ANTIFUNGAL AGENTS:

different classes, different characteristics

Katrien Lagrou

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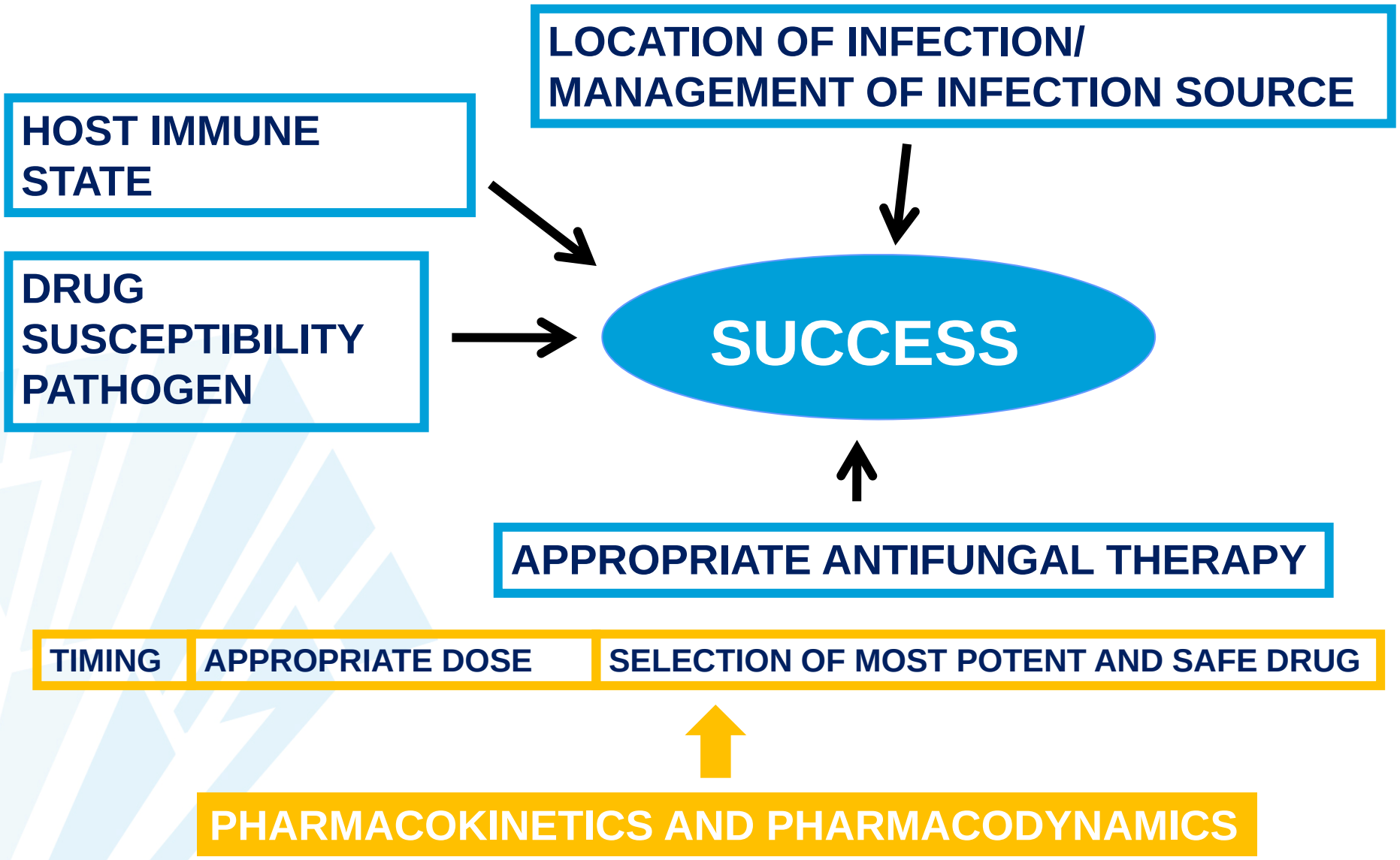

LOCATION OF INFECTION/
MANAGEMENT OF INFECTION SOURCE
HOST IMMUNE
STATE
DRUG
SUSCEPTIBILITY
PATHOGEN
SUCCESS
APPROPRIATE ANTIFUNGAL THERAPY
TIMING
APPROPRIATE DOSE
SELECTION OF MOST POTENT AND SAFE DRUG
PHARMACOKINETICS AND PHARMACODYNAMICS

TARGET

DNA/RNA synthesis

5-FC

CELL WALL

Caspofungin

Anidulafungin

Micafungin

CELL MEMBRANE

Miconazole

Ketoconazole

Fluconazole

Itraconazole

Posaconazole

Isavuconazole

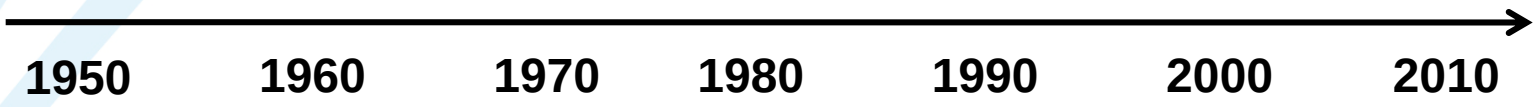
Nystatin

Amphotericin B

Terbinafine

L-AmB, ABLC

ABCD



No single antifungal agent is appropriate for all patients for a given mycosis because of:

