

SOURCES OF FUNGI:		
Endogenous human	<ul style="list-style-type: none"> <li>Candida spp.</li> <li>Pneumocystis jirovecii</li> </ul>	Yeasts
Ubiquitous environmental	<ul style="list-style-type: none"> <li>Aspergillus</li> <li>Zygomycetes (Mucorales)</li> </ul>	Moulds
Regional endemic mycoses	<ul style="list-style-type: none"> <li>Histoplasma</li> <li>Coccidioides</li> <li>Blastomyces</li> <li>Paracoccidioides</li> </ul>	Dimorphic
Widespread endemic mycoses	<ul style="list-style-type: none"> <li>Cryptococcus (haploid/diploid)</li> <li>Sporothrix</li> </ul>	

COMMON ADVERSE DRUG REACTIONS:	
HEPATIC	<ul style="list-style-type: none"> <li>All azoles</li> <li>Amphotericin B</li> <li>5-flucytosine</li> <li>Echinocandins</li> </ul>
KIDNEY	<ul style="list-style-type: none"> <li>Amphotericin B</li> <li>Cycloheximide possibly toxic (IV voriconazole)</li> </ul>
PSYCHIATRIC	<ul style="list-style-type: none"> <li>Voriconazole = hallucinations etc</li> </ul>
VISUAL	<ul style="list-style-type: none"> <li>Voriconazole</li> </ul>
DERM	<ul style="list-style-type: none"> <li>All antifungal agents = rash</li> <li>Voriconazole = photosensitivity/malignancy?</li> </ul>
GI	<ul style="list-style-type: none"> <li>Itraconazole, posaconazole</li> <li>5-flucytosine</li> </ul>
CARDIAC	<ul style="list-style-type: none"> <li>Itraconazole = cardiomyopathy</li> <li>All azoles = QTc prolongation</li> </ul>
INFUSION REACTIONS	<ul style="list-style-type: none"> <li>Amphotericin B</li> <li>Echinocandins</li> </ul>
BONE MARROW SUPPRESSION	<ul style="list-style-type: none"> <li>5-flucytosine</li> <li>Amphotericin B (anemia associated with decreased epoetin production)</li> </ul>

SITE OF ACTION OF SELECTED ANTIFUNGAL AGENTS:		
CELL MEMBRANE	<b>Polyenes (IV)</b> → Ergosterol binding	<ul style="list-style-type: none"> <li>Amphotericin B (deoxycholate and lipid)</li> </ul>
	<b>Azoles (PO / IV)</b>  → CYP450 enzyme lanosterol 1,4-demethylase inhibition	<ul style="list-style-type: none"> <li>Fluconazole</li> <li>Itraconazole</li> <li>Voriconazole</li> <li>Posaconazole</li> <li>Isavuconazole (US only)</li> </ul>
CELL WALL	<b>Echinocandins (IV)</b> → 1-3 D-glucan synthase inhibition	<ul style="list-style-type: none"> <li>Caspofungin</li> <li>Micafungin</li> <li>Anidulafungin</li> </ul>
NUCLEOSIDE ANALOGS	<b>DNA synthesis inhibitors</b>	<ul style="list-style-type: none"> <li>5-flucytosine</li> </ul>

RISK FACTORS FOR INVASIVE FUNGAL INFECTIONS:	
ASPERGILLOSIS	<ul style="list-style-type: none"> <li>Hematologic malignancy</li> <li>Prolonged and profound neutropenia                             <ul style="list-style-type: none"> <li>&gt; 10 days ANC &lt; 500/UL</li> </ul> </li> <li>Prolonged immunosuppression                             <ul style="list-style-type: none"> <li>Acute leukemia or myelodysplastic syndrome receiving induction chemotherapy</li> <li>Allogenic HSCT</li> <li>Solid organ transplant</li> <li>Other immunosuppressed patients</li> </ul> </li> </ul>
CANDIDIASIS	<ul style="list-style-type: none"> <li>Hematologic malignancy</li> <li>Age &lt; 1 month or &gt; 65 years old</li> <li>Recent surgery                             <ul style="list-style-type: none"> <li>Abdominal surgery w/ anastomotic leaks</li> </ul> </li> <li>Use of central venous catheter</li> <li>Use of broad spectrum antibacterial agents</li> <li>PLUS:                             <ul style="list-style-type: none"> <li>Prolonged ICU stay</li> <li>Total parenteral nutrition</li> <li>Mucosal Candida spp. Colonization</li> <li>Renal failure</li> </ul> </li> </ul>

