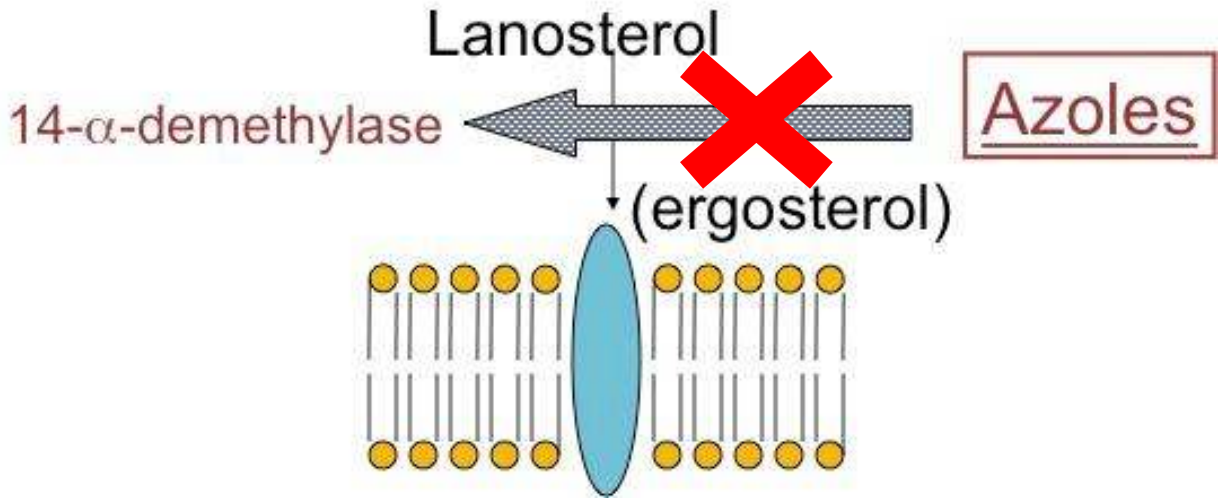
- Polymerase chain reaction (PCR)
  - Can identify Candida to the species level
  - to date, there is no commercially available approved PCR test to detect Candida species

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

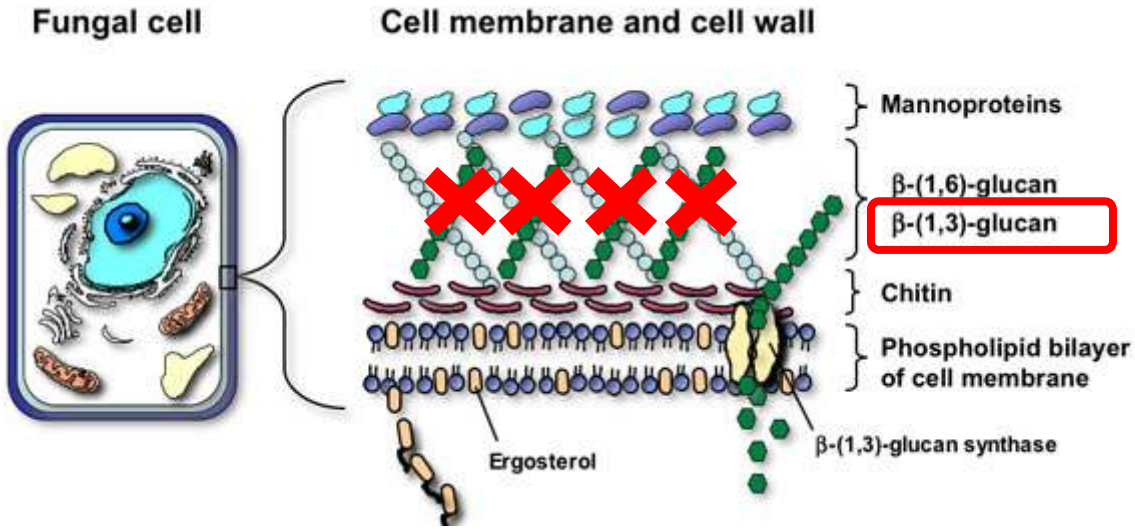
- Fluconazole
  - Coverage
    - General good coverage for candida species
    - except some C. glabrata isolates and all C. krusei
  - Administration
    - Available in intravenous and oral formulations (highly bioavailable)
    - Recommended dose for candidiasis, 800mg loading then 400mg daily
  -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

