
بسم الله الرحمن الرحیم

A clinical summary of Systemic Antifungals

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TABLE 1 Dual nomenclature of pathogenic pleomorphic fungi (Table view)

Category	Anamorph (asexual)	Teleomorph (sexual)
Dimorphic fungi	*Histoplasma capsulatum*	*Ajellomyces capsulatus*
	Blastomyces dermatitidis	*Ajellomyces dermatitidis*
	Emmonsia parva (synonym *Chrysosporium parvum*)	*Ajellomyces crescens*
Hyaline hyphomycetes	*Aspergillus fumigatus*	*Neosartorya fumigata*
	Paecilomyces	*Byssochlamys Chromocleista Talaromyces*
Dematiaceous fungi	*Scedosporium apiospermum* (synanamorph *Graphium eumorphum*)	*Pseudallescheria boydii*

- **Molds : development of filamentous hypha .**
- **dimorphic fungi : fungi that can exist in the form of both mold and yeast.**
- **candidiasis** sporotrichosis blastomycosis

Candida albicans growing as yeast cells and filamentous (hypha) cells

- **Hyaline molds : fungi that grow predominantly in a filamentous form with colorless hyphae : Aspergillous , *Fusarium***

- Dematiaceous Fungi darkly pigmented because of their melanin-containing cell walls.

- Mucorales: formerly called zygomycoses
- the genera of Mucor, Rhizopus, or Rhizomucor.

Antifungal Agents

Polyenes	Triazoles	Echinocandin
Amphotericin B	Fluconazole Itraconazole* Voriconazole* Posaconazole* Isavuconazole*	Caspofungin Micafungin Anidulafungin