SPECTRUM OF ACTIVITY:									
	AmB	Flu	Itr	Vor	Pos	Caspo	Mica	Flucyt	
Aspergillus	+	-	+	+	+	+	+	+	-
A. flavus	+/-	-	+	+	+	+	+	+	-
A. fumigatus	+	-	+	+	+	+	+	+	-
A. niger	+	-	+/-	+	+	+	+	+	-
A. terreus	-	+	+	+	+	+	+	+	-
Candida	+	+	+	+	+	+	+	+	+
C. albicans	+	+/-	+	+	+	+	+	+	+
C. glabrata	+	-	+	+	+	+	+	+	+
C. krusei	+	+	+	+	+	+	+	+	+/-
C. lusitaniae	-	+	+	+	+	+	+	+	+
C. parapsilosis	+	+	+	+	+	+	+/-	+/-	+
C. tropicalis	+	+	+	+	+	+	+	+	+

AZOLE DRUG INTERACTIONS:				
	Fluconazole	Itraconazole	Posaconazole	Voriconazole
<b>Inhibitor</b>				
CYP2C19	+	-	-	+++
CYP2C9	++	+	-	++
CYP3A4	++	+++	+++	++
<b>Substrate</b>				
CYP2C19	-	-	-	+++
CYP2C9	-	-	-	+
CYP3A4	+	+++	-	+

CYP2C19 = omeprazole, CYP2C9 = warfarin, CYP3A4 = cyclosporine, statin, phenytoin, VCR

GENETIC VARIABILITY IN METABOLISM OF VORICONAZOLE:	
•	Poor metabolizers – Asian and Pan-Pacific (14-19%)
•	Rapid clearance – pediatrics (up to 12 mg/kg q12h)

PHARMACOKINETIC CONSIDERATIONS:		
HEPATIC	VORICONAZOLE	Decrease dose for mild-mod cirrhosis
	CASPOFUNGIN	Decrease dose for moderate insufficiency
RENAL	FLUCONAZOLE	Decrease dose
	ITRACONAZOLE	Caution with IV prep for CrCl < 30 mL/min
	VORICONAZOLE	Caution with IV prep for CrCl < 50 mL/min
	FLUCYTOSINE	Decrease dose

POTENTIAL SITES OF FUNGAL INFECTION:	
ASPERGILLOSIS	<ul style="list-style-type: none"> <li>An airborne = respiratory tract &amp; sinuses are major port of entry and site of infection</li> </ul>
CANDIDIASIS	<ul style="list-style-type: none"> <li>Bloodstream infection = access through the skin (Hickman line access) or GI tract (mucositis)</li> </ul>

DIAGNOSIS OF INVASIVE FUNGAL INFECTIONS:	
•	Criteria based on host factors, clinical and mycological criteria <ul style="list-style-type: none"> <li>Proven = culture from sterile site</li> <li>Probable = Galactomannan positive or BAL positive</li> <li>Possible = most common, CT scan positive</li> </ul>
•	Diagnosis should be aggressively pursued whenever possible and treatment started early due to anginoinvasive nature of pathogen
<b>GOLD STANDARD</b>	<ul style="list-style-type: none"> <li>Fluid and tissue specimens (but low yield)</li> </ul>
ASPERGILLUS	<ul style="list-style-type: none"> <li>CT scan of lung: lesion with halo sign                             <ul style="list-style-type: none"> <li>Air crescent sign (non-sensitive)</li> </ul> </li> <li>Most common type of aspergillus = A. fumigatus</li> </ul>
CANDIDIASIS	<ul style="list-style-type: none"> <li>Isolation of yeast from blood culture</li> <li>"Bull's eye" lesions in the liver or spleen within 2 wks of candidemia = hepatosplenic candidiasis</li> <li>Fundoscopy exam on all patients (IDSA)</li> </ul>
<b>NON-CULTURE BASED DIAGNOSIS</b>	<ul style="list-style-type: none"> <li>Galactomannan Antigen serum &amp; BAL                             <ul style="list-style-type: none"> <li>More commonly used in HSCT or hem malignancy not SOT</li> </ul> </li> <li>PCR – promising but needs standardization</li> <li>Used in combination with CT findings for early initiation of therapy and to assess response</li> <li>Be aware of false positive results (plasmalyte)</li> <li>Combination of tests = high sensitivity</li> </ul>

**TREATMENT OF PULMONARY ASPERGILLOSIS:**

<b>AMP B</b>	<ul style="list-style-type: none"> <li>Equally efficacious</li> <li>Lipid formulations less toxic</li> <li>Costly</li> </ul>	
<b>TRIAZOLES</b>	<b>FLUCONAZOLE</b>	<ul style="list-style-type: none"> <li>No activity against aspergillus</li> </ul>
	<b>ITRACONAZOLE</b>	<ul style="list-style-type: none"> <li>No good evidence for primary treatment</li> <li>Absorption issues</li> </ul>
	<b>VORICONAZOLE</b>	<ul style="list-style-type: none"> <li>Good evidence for primary therapy</li> <li>IV is costly</li> </ul>
	<b>POSACONAZOLE</b>	<ul style="list-style-type: none"> <li>Only salvage therapy and prophylaxis data</li> </ul>
	<b>ECHINOCANDINS</b>	<ul style="list-style-type: none"> <li>No large RCTs</li> <li>Salvage data</li> <li>Static</li> </ul>
<b>COMBO THERAPY</b>	<ul style="list-style-type: none"> <li>No difference in 6-week mortality rates</li> <li>IDSA does not recommend combo as primary therapy</li> </ul>	