1. Mora-Duarte J, Betts R, Rotstein C, et al. Comparison of caspofungin and amphotericin B for invasive candidiasis. N Engl J Med 2002; 347:2020
2. Reboli AC, Rotstein C, Pappas PG, et al. Anidulafungin versus fluconazole for invasive candidiasis. N Engl J Med 2007; 356:2472.
3. Bennett JE. Echinocandins for candidemia in adults without neutropenia. N Engl J Med 2006; 355:1154.

Echinocandins

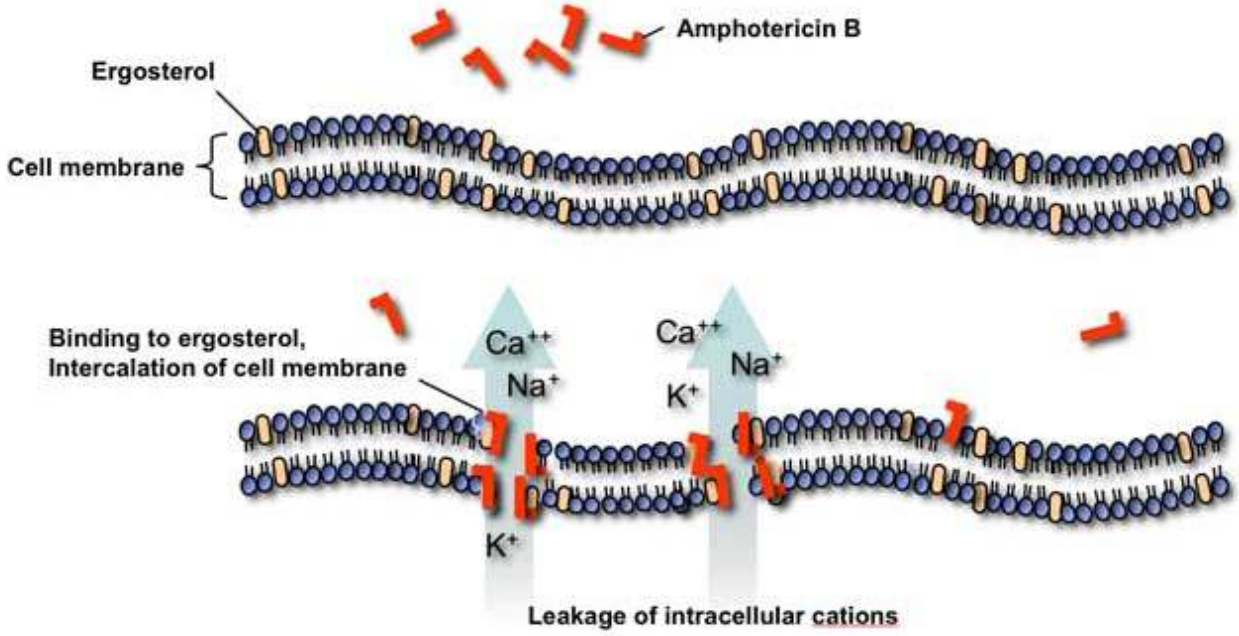
- Less drug-drug interaction
  - Not primarily metabolized by cytochrome P450, nor are they substrates or inhibitors of P-glycoprotein pumps
- Anidulafungin, Micafungin, Caspofungin
  - Share similar spectrum of activity and mechanism of action
  - Only available in intravenous formulations
  - non-dialyzable, 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

Treatment

General patterns of susceptibility of commonest Candida species

Species	Fluconazole	Voriconazole	Echinocandins	Amphotericin B
Candida albicans	S	S	S	S
Candida glabrata	**S-DD to R**	S to R	S	**S to I**
Candida parapsilosis	S	S	**S to R**	S
Candida tropicalis	S	S	S	S
Candida krusei	**R**	S	S	**S to I**