**mold-active triazoles*

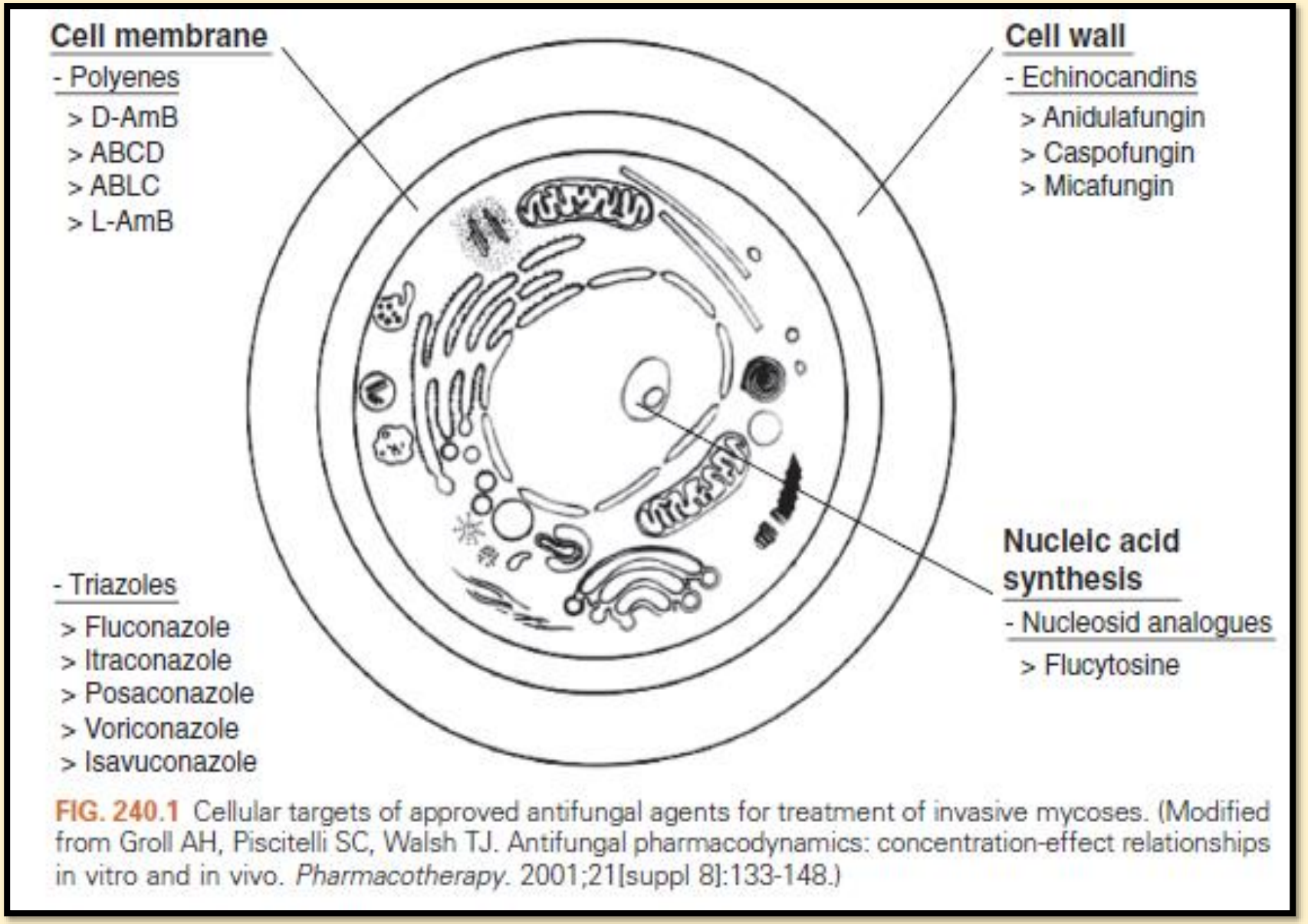

FIG. 240.1 Cellular targets of approved antifungal agents for treatment of invasive mycoses. (Modified from Groll AH, Piscitelli SC, Walsh TJ. Antifungal pharmacodynamics: concentration-effect relationships in vitro and in vivo. *Pharmacotherapy*. 2001;21[suppl 8]:133-148.)

AZOLES

Table 1: The interest members of azoles and their available formulations

Agents class	Examples	Available formulations
Imidazole group	Clotrimazole[12],	Topical lotion, cream and powder, buccal troche and lozenge, vaginal cream and suppository
	Econazole[13],	Topical cream, spray foam and powder, vaginal cream and suppository
	Miconazole[14],	IV injection, oral suspension, gel and tablet, topical cream, vaginal cream and suppository
	Butaconazole[15],	Topical cream and ointment, vaginal cream and suppository
	Ketoconazol[16]	Oral tablet, topical cream and shampoo vaginal cream and suppository
Triazole group	Teraconazole[17],	Topical cream, ointment and gel, vaginal cream and suppository
	Itraconazole[18],	IV injection, oral suspension and capsule
	Fluconazole[19],	IV injection, oral suspension and capsule
	Voriconazole[20]	IV injection, oral tablet

AZOLES

- **Active on dermatophytes, candida and other deep mycoses**
- **Triazoles are greater efficacy/lesser side effect and drug interaction: with QTc prolongation**
- **Azole therapy has been associated.**

Fluconazole

- not active against molds
- is used in the treatment of invasive candidiasis, cryptococcosis, and coccidioidomycosis.
- but not against *Aspergillus* spp. and other hyaline or dematiaceous molds.
- intermediate activity against *C. glabrata*
- direct fungicidal activity against *C. albicans*.
- the possibility that fluconazole may ultimately be able to eliminate *Candida* spp. without help from host defenses.

• FLUCONAZOLE

- penetrates the brain. cerebrospinal fluid (CSF) concentrations : 50% to 70% of serum .
- excellent concentrations in the saliva, sputum, urine, and other body fluids and tissues : only fluconazole has significant concentrations in urine
- A loading dose of twice the daily dose is recommended :.. once-daily dosing of fluconazole
- In creatinine clearance <50 mL/min a dose reduction of 50% is required
- creatinine clearance <20 mL/min require a reduction to 25% of the normal dose.
- Patients receiving dialysis should receive 100% of the normal daily dose after each dialysis session and on nondialysis days a reduced dose according to their creatinine clearance.
- Preterm infants (body weight <1000 g) : fluconazole prophylaxis : 3 to 6 mg/kg twice weekly for 6 weeks.