Patient specific co morbid conditions

Hypersensitivities

Risk of drug interactions

Site of infection

Risk of infection with a resistant-pathogen

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SPECTRUM

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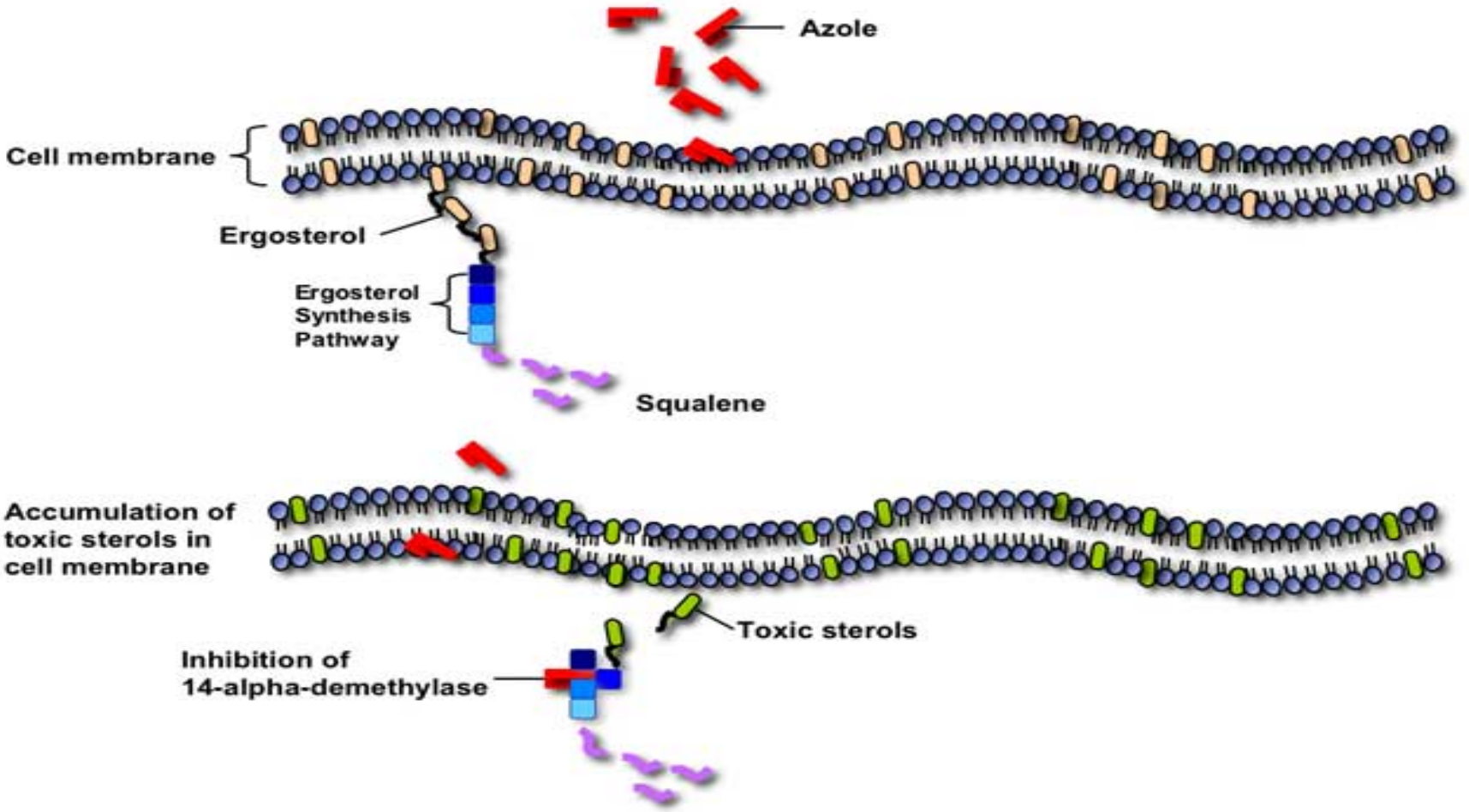
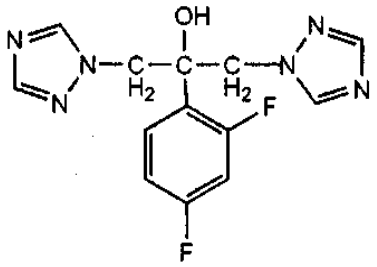
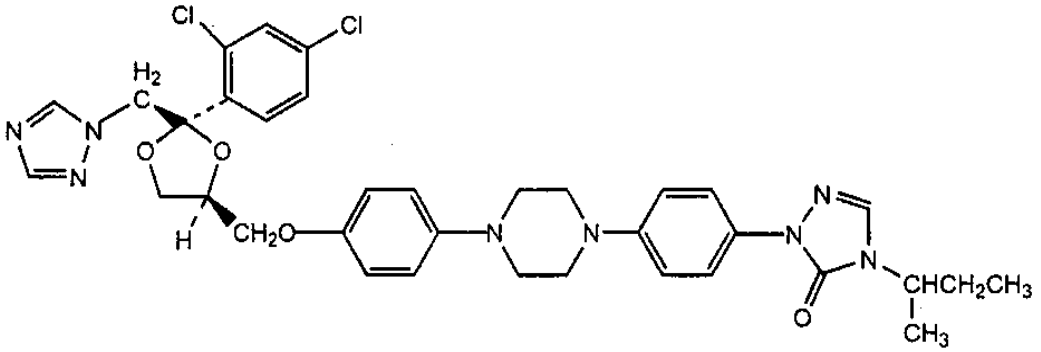

Azole
Cell membrane
Ergosterol
Ergosterol
Synthesis
Pathway
Squalene
Accumulation of
toxic sterols in
cell membrane
Toxic sterols
Inhibition of
14-alpha-demethylase

