SYSTEMIC CHEMOTHERAPEUTIC AGENTS AGAISNT SYSTEMIC INFECTIONS					
POLYENES	AMPHOTERICIN B				LIPID ENCAPSULATED FORMULATIONS OF AmB
Uses	• Broad spectrum anti-fungal against most species including *Candida, Cryptococcus, Aspergillus,* endemic mycoses pathogens and other molds				• Only used in patients intolerant or non-responsive to conventional AmB therapy • Expensive alternatives to conventional therapy
Mechanism of Action	• Binds to ergosterol in fungal cell membrane and forms pores, directly leading to cell death				
Pharmacokinetics	• Nearly insoluble in water; formulated for IV injection by complexing with deoxycholate • More than 90% protein bound • Drug plasma half-life is long				• PK properties are different for different formulations
Mechanism of Resistance	• Rarely occurs - intrinsic resistance in some species was observed				
Side/Adverse Effects; Toxicities	• Infusion-related toxicity • Nephrotoxicity – limits its use				• Reduced nephrotoxicity compared to conventional AmB therapy
AZOLES	KETOCONAZOLE	FLUCONAZOLE	ITRACONAZOLE	VORICONAZOLE	POSACONAZOLE
Uses	• Endemic mycosis and dermatophytoses • Largely replaced by the newer generation triazoles	• Narrow spectrum • Active against *Candida* and *Cryptococcus*	• Endemic mycosis and dermatophytoses • Broader spectrum than fluconazole	• Broad spectrum • Active against *Apergills, Candida* and other molds • Drug of choice for Aspergillus systemic infxn	• **Broadest spectrum** • Spectrum similar to that of voriconazole but also active against Mucorales such as Mucor and Rhizopus
Mechanism of Action	• Important alternative to AmB in systemic anti-fungal treatment • Inhibition of fungal sterol-14a-demethylase (CYP1) and ergosterol production, disrupting cell membrane integrity				
Pharmacokinetics	• Oral	• IV and oral • Good bioavailability • Excellent CNS penetration	• IV and oral • Poor bioavailability and CNS penetration • Extensive hepatic bio-transformation • Absorption increased by lower gastric pH	• IV and oral • Well absorbed orally • Extensive metabolism by hepatic enzyme before renal dysfunction	• Oral • Well-absorbed orally, relatively high bioavailability • Eliminated primarily unchanged in feces
Side/Adverse Effects; Toxicities	• Relatively well tolerated	• Has the least side effects (because of relatively low affinity for CYP450)	• Relatively well tolerated	• Better tolerated than AmB • May cause hepatotoxicity and visual disturbances	• Generally well-tolerated
Drug Interactions	• Wide spectrum of drug interaction due to potent inhibition of CYP450		• Large number of drug interactions	• Relatively low number of drug interactions	• Inhibitor of CYP3A4 (quinidine, cimetidine, phenytoin)
ECHINOCANDIN	CASPOFUNGIN		MICAFUNGIN		ANIDULAFUNGIN
Uses	• Systemic and cutaneous infections of *Candida* and *Aspergillus*		• Approved in Canada for the treatment and prophylaxis of *Candida* infections • Prophylaxis usage in transplant recipients on immune-suppressive therapy		• Approved in Canada for treating invasive *Candida* infections
Mechanism of Action	• Inhibition of beta (1,3) glucan synthase and fungal cell wall synthesis				
Mechanism of Resistance	• Rarely occurred; may involve the alterations of beta (1,3) glucan synthase or the increase efflux of intracellular concentration of drugs				
Pharmacokinetics	• IV only • Extensive non-enzymatic and hepatic metabolism • Excreted as metabolites through renal & fecal route		• IV only • Extensive biotransformation in the liver • Excrete as metabolites mainly through bile		• IV only • Metabolism is largely non-enzymatic • Excretion mainly through fecal route
Side/Adverse Effects; Toxicities	• Well tolerated • GI disturbances • Infusion-related pain		• Well tolerated • Less infusion related pain reported than casopfungin		
Drug Interactions	• Concurrent administration cyclosporine will increase free caspofungin		• May increase serum level of nifedipine		

SYSTEMIC AGENTS AGAINST DERMATOPHYTOSES		
	GRISEOFLUVIN	**TERBINAFINE (Allylamines)**
Uses	• Dermatophytoses only • Drug has to be administered for a long period to produce therapeutic effects • Largely replaced by Terbinafine	• Dermatophytoses only • Long treatment duration for nail infections
Mechanism of Action	• Molecular target unknown • Targets dividing cells by inhibiting mitotic spindle formation	• Inhibits squalene expoxidase
Pharmacokinetics	• Oral (given in micro-crystalline form) • Poor water-solubility	• Oral • Metabolized by multiple CYP450 isoenzymes
Side/Adverse Effects; Toxicities	• Allergic reaction • Hepatitis	• Rare - GI upset and headache • Hepatic toxicity is rare but could be clinically significant
Drug Interactions	• Warfarin and phenytoin	• No significant drug interactions noted