Antifongiques systémiques

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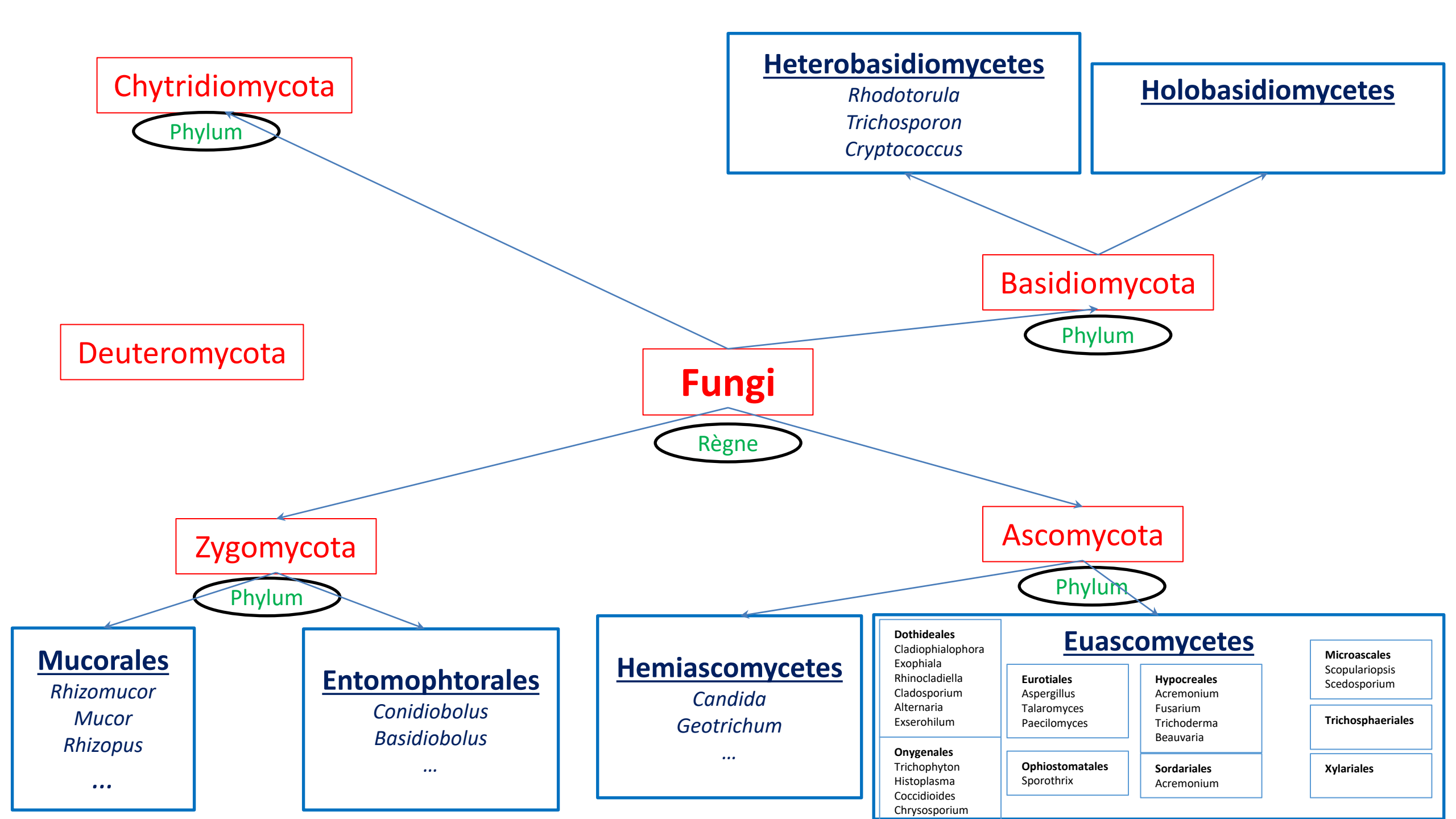
Maladies Infectieuses Bicêtre