•FLUCONAZOLE

- **Although echinocandins are recommend first-line treatment agents in cases of candidemia, fluconazole is an acceptable alternative in selected patients who are not critically ill and are unlikely to have a fluconazole resistant *Candida* spp.**
- **Transition from an echinocandin to fluconazole (step-down therapy) is recommended for patients following clinical improvement and clearance of fungemia.**
- **After initial therapy and clearance of blood cultures in candidal endocarditis, fluconazole is often used to prevent relapse.**

•Voriconazole (Vfend; generic forms)

- activity against *Candida* spp., *Aspergillus, C. neoformans* and other hyaline molds, dematiaceous molds, and dimorphic molds
- **Mucorales: voriconazole is intrinsically inactive.**
- Against *Candida* spp : fungistatic activity
- against *Aspergillus :* fungicidal activity.
- Oral bioavailability exceeds 90% in adults in the fasted state , but
- it is considerably lower (65%) in children
- Tissue and CSF levels may exceed trough plasma levels several fold.
- The plasma half-life is 6 hours
- potential advantages over itraconazole: gastrointestinal tolerance and bioavailability

• VORICONAZOLE : Aspergillosis

- a randomized multicenter trial of invasive aspergillosis.
- At week 12: successful outcome in 52% of voriconazole group compared with only 31% in the amphotericin B deoxycholate group: significant
- The survival rates : 71% in the voriconazole group vs. 58% in the amphotericin B deoxycholate group : significant
- Voriconazole Efficacy in CNS aspergillosis and other disseminated forms even in severe infections.

- **Voriconazole : hepatotoxicity and QTc prolongation.**

- Visual disturbances, including photopsia (the perception of flashing lights), photophobia, and color changes
- No irreversible ocular toxicity
- Neurologic : confusion, agitation, and myoclonus: rare
- Alopecia, xerosis, and nail changes : long-term use
- Bone pain, elevated serum alkaline phosphatase levels, and periosteal elevation is observed on radiographic imaging, and bone scans

- **Voriconazole *Adverse effects.***

- **transient liver enzyme abnormalities (10–20%), skin reactions (<10%), visual hallucinations or confusion (<10%), and transient, dose-related visual disturbances (photopsia with altered or enhanced perception of light, blurred vision; 25% to 45%).**
- **Serious hepatic reactions, including hepatic failure, have been observed**
- **evaluation of liver function tests before and during treatment with voriconazole is advised.**
- **QTc prolongation : voriconazole should be administered with caution to patients with proarrhythmic conditions.**
- **Phototoxicity in close to 50% of children treated for 6 months or longer.**

- **Voriconazole *Adverse effects.***
- **Cutaneous rashes : 7% of patients : may lead to skin carcinoma following long-term therapy.**
- **A possible link between long-term use of voriconazole, immunosuppression, and chronic phototoxicity with aggressive squamous cell carcinoma and melanoma has been reported .**
- **As a consequence, the indication for further and prolonged voriconazole treatment in immunocompromised patients who develop phototoxicity needs to be evaluated extremely carefully.**
- **Caution is also warranted with the concurrent use of methotrexate, as severe skin toxicity has been observed.**
- **fluorosis and periostitis reported : long-term voriconazole use because of its elevated fluoride content.**

- ***Drug interactions.*** **Voriconazole**

- **significantly increases exposure to cyclosporine, tacrolimus, benzodiazepines, methadone, fentanyl, alfentanil, oxycodone, vinca alkaloids,statins, omeprazole, warfarin, sulfonylurea drugs, phenytoin, proteaseinhibitors other than indinavir, and non-nucleoside reverse transcriptase inhibitors**
- **Voriconazole exposure is significantly decreased phenytoin, ritonavir, efavirenz, rifabutin, carbamazepine, rifampin, and phenobarbital.**
- **Concurrent use of the last three enzyme inducers [carbamazepine, rifampin, and phenobarbital] with voriconazole is contraindicated (risk for subtherapeutic levels of voriconazole), as is the concurrent use of terfenadine, astemizole, cisapride, quinidine,pimozide (risk of QTc rolongation resulting from increased exposure to these agents), ergotamine (risk for ergotism resulting from increased exposure), and sirolimus (increased exposure).**

- In patients with renal insufficiency, no adjustment of dosage is needed for the oral formulation;
- In mild to- moderate hepatic function abnormalities, half of the daily maintenance dosage is recommended after the initial loading dose.
- therapeutic drug monitoring should be performed in pediatric patients with life-threatening invasive fungal infections.