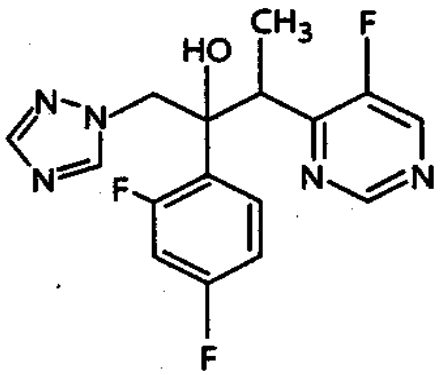
TRIAZOLES



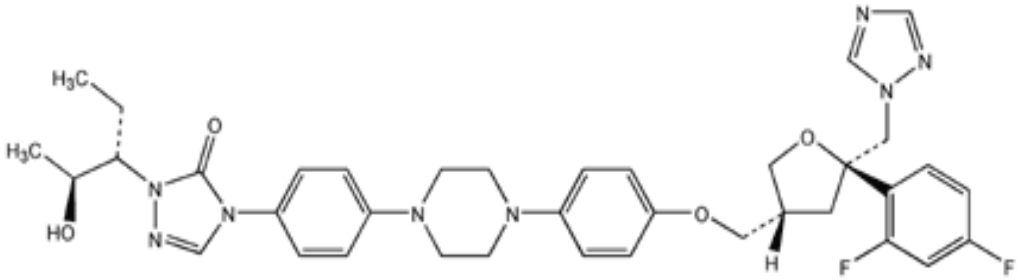
FLUCONAZOLE



ITRACONAZOLE



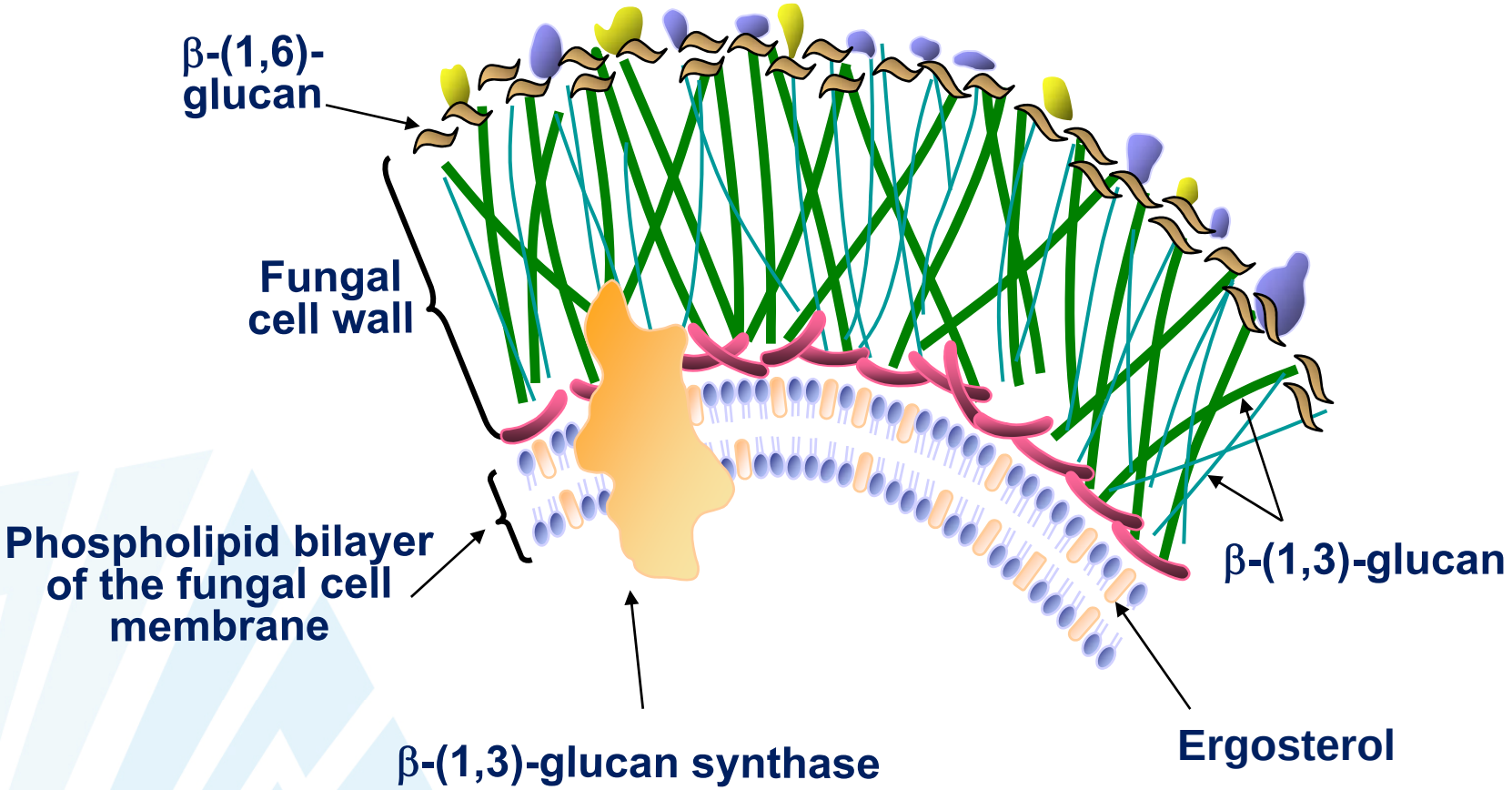
VORICONAZOLE



POSACONAZOLE

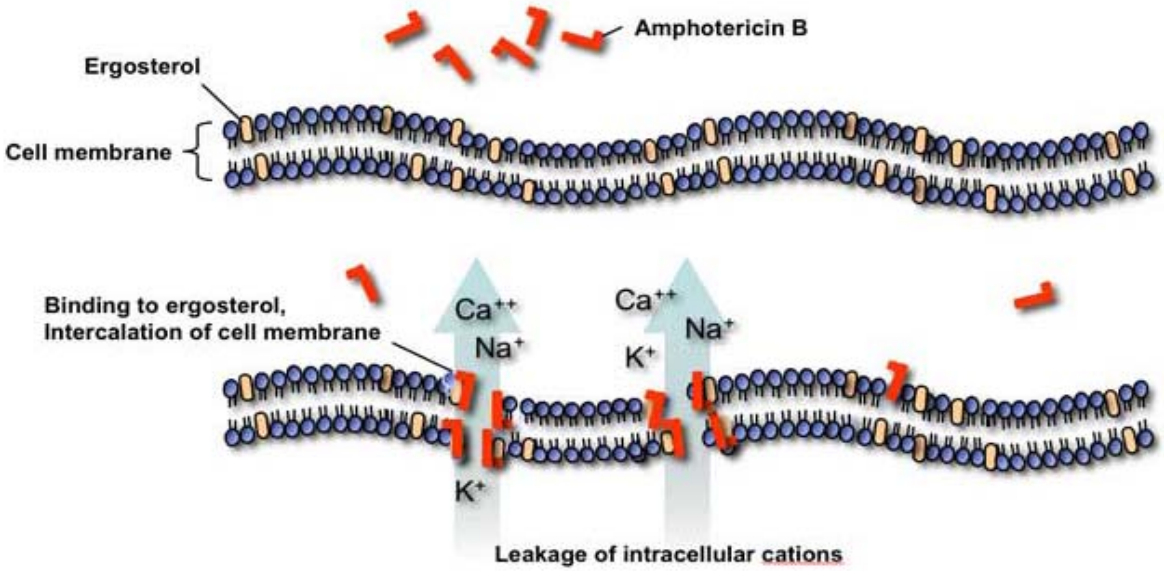
Activity of azoles

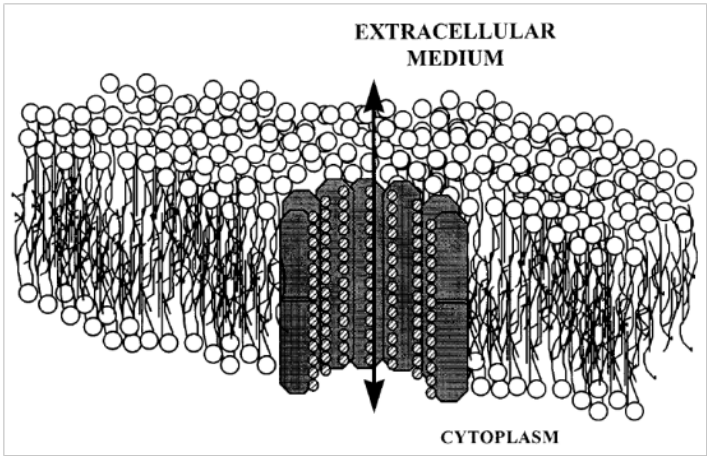
- Differences in the conformation of the 14α-demethylase binding pocket and azole structure largely define the binding affinity of each drug
- Resistance mainly results from mutations in the azole binding pocket and/or overexpression of efflux pumps
  - *C. krusei*: impaired binding of fluconazole to 14α-demethylase, newer triazoles retain activity
  - *C. glabrata*: often due to expression of multidrug efflux pumps, cross resistance may occur



Development of echinocandin resistance during therapy is a relatively rare clinical phenomenon.

Mutations in 'hot spot' regions of the FKS1 and FKS2 catalytic subunits of the glucan synthase are associated with reduced inhibitory activity.





Development of amphotericin B resistance during therapy is a rare clinical phenomenon:

- Alternative cell wall sterols
- Increased resistance to oxidative damage in the cell membrane through increased production of neutralizing enzymes