**VORICONAZOLE:**

- Voriconazole 6 mg/kg IV q12h x 2 loading dose, then 4 mg/kg IV q12h until able to take PO
  - Loading dose very important
  - PO dose > 40 kg: 200 mg PO BID
- Monitoring:

<b>EFFICACY</b>	<ul style="list-style-type: none"> <li>TDM trough &gt; 1 mcg/mL 5-7 days after starting therapy</li> <li>Monitor levels for suspected failure &amp; toxicity</li> </ul>
<b>ADRs</b>	<ul style="list-style-type: none"> <li>Visual impairment or photopsia (30-45%)</li> <li>LFT changes (10% AST, ALT, alk phosp. Bili)</li> </ul>
<b>TOXICITY</b>	<ul style="list-style-type: none"> <li>Visual +/- auditory hallucinations reported as often funny and not disturbing                             <ul style="list-style-type: none"> <li>May be associated with high levels (&gt; 5.5 – 6 mcg/mL) and requires D/C of therapy</li> </ul> </li> <li>Polymorphisms in gene encoding CYP2C19 enzyme → variable rates of metabolism</li> </ul>
<b>RENAL FXN</b>	<ul style="list-style-type: none"> <li>Accumulation of IV vehicle in CrCl &lt; 50, use PO in renal dysfunction</li> </ul>

**DURATION OF THERAPY:**

- Treat until resolution of S/S of infection (min. 6-12 weeks)
- Repeat CT chest in 2-4 weeks, not earlier
  - Unless worsening, then PRN until resolution
- Continue fungal treatment in patients undergoing prolonged immunosuppression (steroids or chemotherapy)
- Monitor absolute neutrophil count

**ROLE OF FLUCONAZOLE TO PREVENT AGAINST INVASIVE CANDIDIASIS IN ICU:**

- Not routinely used prophylactically in adults with community acquired intra-abdominal infections
- Not indicated unless patient is high risk
  - Recurrent gastro-duodenal perforation, anastomotic leaks, or acute necrotizing pancreatitis

**IDSA GUIDELINES FOR INTRA-ABDOMINAL INFECTIONS:**

- Fungal treatment in severe community-acquired or health care-associated infection is recommended if Candida is grown from intra-abdominal cultures
- C. albicans:** fluconazole = drug of choice?
  - Fluconazole resistant sp: echinocandin drug of choice
    - IDSA considers all 3 therapeutically equivalent, but more experience with caspofungin
  - Critically ill: start with echinocandin
- AmphoB not recommended due to toxicity

**DURATION OF THERAPY:**

- Two weeks after last positive blood culture and resolution of signs and symptoms of illness

**SUMMARY OF TREATMENT GUIDELINES FOR PROBABLE/PROVEN CANDIDA:**

- Initiate antifungal agents within 24 hours of positive culture
- Echinocandins not drug of choice in:
  - Candiduria
  - CNS infections
  - Endocarditis
  - Endophthalmitis
  - C. parapsilosis invasive infections
- Switch to PO azole where appropriate when species is identified and susceptibilities are known
- Restrict voriconazole PO to fluconazole-resistant isolates (ex// C. krusei)
- Fundoscopy exam is recommended in all patients with invasive candidiasis
- Removal of any intravenous catheters is recommended
- Repeat blood cultures to document negative cultures

**CHALLENGES IN IMMUNOCOMPROMISED PATIENTS:**

- Know the changing epidemiology of invasive fungal infections (IFI)
- Non-specific presentation of IFI
- Inadequate diagnostic methods
- Antifungal prophylaxis – does it work?
- Breakthrough infections while on antifungal therapy
- Refractory to antifungal treatment

**ANTIFUNGAL THERAPEUTIC DRUG MONITORING:**

	Target range	Comment
<b>VORICONAZOLE</b>	Efficacy: trough > 1-2 mcg/mL (≥ 2 more severe infxn)  Safety: peak < 5-6 mcg/mL (<4 mcg/mL in Japanese)	After 5-7 days of therapy
<b>POSACONAZOLE</b>	Efficacy: trough > 0.7 mcg/mL (px), > 1 mcg/mL (tx)	SUSP: after day 5 IV/tabs: after day 2-3
<b>FLUCYTOSINE</b>	20-50 mcg/mL	Obtain 2 hr after oral dose  Toxicity seen with > 100 mcg/mL

TDM not recommended for: amphotericin B, fluconazole, isavuconazole echinocandins