

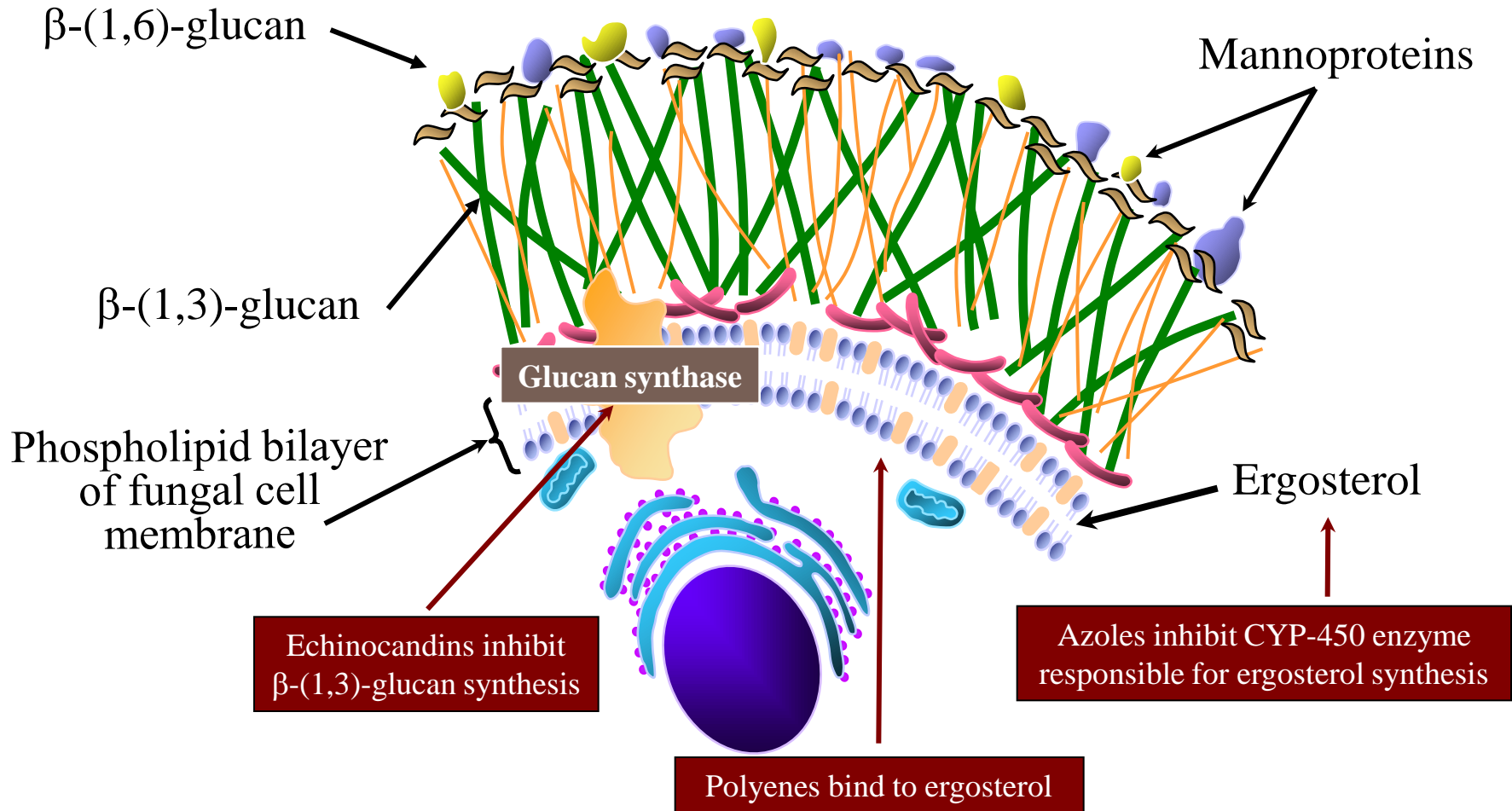
The Echinocandins: For and Against

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Outline

- “For”
 - Mechanism of action
 - Spectrum
 - Pharmacology
 - Efficacy
- “Against”
 - *Candida parapsilosis* ?
 - Where echinocandins can't go
 - Cost?