Organism	MIC90 (mg/L)					
	AmB	Flu	Itr	Vor	Pos	Isa
Candida species						
C. albicans	0.5-1	0.25-16	0.016-0.06	0.03-0.06	<0.016-0.25	<0.002-0.03
C. glabrata	0.5-2	32->64	1	1-4	2-4	0.5-8
C. krusei	0.5-4	64->64	0.5	1-4	1	0.25-1
C. parapsilosis	0.5-2	1-8	0.063	0.06-0.125	0.125	0.03-0.125
Aspergillus species						
A. fumigatus	0.5-8	>64	1->8	0.5-2	0.25-1	0.5-2
A. flavus	1-4	>64	0.5	0.5-2	0.5	1-16
A. niger	0.5-2	>64	2	1-2	0.5-1	2-4
A. terreus	1-8	>64	0.25-1	0.5-2	0.5	0.5-4

Thompson and Wiederhold. Mycopathologia, 2010, 170: 291-313.

Cidal activity

Organism	MIC90 (mg/L)		
	Casp	Ani	Mica
***Candida* species**			
C. albicans	0.03-1	0.015	0.015
C. glabrata	0.125-0.25	0.06-0.125	0.015
C. krusei	0.25-0.5	0.125	0.125
C. parapsilosis	1-2	4-8	2
***Aspergillus* species**			
A. fumigatus	0.06-0.5	0.015	0.015
A. flavus	0.03-0.25	0.015->8	0.03
A. niger	0.125-0.25	0.015	0.015
A. terreus	0.06-0.5	0.015	0.015-0.06

Static activity

Thompson and Wiederhold. Mycopathologia, 2010, 170: 291-313.

Organism	Antifungal agents								
	AmB	Flu	Itr	Vor	Pos	Isa	Ani	Casp	Mica
Cryptococcus neoformans	+	+	+	+	+	+	-	-	-
Mucorales	+	-	-	-	+	+	-	-	-
Fusarium species	±	-	-	±	±	±	-	-	-
Scedosporium apiospermum	±	-	±	±	±	±	-	-	-
Scedosporium prolificans	-	-	-	-	-	-	-	-	-