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

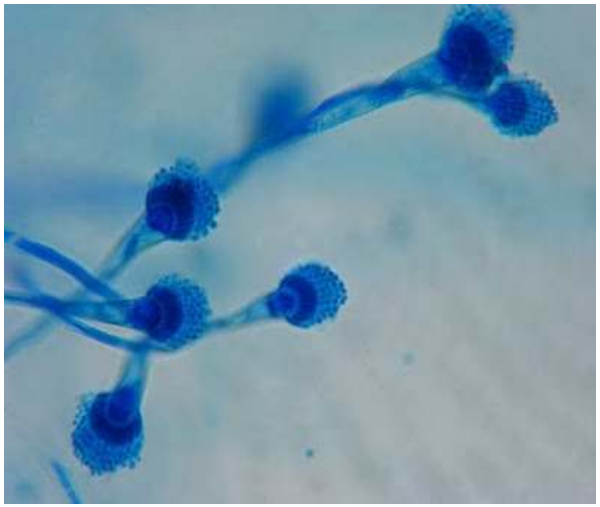
Treatment

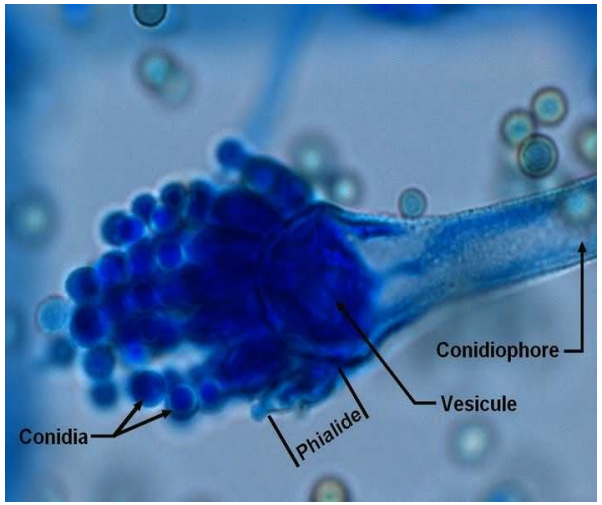
- Fluconazole: usually the first line prophylactic or empirical antifungal agent
- Increased isolation of non-albicans species of candida namely C. glabrata, C. parasilosis, C. tropicalis and C. krusei.
- Some C. glabrata isolates : resistant to fluconazole
- All C. Krusei isolates: resistance to fluconazole

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 corticosteriod use
  - Severe hepatic failure
- Crude mortality rate for IA is higher (97% among patients with proven IA in one survey) [1]

1. Meersserman W, Vandecasteele SJ, Wilmer A, Verbeken E, Peetermans WE, van Wijngaerden E. Invasive aspergillosis in critically ill patients without malignancy. Am J Respir Crit Care Med 2004;70:621-5.
2. Meersserman W, van Wijngaerden E. Invasive aspergillosis in the ICU:an emerging disease. Intensive Care Med 2007;33:1679-81.

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]

1) Neofytos D, Horn D, Anaissie E, et al. Epidemiology and outcome of invasive fungal infection in adult hematopoietic stem cell transplant recipients: a nalysis of Multicenter Prospective Antifungal Therapy (PATH) Alliance registry. Clin Infect Dis 2009; 48:265.
2) Kontoyiannis DP, Marr KA, Park BJ, et al. Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001-2006: overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database. Clin Infect Dis 2010; 50:1091.

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 ≥ 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 patient, 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)

1. Pfeiffer CD, Fine JP, Safdar N. Diagnosis of invasive aspergillosis using a galactomannan assay: a meta-analysis. Clin Infect Dis 2006; 42:1417.
2. D'Haese J, Theunissen K, Vermeulen E, et al. Detection of galactomannan in bronchoalveolar lavage fluid samples of patients at risk for invasive pulmonary aspergillosis: analytical and clinical validity. J Clin Microbiol 2012; 50:1258.

Treatment of IA

- Azoles – Voriconazole
- Polyenes – Amphotericin B
- Echinocandins – limited role in initial treatment

Treatment of IA

- For establised diagnoisis 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 aspergiollosis is estalished -> 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
  - Cryptococcosis, Fusariosis, zygomycosis, mucormycosis and Trichosporon spp. should be considered

The End