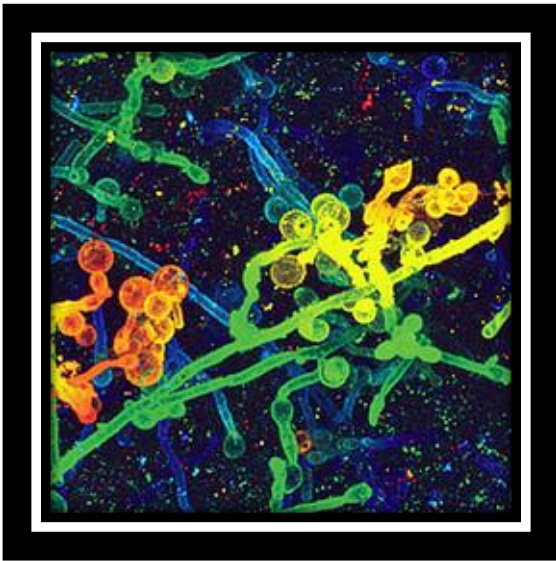
Mechanism of Action: Targets of Different Antifungal Classes



In Vitro Activity

	Caspofungin	Micafungin	Anidulafungin
<i>Candida</i> spp	<i>C albicans</i> <i>C glabrata</i> <i>C parapsilosis</i> <i>C tropicalis</i> <i>C krusei</i> <i>C dubliniensis</i> <i>C guilliermondii</i> <i>C kefyri</i> <i>C lipolytica</i> <i>C lusitaniae</i> <i>C rugosa</i>	<i>C albicans</i> <i>C glabrata</i> <i>C parapsilosis</i> <i>C tropicalis</i> <i>C krusei</i>	<i>C albicans</i> <i>C glabrata</i> <i>C parapsilosis</i> <i>C tropicalis</i>
<i>Aspergillus</i> spp	<i>A fumigatus</i> <i>A flavus</i> <i>A niger</i> <i>A nidulans</i> <i>A terreus</i> <i>A candidus</i>		

The Role of Biofilm



- One of the reasons why antifungals fail in spite of in vitro sensitivity
- β -1,3-Glucan major component of biofilm matrix
- Speed of biofilm production
- Efficacy of antifungals against *Candida* biofilm

Pharmacology: Metabolism, Elimination, Bioavailability, and Protein Binding

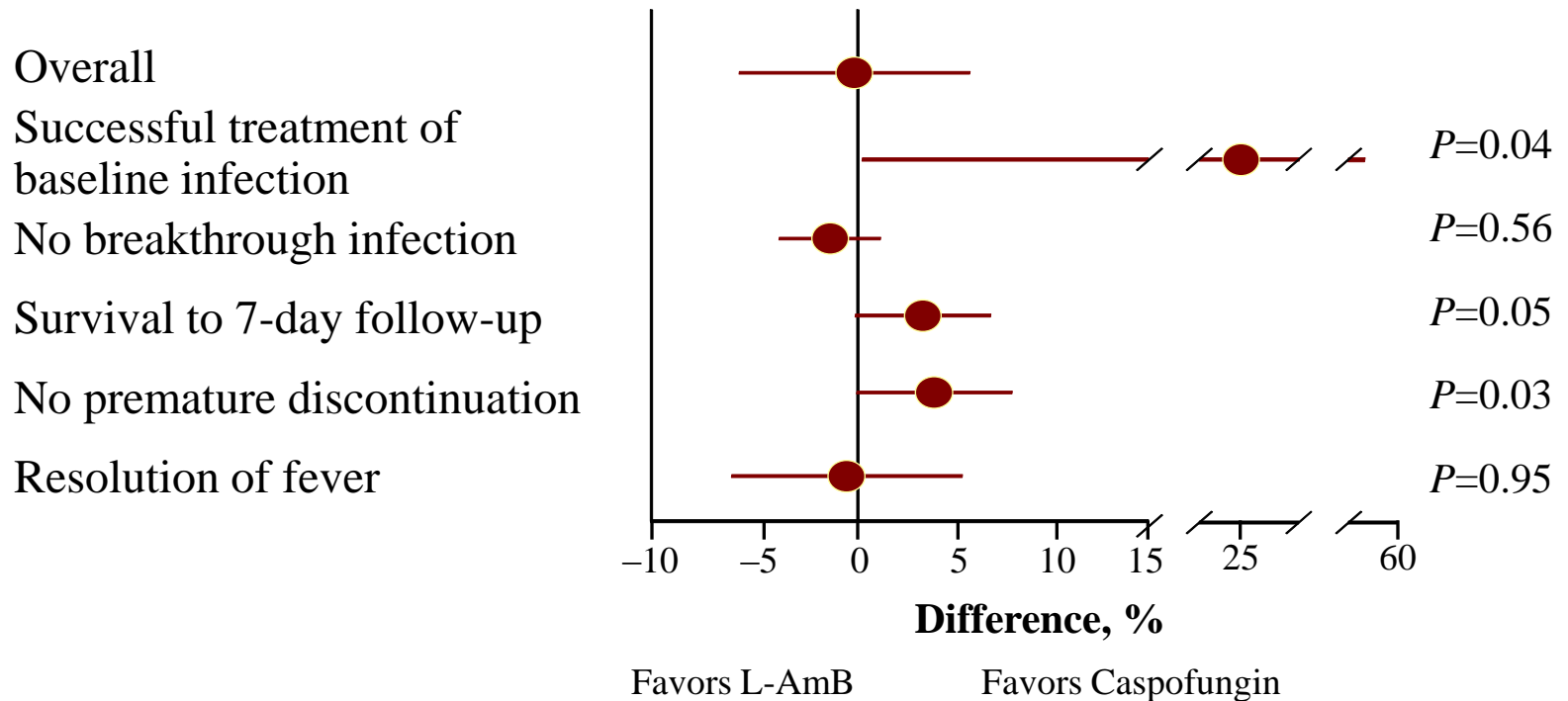
	Caspofungin	Micafungin	Anidulafungin
Metabolism	Hepatic metabolism by hydrolysis and N-acetylation Spontaneous nonhepatic chemical degeneration	Hepatic metabolism by arylsulfatase and catechol-O- methyltransferase	Nonhepatic chemical degradation
Elimination/excretion	Urine 41% Feces 34%	Urine + feces 82.5% Feces 71%	Urine <1% Feces ≈30%
Protein Binding	97%	>99%	>99%
Oral Bioavailability	<5%	<5%	<5%
Dialyzable	No	No	No