PHARMACOKINETIC CONSIDERATIONS

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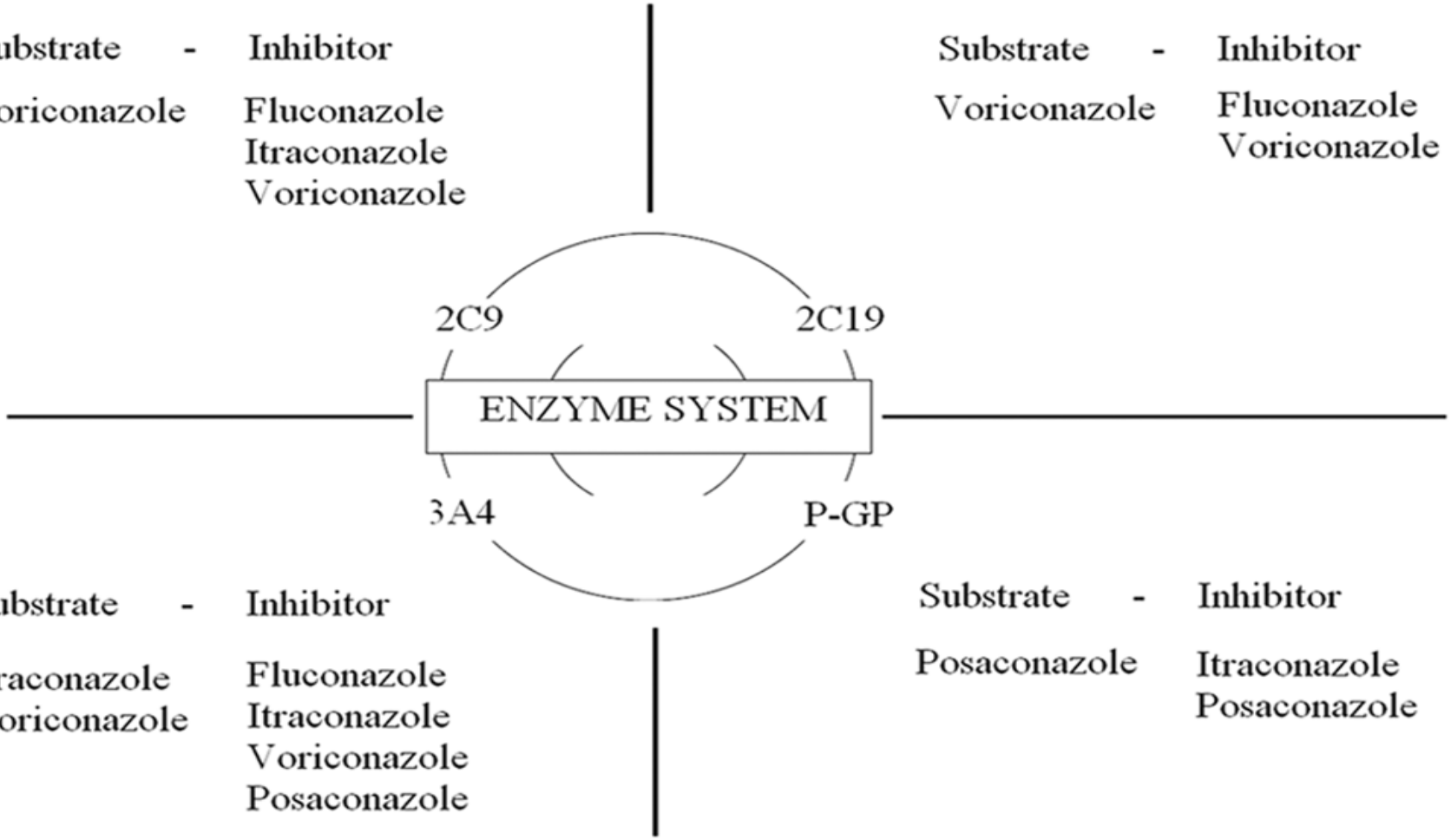
Azoles

- Voriconazole: high variable plasma levels due to non-linear kinetics (not children) and genetic variation in metabolism (CYP2C19)
- Posaconazole: oral absorption can be unpredictable
  - Reformulation of oral suspension
  - Intravenous dosage form

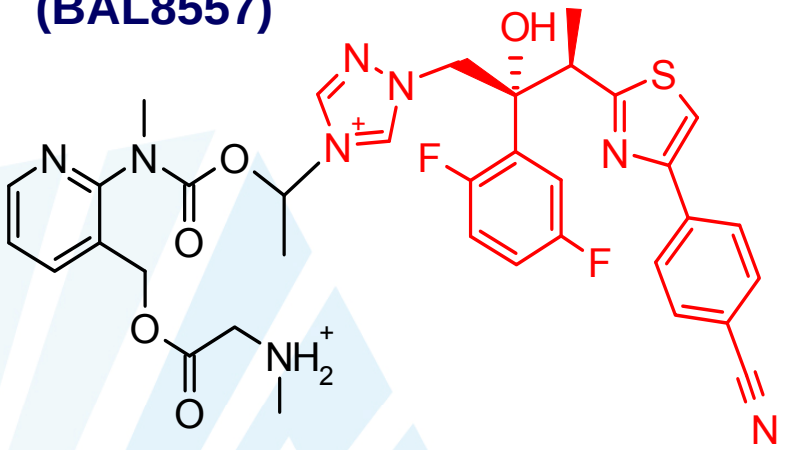
Involvement of cytochrome P450 enzymes and P-glycoprotein (P-gP) in the metabolism of azole antifungal drugs



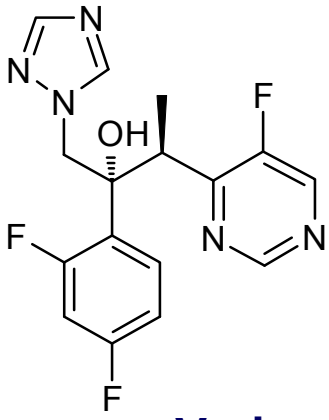
R.J.M. Brüggeman et al., CID, 2009, 48: 1441-1457.