12 Mars 2025

Hôpitaux universitaires Paris-Sud
Antoine-Béclère Bicêtre Paul-Brousse

Au menu

- Les champignons d’intérêt medical
- Les classes principales
- Polyènes
- Azolés
- Echinocandines
- Fluorocytosine
- Nouvelles molécules
- Conclusion


Chytridiomycota
Phylum
Heterobasidiomycetes
Rhodotorula
Trichosporon
Cryptococcus
Holobasidiomycetes
Basidiomycota
Phylum
Deuteromycota
Fungi
Règne
Zygomycota
Phylum
Ascomycota
Phylum
Mucorales
Rhizomucor
Mucor
Rhizopus
...
Entomophtorales
Conidiobolus
Basidiobolus
...
Hemiascomycetes
Candida
Geotrichum
...
Euascomycetes
Dothideales
Cladiophialophora
Exophiala
Rhinocladiella
Cladosporium
Alternaria
Exserohilum
Onygenales
Trichophyton
Histoplasma
Coccidioides
Chrysosporium
Eurotiales
Aspergillus
Talaromyces
Paecilomyces
Ophiostomatales
Sporothrix
Hypocreales
Acremonium
Fusarium
Trichoderma
Beauvaria
Sordariales
Acremonium
Microascales
Scopulariopsis
Scedosporium
Trichosphaeriales
Xylariales