Pharmacology: Key Points

- The clinical significance of protein binding for the echinocandins has not been established
- With standard dosing in different clinical studies, caspofungin and anidulafungin reached target concentration after first day loading dose. Micafungin required 3 doses to reach target concentration
- None of the echinocandins require dose adjustments based on gender, race, age, or renal dysfunction
- All echinocandins can be used for mild to moderate hepatic dysfunction. Anidulafungin can be used in severe hepatic dysfunction

Efficacy of Echinocandins: Neutropenic Patients

- Phase 3, randomized, double-blind, multicenter study in adults of caspofungin 50 mg/day (70 mg on day 1) versus L-AmB 3 mg/kg/day (N=1111)
 - Overall favorable response: Caspofungin 34% (n=556) versus L-AmB 34% (n=539)**



Efficacy of Echinocandins

- In randomised trials, comparator drug more often than not amphotericin B / lipid formulation
- One randomised trial comparing fluconazole with anidulafungin
- Treatment successful in 75.5% of patients in anidulafungin group, versus 60.2% in fluconazole group (95% CI = 3.9 – 27.0)

Efficacy: Observational Studies

- Single centre study comparing mortality between two time periods
- 433 episodes of candidemia were analysed for period 1994 – 2003 and 2004 - 2008
- *Candida albicans* was most frequent species (49%)
- Overall mortality was 30% with 94 cases in period A (36%) versus 38 in period B (22%, $P=0.03$)
- Echinocandin alone or in combination was associated with better outcome (OR=0.22, 95% CI=0.06-0.81, $P=0.02$)

Against: *C parapsilosis* ?

- Meta-analysis of 5 randomised, blinded comparative trials
- Success rate of echinocandin group similar versus other antifungal treatment groups (76.5% vs 73%, RR=1.03, 95% CI 0.88-1.21)
- Conclusion: “Echinocandins were as effective as comparator drugs for treatment of candidemia or invasive candidiasis due to *C parapsilosis*”

Where Echinocandins Can't Go...

- Low or undetectable levels in
 - Urine
 - CSF
 - Vitreous fluid

Cost?

- All relative
- Cost of ICU bed for 1 day \approx R20 000/day
- Cost of alternatives:
 - Liposomal amphotericin R13000 – R18000 / day

Conclusion: The “Ideal” Antifungal Drug

- Broad spectrum anti-Candida activity
- Fungicidal
- Formulations: IV + / - Oral
- Clinical efficacy
- Safety, toxicity
- Cost / benefit ratio