Isavuconazole

Prodrug (BAL8557)



Isavuconazole (BAL4815)



Voriconazole

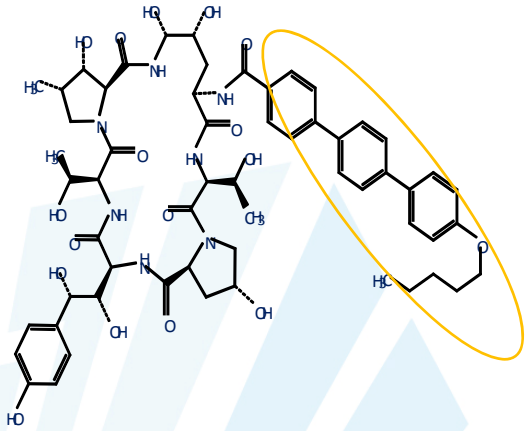
High water solubility of prodrug isavuconazonium sulfate

PK in Healthy Volunteers

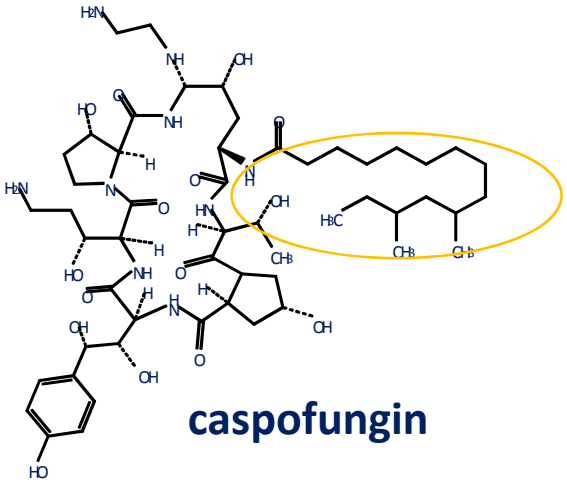
- Oral bioavailability > 90%
- Pro-drug is immediately and quantitatively converted to isavuconazole
- Isavuconazole characterized by
  - a large volume of distribution (> 400 L),
  - a long elimination half-life (30-120 h)
  - plasma protein binding: 98%
  - elimination by metabolism

ECHINOCANDINS

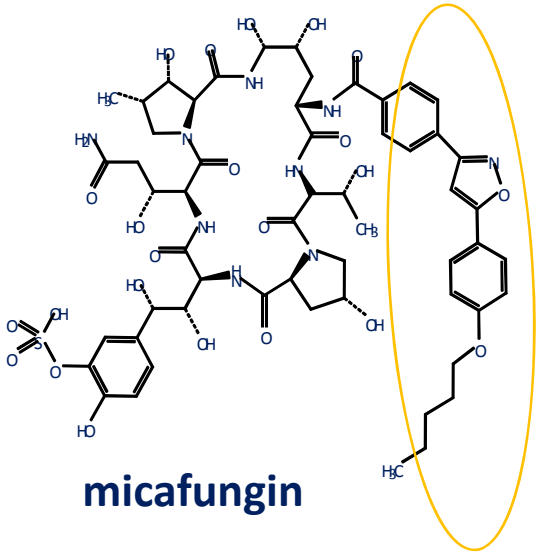
PK is specific for each echinocandin



anidulafungin



caspofungin



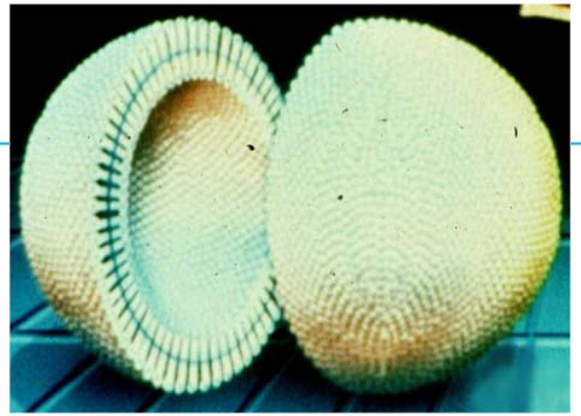
micafungin

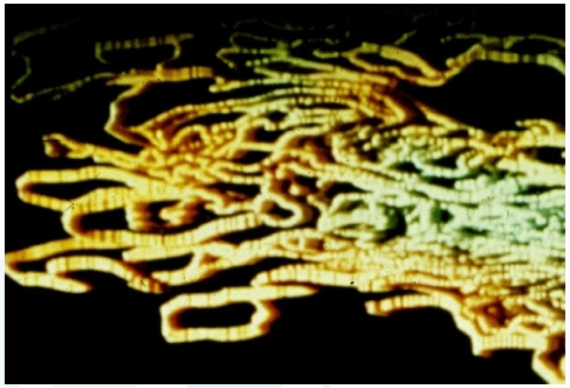
Side chain determines:

- Activity: interaction with the cell wall
- Pharmacokinetics: more lipophilic → higher distribution volume

Poor CNS, urine, eye penetration

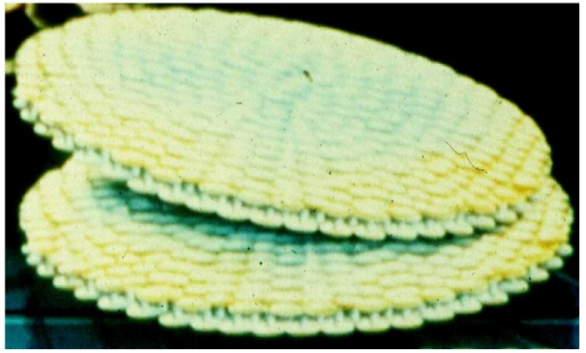
- liposomal amphotericin B
  (0.08 µm)





- amphotericin B lipid complex: phospholipid ribbons
  (1.6-11µm)

- amphotericin B colloidal dispersion: cholesteryl sulfate complex
  (0.12-0.14 µm)