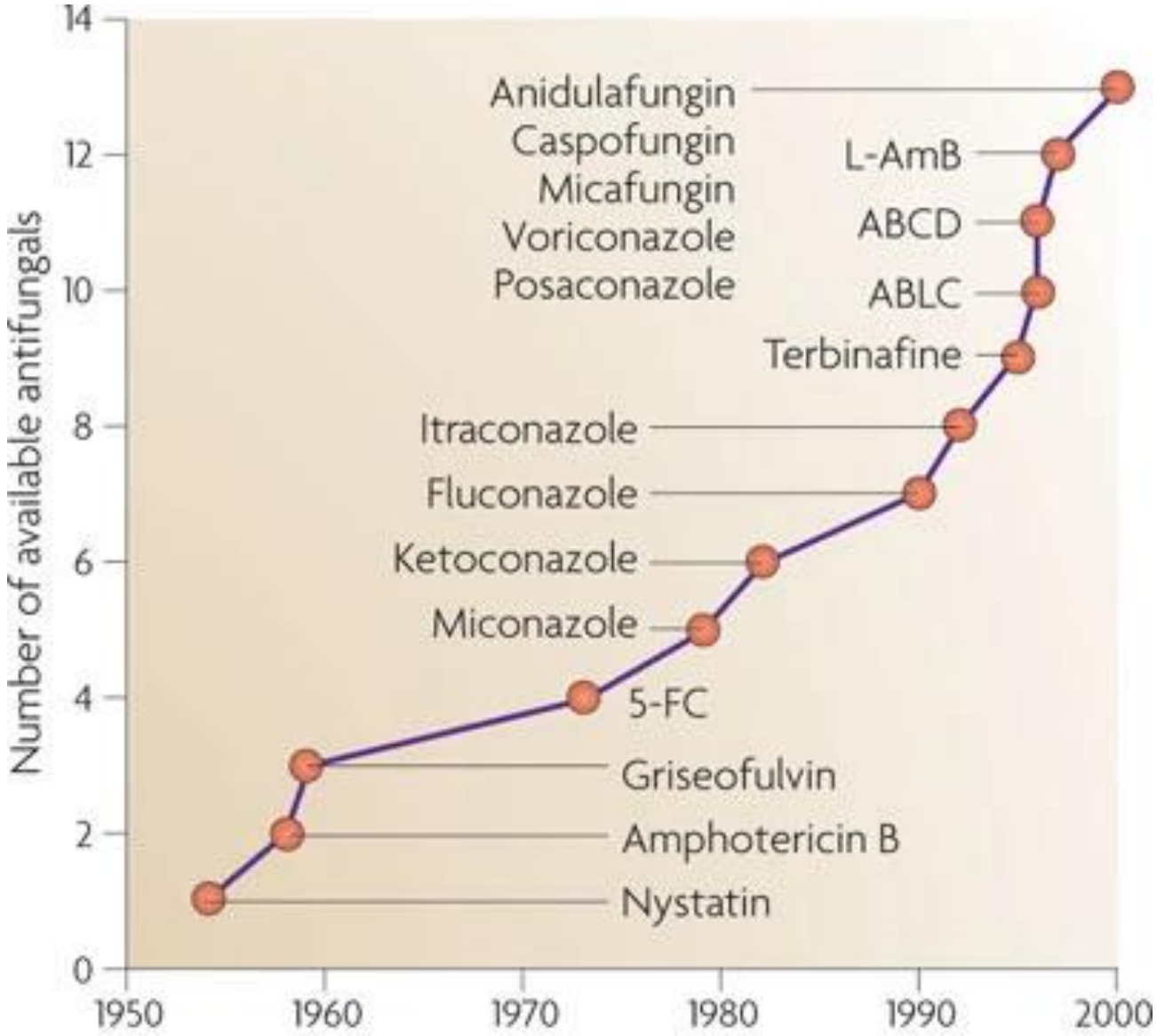
Champignons d'intérêt médical

Levures	**Filamenteux**	**Dimorphiques**	***Pneumocystis***
Candida *Cryptococcus*	*Aspergillus* Mucorales Dermatophytes *Scedosporium* *Fusarium*	*Histoplasma* *Coccidioides* *Blastomyces* *Sporothrix*	
Trichosporon *Geotrichum* *Malassezia* *Rhodotorula* ...	*Alternaria* *Scopulariopsis* Exophiala ...	*Paracoccidiodes* ...	