• Other Mycoses

- **Voriconazole is also effective in the treatment of mucosal and invasive candidiasis**
- **little benefit over fluconazole for most *Candida* infections.**
- **not useful in the treatment of mucormycosis**

IDSA

- **During prolonged neutropenia for those who are at high risk for IA : recommend prophylaxis with voriconazole OR posaconazole**

- Prophylaxis with itraconazole is effective

•*Posaconazole*

- **fungistatic against *Candida* and fungicidal against *Aspergillus* spp.**
- activity against some Mucorales
- activity ON organisms that often are refractory to existing triazoles or amphotericin B or to echinocandins, such as ***C. glabrata, C. krusei, A. terreus,* and *Fusarium* spp.**
- oral suspension, tablet, and intravenous solution
- **The oral suspension achieves optimal exposure when it is administered in two to four divided doses with food or a nutritional supplement**
- nausea (8%), vomiting (6%), headache (5%), abdominal pain (4%), and diarrhea (4%) abnormal liver function test in 3%

•Posaconazole

- **strong antifungal efficacy in immunocompromised patients with primary or refractory oropharyngeal and esophageal candidiasis.**

- **as salvage therapy in patients with invasive fungal infections intolerant to or refractory to standard therapies**
- **aspergillosis**
- **zygomycoses**
- **coccidioidomycosis**
- **candidiasis**
- **cryptococcosis**

•Posaconazole

- **Following improvement with a polyene for mucormycoses , posaconazole is often used as oral step-down therapy**.
  - **Posaconazole decreases the incidence of fungal infections in high-risk patients during graft-versus-host disease following allogeneic bone marrow**
  - **prophylaxis in patients with neutropenia following chemotherapy**

    (prophylaxis of invasive *Candida* and *Aspergillus* infections in high-risk patients 13 years of age and older with HSCT and GVHD or those with hematologic malignancies and prolonged neutropenia)

IDSA

- **During prolonged neutropenia for those who are at high risk for IA : recommend prophylaxis with posaconazole OR voriconazole**

- **Prophylaxis with itraconazole is effective**

• posaconazole

- effectively used in a number of other invasive mycoses, including refractory aspergillosis, fusariosis, coccidioidomycosis and histoplasmosis .
- clinical efficacy against cryptococcal meningitis
- second-line or consolidation therapy of mucormycosis.
- approved for treatment of oropharyngeal candidiasis, including refractory to itraconazole or fluconazole .

TABLE 240.11 Principal Pharmacokinetic Properties of Posaconazole, Voriconazole, and Isavuconazole

	Posaconazole	Voriconazole	Isavuconazole
Formulation	PO	PO, IV	PO, IV
Dose linearity	Yes	No	Yes
Oral bioavailability (%)	>50	>90	>90
Protein binding (%)	>95	58	>99
Volume of distribution (L/kg)	>5	2	>5
Elimination half-life (h)	25	6	>80
Substrate/inhibitor of CYP450	—/3A4	3A4, 2C9, 2C19 / 3A4, 2C9, 2C19	3A4, 3A5/CYP3A4, CYP2C8, CYP2C9, CYP2C19,CYP2D6.
Elimination through			
Feces (%/% metabolites)	77/—	<20/?	46/100
Urine (%/% metabolites)	14/100	80/100	45/98

Data from references 134, 135, 243, 360, 533, 582, 583, 709.

UDP-GT, UDP glucuronosyltransferase.

Therapeutic Drug Monitoring

Antifungal	Goal/Rationale	Target	
Itraconazole	Confirm absorption	Prophylaxis	Trough: >0.5-1 mcg/mL
		Treatment	Trough: >0.5-1 mcg/mL
Voriconazole	High intrasubject variability, drug interactions, toxicity	Prophylaxis	Trough: 2-5.5 mcg/mL
		Treatment	Trough: 2-5.5 mcg/mL
Posaconazole	High intrasubject variability	Prophylaxis	Trough: >0.7 mcg/mL
		Treatment	Trough: >1 mcg/mL
Isavuconazole	Minimize gastrointestinal toxicities	Prophylaxis	Trough: 2.5-5 mcg/mL
		Treatment	Trough: 2.5-5 mcg/mL

• *Amphotericin B Deoxycholate*

- not orally or intramuscularly absorbed : virtually insoluble in water.
- cell membrane of most fungi.
- A second mechanism of action of amphotericin B may involve oxidative damage of the cell through oxidative reactions .
- amphotericin B and its lipid formulations differentially augment innate host defense against fungal pathogens.