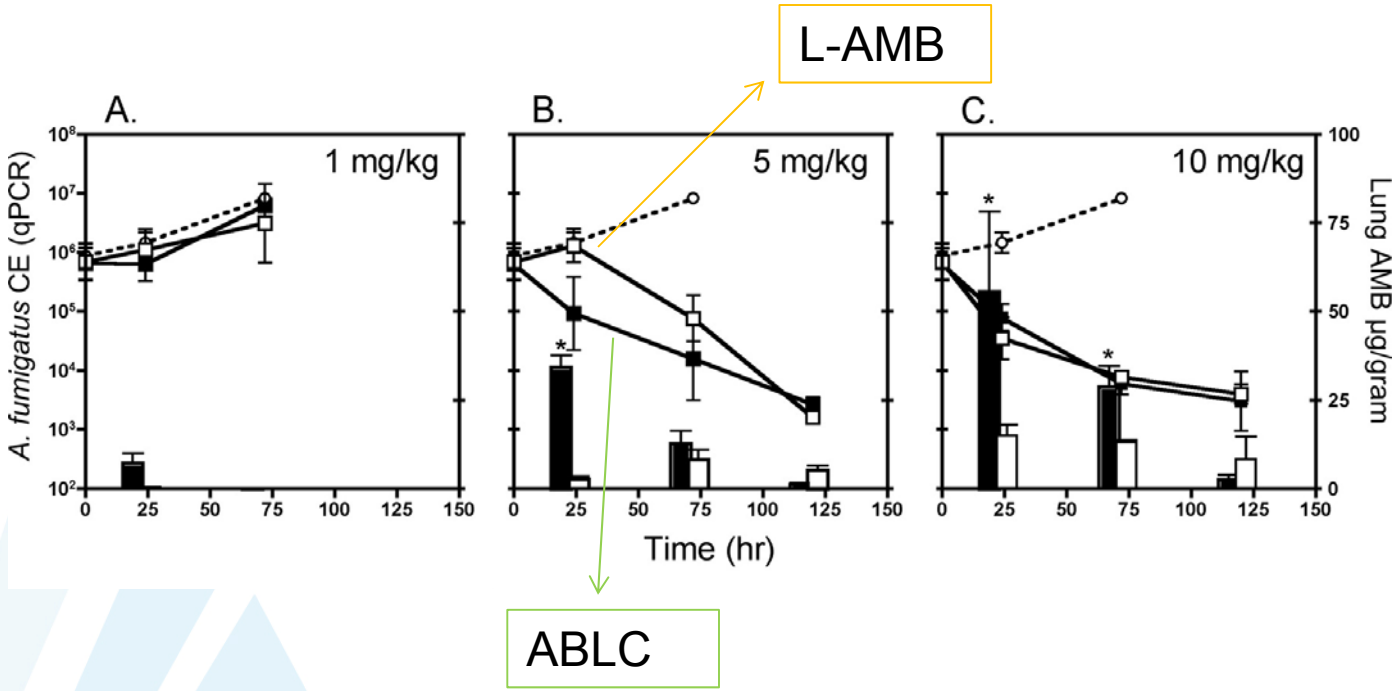


Principal advantage is reduced distribution of amphotericin B to the kidneys

Lipid-Formulated amphotericin B

	L-Amb	ABLC
C_{max}	83.0 mg/L	1.7 mg/L
Toxicity	20 mg/kg: minimal nephrotoxicity (rats)	10 mg/kg: mild nephrotoxicity (rats)
Mode of action	Liposome targeting to fungal cell wall with release of AMB into fungus	Release of AMB from complexes by phospholipases?
Drug localisation – therapeutic effect	Comparable efficacy to ABLC even with lower tissue concentrations	Higher concentrations in lung, liver and spleen Taken primarily up by tissues of RES

Differences in kinetics of AMB lung accumulation and fungal clearance between ABLC and L-AMB in a murine model of IPA



After 3 and 5 days of treatment: no difference in lung fungal burden and AMB lung concentration.

The clinical significance of pharmacokinetic differences is yet to be fully elucidated.

Lewis, R. E. et al. 2007. Antimicrob. Agents Chemother. 51(4):1253-1258

Site of infection

- Fluconazole, voriconazole and 5-FC have the best penetration in the CSV and vitreous chamber of the eye
- L-AMB and perhaps other triazoles and echinocandins may still achieve concentrations in the brain parenchyma sufficient to be clinically effective.
- Candiduria: no role for lipid AMB, newer triazoles and echinocandins

PHARMACODYNAMIC CONSIDERATIONS

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Triazoles

PK/PD relationship *in vivo* associated with effective therapy:

Candida and *Aspergillus*: $AUC_{(f)}/MIC > 25$

Lewis RE, Mayo Clin Proc, 2011, 86: 805-817.

Echinocandins

PK/PD relationship *in vivo* associated with effective therapy:

- $AUC_{(f)}$/MIC >20 for *C. albicans*
- $AUC_{(f)}$/MIC > 7 *for C. glabrata,*

  OK if MIC < 0.5 mg/L

- C_{max}/MEC >10 (*Aspergillus* spp.)

Lewis RE, Mayo Clin Proc, 2011, 86: 805-817.

Amphotericin B

PK/PD relationship *in vivo* associated with effective therapy:

AMB: C_{max}/MIC > 4-10
L-AMB: C_{max}/MIC >40

- OK if MIC < 2 mg/L
- But dosage of 10 mg/kg provided no benefit over the 3 mg/kg dosage in AmBiLoad trial.

Lewis RE, Mayo Clin Proc, 2011, 86: 805-817.