Les grandes classes d'antifongiques

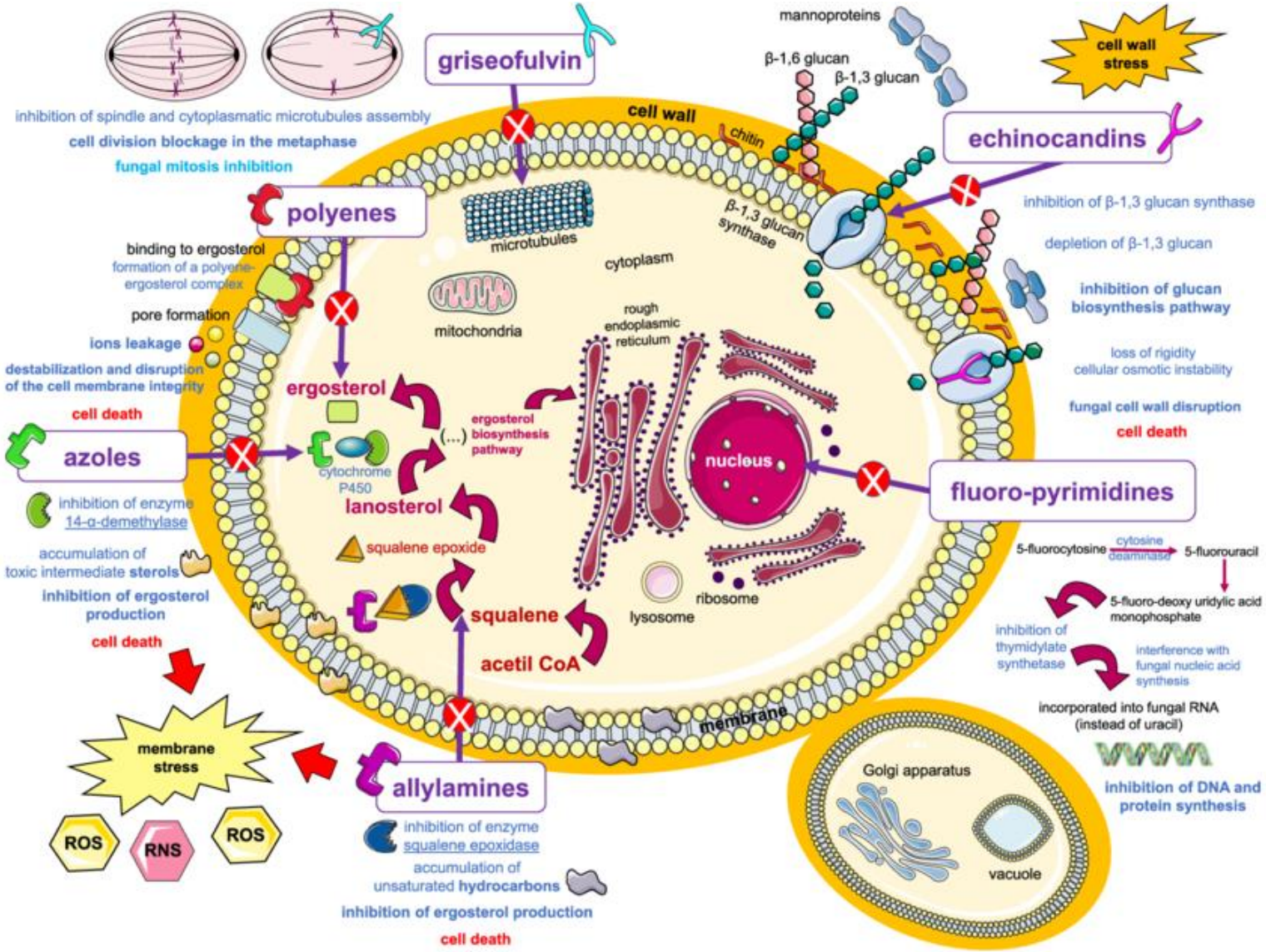
Polyènes	**Azolés**	**Echinocandines**	**Antimétabolites**	***Nouveaux***
Amphotéricine B Nystatine	Fluconazole Itraconazole Voriconazole Posaconazole Isavuconazole	Caspofungine Anidulafungine Micafungine Rezafungine	Flucytosine	Olorofim Ibrexafungerp Fosmanogepix Opelconazole