• *Antifungal activity.*

- On most pathogenic fungi in humans
- Resistance to amphotericin B : *Candida lusitaniae, Candida guilliermondii,* and *Candida lipolytica*, Some of *Candida glabrata, Candida parapsilosis,* and *Candida tropicalis , Aspergillus terreus* and ….
- Acquisition of secondary resistance is an uncommon occurrence

• *Amphotericin*

- ***Indications.*** **With the exception of resource-limited settings, few indications are left for antifungal treatment of opportunistic mycoses with D-AmB.**
- **These indications include candidemia and acute tissue invasive candidiasis, particularly in neonates, and induction therapy for cryptococcal meningitis**
- **the recommended daily dosage : 0.7 to 1 mg/kg per day administered over 2 to 4 hours as tolerated.**
- **fever is more pronounced with infusion intervals of only 45 minutes than with infusion lasting 4 hours.**
- **Rapid infusion in patients with severely compromised renal function may lead to acute, marked hyperkalemia and ventricular fibrillation.**

•*Amphotericin*

- **Particularly with infusions of prolonged length, shielding the infusion bottle from light would reduce drug decay from light sensitivity.**
- **Continuous infusion has no pharmacodynamic rationale, no significant impact on renal toxicity, and should not be used. single daily doses rather than continuous infusion will be most effective.**
- **For empirical antifungal therapy in the persistently febrile neutropenic host, the historical standard dosage has been 0.5 to 0.6 mg/kg per day.**
- **treatment should be started at the full target dose**

• *Amphotericin B Deoxycholate*

- a prolonged postantifungal effect (PAFE) of amphotericin B of up to 12 hours' duration has been demonstrated in *C. albicans* and *C. neoformans.*
- Tissue levels in laboratory animals are highest in liver, spleen, bone marrow, kidney, and lung; concentrations in body fluids other than plasma are generally low.
- despite mostly undetectable concentrations in the cerebrospinal fluid (CSF) and comparatively low concentrations in brain tissue across all species, amphotericin B is effective in the treatment of fungal infections of the central nervous system (CNS).
- adjustment of dose is not necessary in patients with unrelated renal or hepatic dysfunction.

• *Amphotericin* lipid formulation:

- at least equivalent therapeutic efficacy and reduced nephrotoxicity
- Infusion-related side effects of fever, chills, and rigor were less frequent with L-AmB
- Substernal chest discomfort, respiratory distress, and sharp flank pain may occur during infusion of L-Am
- Mild increases in serum bilirubin, serum transaminases and alkaline phosphatase have been observed
- An increased rate of hyperphosphatemia has been reported
- pilot study was conducted in children at risk for developing invasive fungal infections who <u>received once-weekly, high-dose L-AmB (10 mg/kg over 2 hours) as prophylaxis</u>: well tolerated and showed measurable amphotericin B plasma concentrations 7 days after
- These findings suggest that once weekly as well as twice weekly administration may provide useful protection against fungal infections.

Amphotericin

- **Once therapy is well underway, patients receiving a stable daily dose may be changed to an increased double dose on alternate days to reduce the frequency of infusion-associated toxicity, particularly anorexia, and as a convenience for outpatient therapy.**
- **Doses greater than 1.5 mg/kg are not generally given on this schedule because the toxicity of such infusions is not well described.**

Amphotericin

- Comparison of Amphotericin B Deoxycholate and the Lipid-Associated Formulations of Amphotericin B
- LAMB of similar efficacy for cryptococcal meningitis
- Randomized comparisons with ABD as therapy in the persistently neutropenic and febrile cancer patient provide consistent demonstrations of a generally better tolerability profile, but there are few data on differential antifungal effect. Consistent with these results, the aggregate open-label data efficacy rates for the LFABs are similar to those for ABD.
- Although the LFABs are notably more costly (10- to 60-fold) than ABD, the purchase cost of the compound must be balanced against the morbidity and financial costs of monitoring, treating, and managing ABD-related nephrotoxicity. Of importance, such toxicity may be well tolerated in an outpatient with few other comorbidities or in children, whereas ABD-related nephrotoxicity (50% increase in baseline creatinine to a minimum of 2 mg/dL) was associated with a 6.6-fold increased odds of death and an absolute increase in mortality from 16% to 54%.52 In the majority of patients, LAMB or ABLC is preferred over ABD.