THERAPEUTIC DRUG MONITORING

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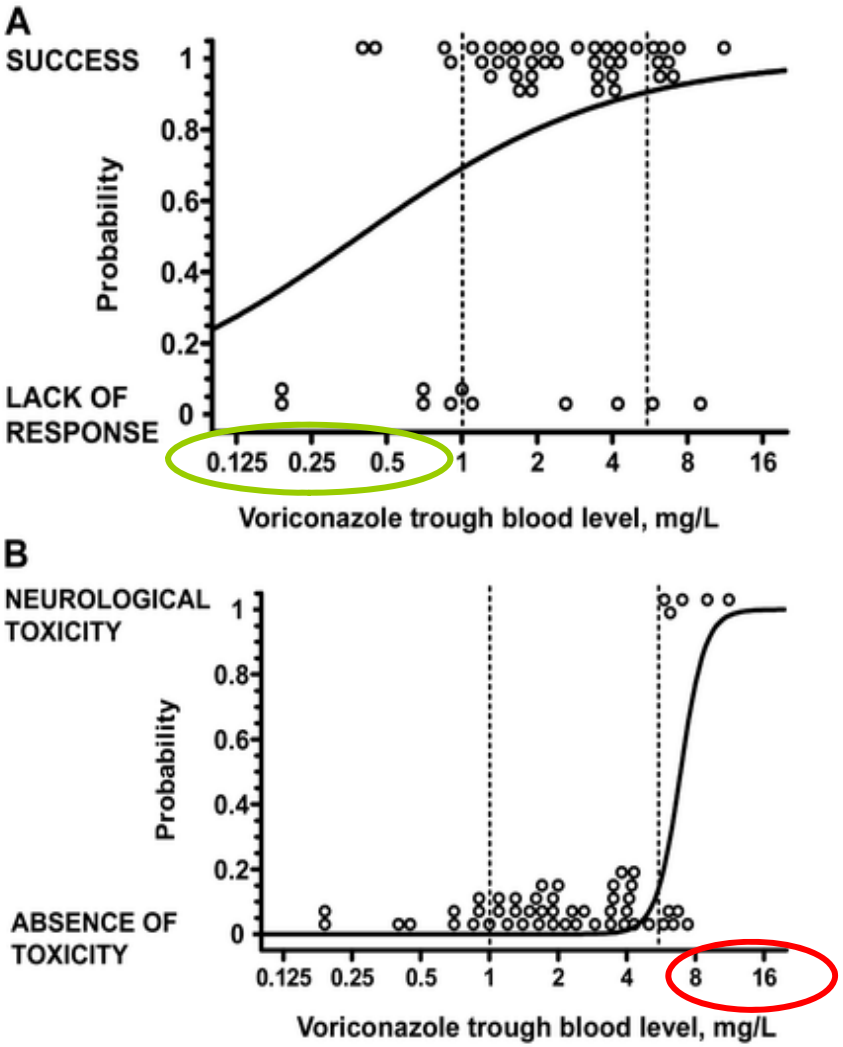
Voriconazole

- Specific recommendations not yet available but accumulating evidence that TDM may play an important role in optimizing the safety and efficacy
- Plasma through levels preferred, provisional therapeutic range:
  - 0.5-2 mg/L for efficacy
  - 6 mg/L for toxicity
- Frequent monitoring after dose adjustments is warranted

Voriconazole

25%: levels < 1 mg/L



52 adult patients:
181 samples

31%: levels ≥ 5.5 mg/L

31% CNS toxicity
19% hepatitis

Pascual A. CID 2008;46:201-211.

MINIREVIEW
Antifungal Therapeutic Drug Monitoring: Established and Emerging indications

Monitoring of voriconazole through concentrations may be considered:

- Early in therapy for all patients (4-7 days)
- Patients with poor clinical response
- Addition of interacting medication
- Change in route of administration
- Deteriorating hepatic function
- Suspected toxicity such a s severe hepatic dysfunction or neurological signs

D. Andes et al. AAC 2009, 53, 24-34.

Monitoring of posaconazole through concentrations may be considered:

- Early in therapy for all patients (4-7 days)
- Patients with poor clinical response
- Addition of interacting medication
- Patient at risk of impaired gastrointestinal absorption (e.g. severe mucositis, vomiting, diarrhea, ileus, GVHD, impaired dietary intake, therapy with proton pump inhibitors)
- Through level for treatment: 0.5-1.5 mg/L
- Through level for prophylaxis: 0.5 mg/L

D. Andes et al. AAC 2009, 53, 24-34.

TOXICITIES

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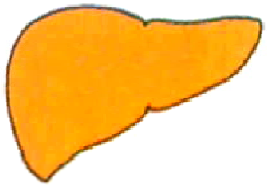
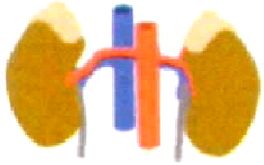
Hepatic



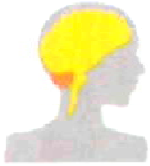
All azoles
Amphotericin B
5-FC
Echinocandins

Renal toxicity



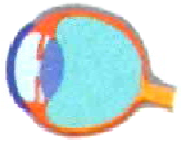
Amphotericin B
Cyclodextrins possibly toxic (IV voriconazole)

CNS



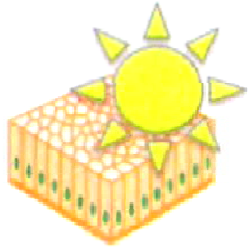
Voriconazole

Photopsia



Voriconazole

Cutaneous



Rash (all antifungal agents)
Photosensitivity/malignancy? (voriconazole)

GI

Itraconazole
Posaconazole
5-FC

Cardiac

Cardiomyopathy (itraconazole)

QTc prolongation (all azoles, especially with drug interactions)

Infusion reactions

Amphotericin B
Echinocandins

Bone marrow suppression

5-FC

Amphotericin B (anemia associated with decreased epoetin production)

‘NEW’ ANTIFUNGALS

Characteristics	Antifungal agents		
	Ravuconazole	**Albaconazole**	**Aminocandin**
Group	Triazole	Triazole	Echinocandin
Mechanism of action	Inhibition of ergosterol synthesis	Inhibition of ergosterol synthesis	Inhibition of 1,3-β-glucan synthesis
Available forms	Oral and iv	Oral	IV
Spectrum	Broad spectrum	Broad spectrum	*Candida, Aspergillus*
Advantages	Broad spectrum, water soluble, long acting, favorable drug tolerability, limited drug interactions	Broad spectrum, good pharmacokinetics, excellent oral bioavailability	Low toxicity, less drug interactions, long acting, potent anti-*Aspergillus* activity, more active than micafungin and caspofungin against *C. parapsilosis*
Disadvantages	Potential for cross resistance with other azoles	Potential for cross resistance with other azoles, low concentration in CSF	IV. Only, limited spectrum compared with new azoles, less active against *C. parapsilosis* and *C. guilliermondii* than the azoles

Türel et al, Expert Rev anti Infect Ther, 2011, 9: 325-338.