Historique: 1950-2000



Ostrosky-Zeichner L *et al.* Nat Rev Drug Discovery 2010

Mode d'action des antifongiques



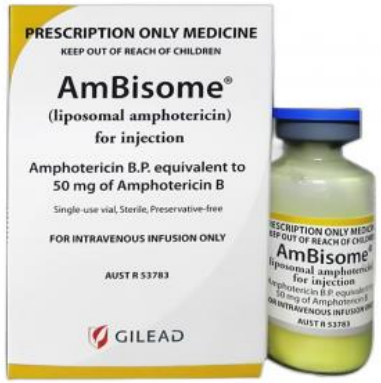
Sousa F *et al.* Adv Drug Delivery Rev 2023

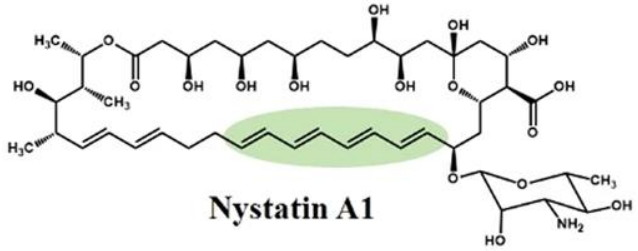
PK/PD des antifongiques

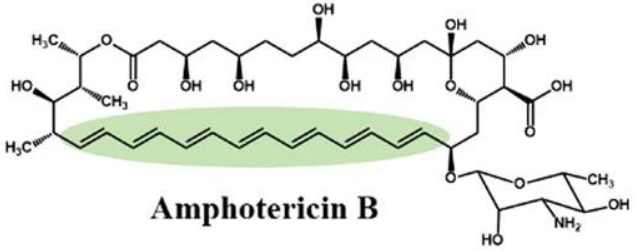
Antifungal agent	Antifungal effect	PK/PD parameter	Long PAE	Reference
Triazoles	Fungistatic	Time-dependent	–	[63]
Amphotericin B	Rapidly fungicidal	Concentration-dependent	Yes	[64]
Echinocandins				
Candida	Fungicidal	Concentration-dependent	Yes	[38, 41, 42, 47, 60]
Aspergillus	Fungistatic	Time-dependent; concentration-dependent histological and microscopic effects[a]	–	[46, 48]