Amphotericin mandel

- They also provide important options for management of the persistently febrile neutropenic patient (particularly when this syndrome develops despite prophylaxis with an azole that has activity against molds) and for treatment of selected cases of candidiasis.

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- **when voriconazole cannot be administered: Amphotericin B (AmB) deoxycholate and its lipid derivatives are appropriate options for initial and salvage therapy of Aspergillus infections :**
  However, AmB deoxycholate should be reserved for use in resource-limited settings in which no alternative agents are available.
- Lipid formulations of AmB should be considered in settings in which azoles are contraindicated or not tolerated
- Aerosolized formulations of AmB may be considered as prophylaxis in patients with prolonged neutropenia (patients receiving induction/reinduction therapy for acute leukemia and allogeneic HSCT recipients following conditioning or during treatment of graft-vs-host disease [GVHD]) and in lung transplant recipients

Echinocandins

- Three echinocandins are currently on the market: **caspofungin**, anidulafungin, and micafungin.

  Another echinocandin, rezafungin.

Echinocandins

- **greater anti-*Candida* activity than fluconazole**
- **less toxic and better tolerated than amphotericin B formulations**
- **against invasive candidiasis : significantly improved survival and greater clinical success rates than amphotericin B or azole (mortality rates: 27%, 35%, and 36%, respectively; *P* < .0001 for echinocandin vs. others).**
- **In subgroup analysis, improved outcomes were evident for patients infected with *C. albicans* and non–*C. albicans* spp.**
- **(IDSA) recommend an echinocandin as the preferred initial agent for treatment of candidemia in both neutropenic and invasive candidiasis in intensive care unit patients.**
- second-line agents against mucosal candidiasis after fluconazole as the first

Echinocandins

- **fungicidal activity against most Candida spp. and fungistatic activity against Aspergillus spp. by inhibiting the synthesis of cell-wall (1→3)-β-D-glucan.**
- **Echinocandins are agents of choice for treatment of candidemia and deeply invasive candidiasis,**
- **inactive against most Mucorales**
- **preventive and therapeutic activity in animal models of *Pneumocystis jirovecii* (formerly *Pneumocystis carinii*) pneumonitis.**

Echinocandins

- have roles in empirical treatment of febrile neutropenia
- prophylaxis against invasive candidiasis in hematopoietic stem cell transplant recipients and liver transplantation and surgery.
- intravenously once daily, without need for renal dose adjustment.
- Drug-drug interactions are minimal, and safety profiles are excellent.
- resistance rates are low : in up to 10% of Candida glabrata at high-risk centers.

• Echinocandins

- **step-down therapy :** If patients with candidiasis demonstrate a clinical response to an echinocandin, guidelines indicate that Fluconazole can be used to complete a treatment course, beginning after 5 to 7 days if patients are infected with an isolate that is known or likely to be fluconazole susceptible.
- Deep-seated candidiasis such as endophthalmitis, meningitis, and urosepsis. : DATA IS less than for candidemia, and echinocandins may be limited by pharmacokinetic considerations in the treatment of diseases
- for intraabdominal candidiasis TREAT as candidemia, with echinocandins as appropriate first-line agents.
- IDSA : as an alternative to amphotericin B formulations for frontline treatment of *Candida* endocarditis and chronic disseminated (hepatosplenic) candidiasis.

- **Invasive Pulmonary Aspergillous Treatment**

IDSA

mandel

- **Primary therapy with an echinocandin is not recommended (strong recommendation)**
- caspofungin can be used in settings in which azole and polyene antifungals are contraindicated .

• Combination Antifungal Therapy

- **<u>Combinations of amphotericin B or azoles with echinocandins</u>** suggest additive or synergistic effects in some preclinical studies: uncertainty
- Routine antifungal susceptibility testing (AFST) of isolates recovered during initial infection is not recommended.
- It is reserved for patients suspected to have an azole-resistant isolate or who are unresponsive to antifungal agents, or for epidemiological purposes .

IDSA

Thanks for your attention