Theuretzbacher U Eur J Clin Microbiol Infect Dis 2004

Polyenes

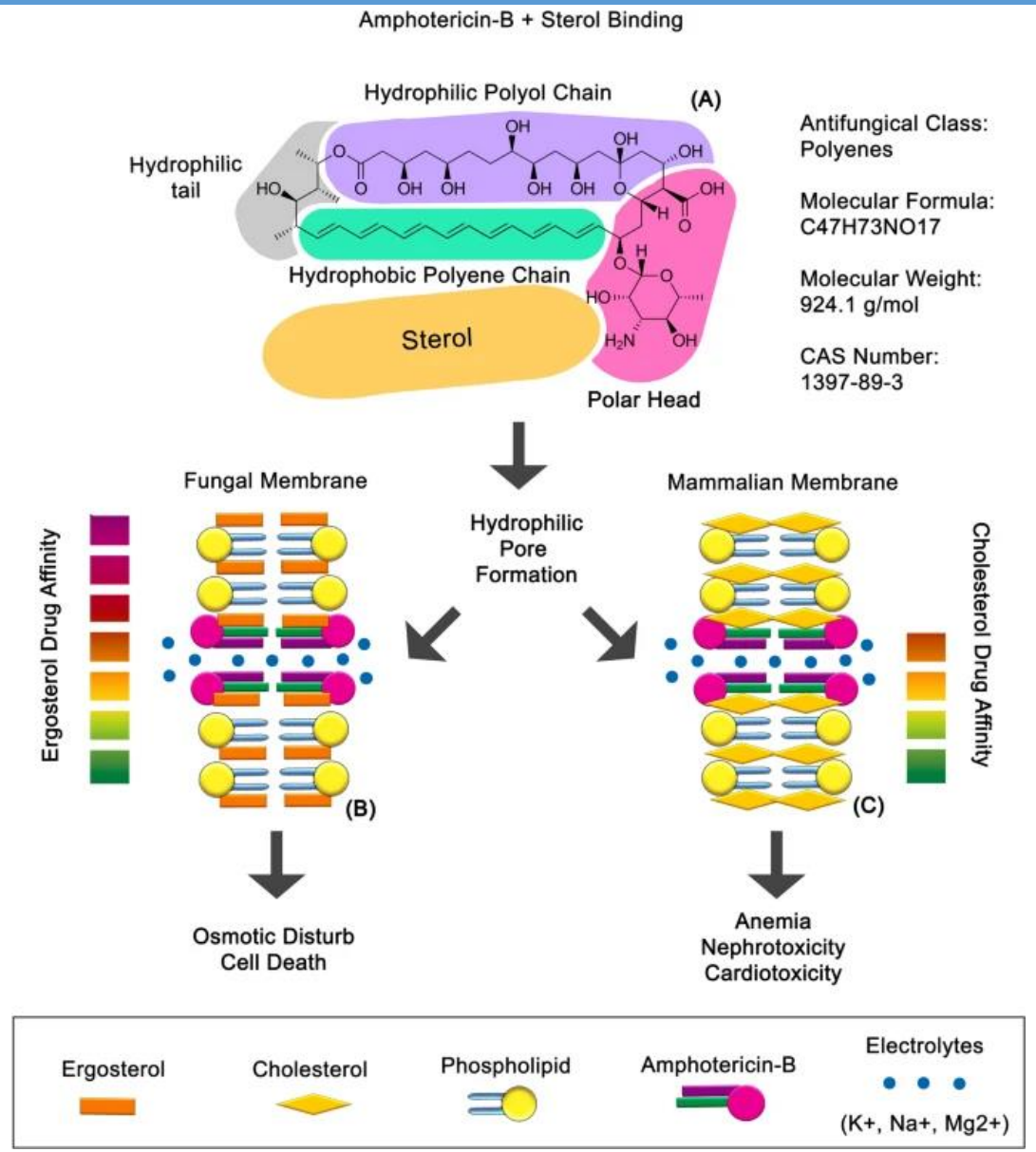






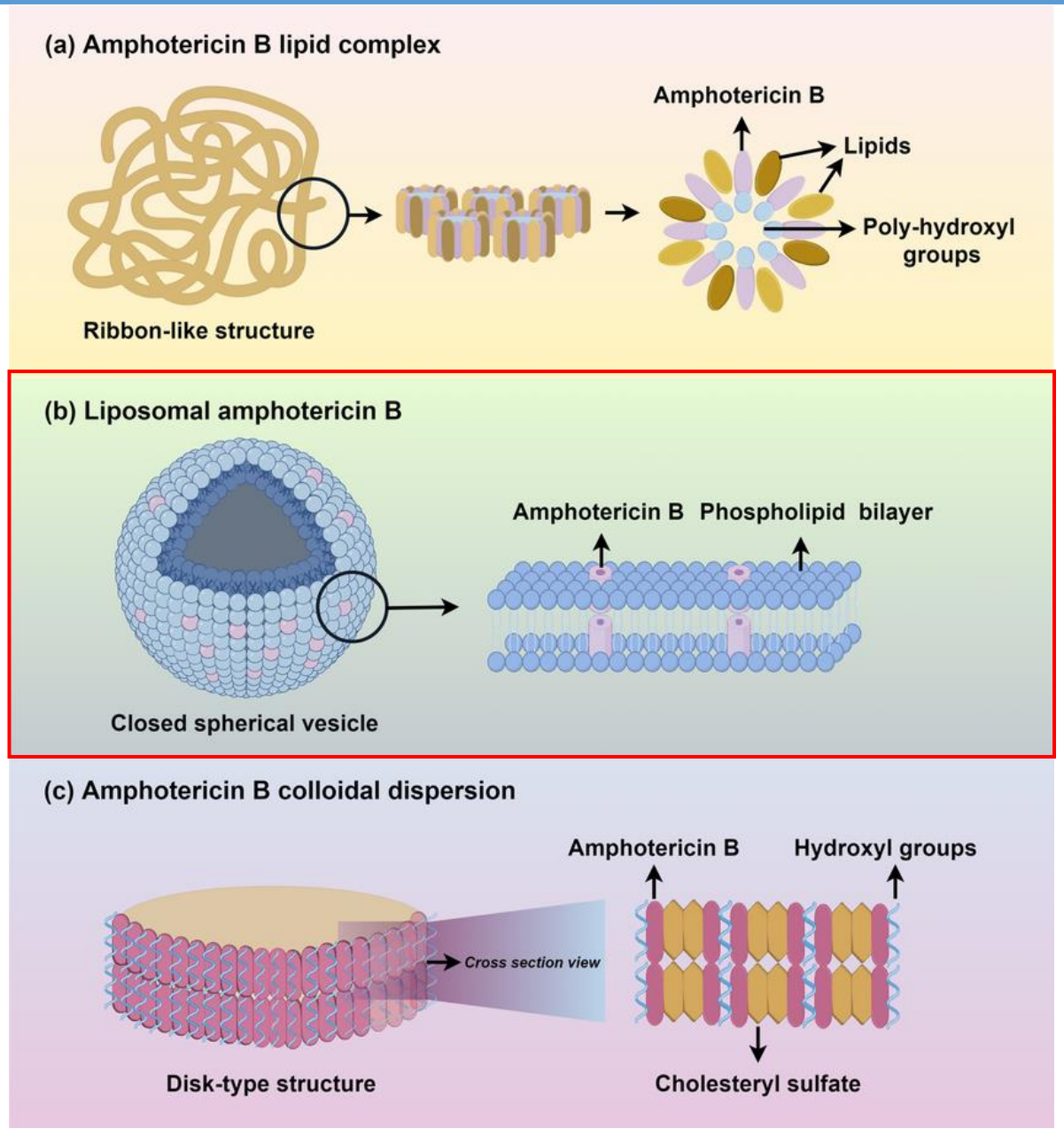
Faustino C *et al.* Pharmaceutics 2020; Kim HJ *et al.* Sci Rep 2018

Amphotéricine B: mode d'action



Cavassin F *et al.* Infectious Diseases and Therapy 2021

Amphotéricine B: formulations lipidiques



Liu M *et al.* J Neurol 2024

Amphotericine B: spectre

Levures	**Filamenteux**	**Dimorphiques**	***Pneumocystis***
Candida *Cryptococcus*	*Aspergillus* Mucorales Dermatophytes *Scedosporium* *Fusarium*	*Histoplasma* *Coccidioides* *Blastomyces* *Sporothrix*	
Trichosporon *Geotrichum* *Malassezia* *Rhodotorula* …	*Alternaria* *Scopulariopsis* Exophiala …	*Paracoccidiodes* …	

Candida lusitaniae
Aspergillus terreus

Amphotéricine B: des pharmacocinétiques différentes

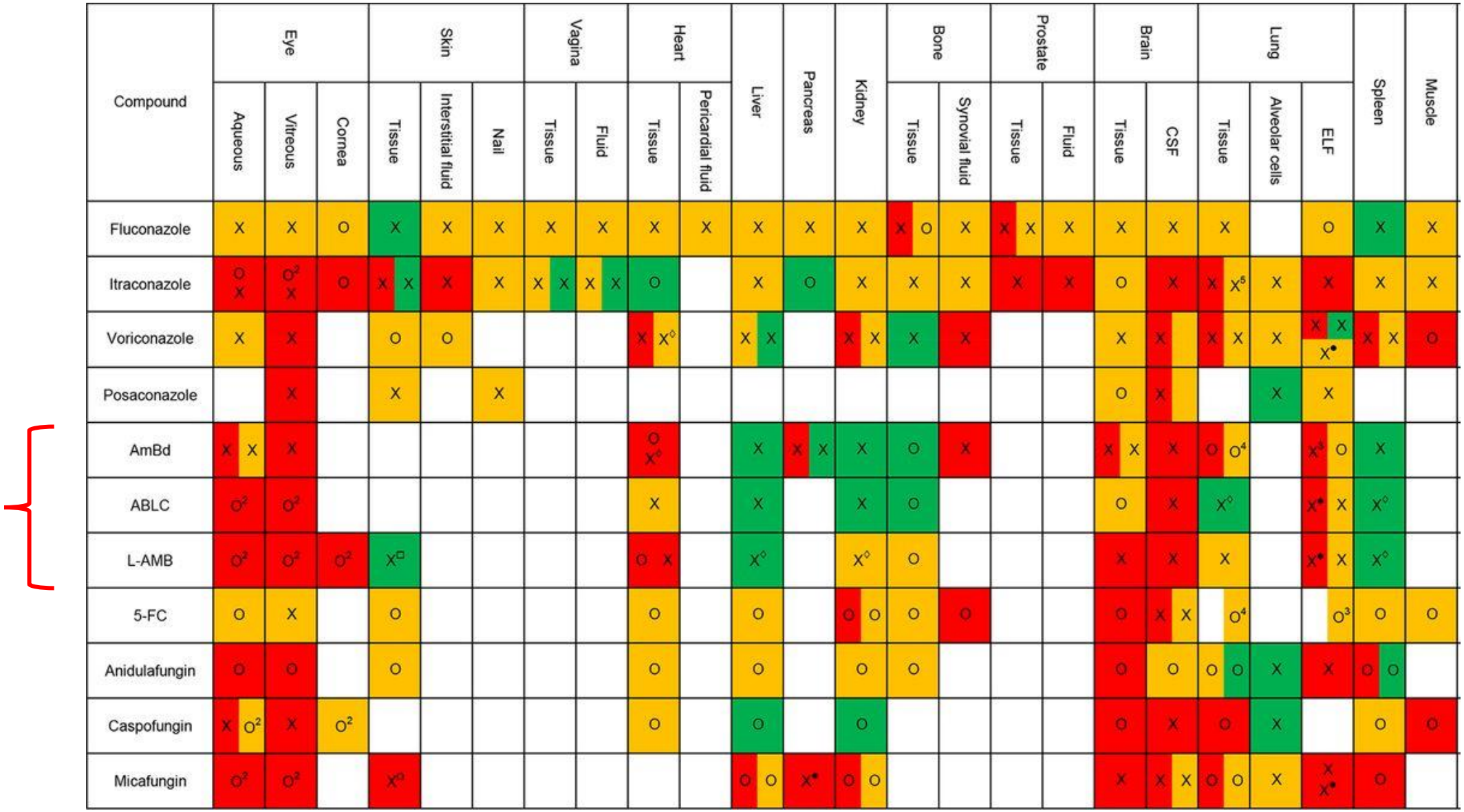
	AmB deoxycholate	AmB liposomale
Biodisponibilité	< 5%	Sans objet
Liaison protéique	95%	95%
Volume de distribution (l/kg)	4	0.1 à 0.16
Demi-vie (h)	24	7-10
Elimination	Urinaire	43% fèces, 33% urine
ECMO	?	Diminution des taux sériques

Ostrosky-Zeichner L *et al.* Nat Rev Drug Discovery 2010

Amphotéricine B: prescrire en pratique

	AmB deoxycholate	AmB liposomale
Voie d'administration	Orale/IV/intrathécale/ intravitréenne/aérosols	IV
Rythme d'administration	1/jour	1/jour
Dose (mg/kg/j)	0.5 à 1.5	3 à 5
Durée de perfusion	1 à 6 h	> 1 h
Diluant	G5%	G5%
Adaptation si insuffisance rénale	Non (éviter)	Non
Adaptation si dysfonction hépatique	Non	Non
Adaptation si obésité	?	Poids ajusté/réel selon gravité
Grossesse	Oui si besoin Surveiller la fonction rénale de l'enfant	
Allaitement	Oui si besoin	

Amphotéricine B: diffusion tissulaire



Felton T *et al.* CMR 2014

Amphotéricine B: toxicités

Réaction à l'injection: fièvre, céphalées, frissons, NV
prévenue par prémédication

Veinite: prévenue par VVC, perfusion lente, dilution suffisante (HC?Héparine?)

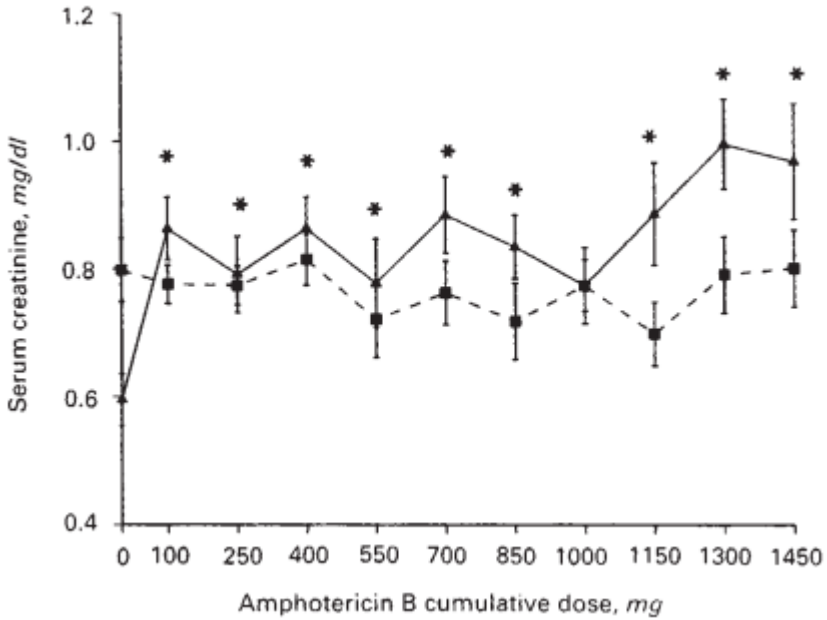
Néphrotoxicité: élévation créatinine < insuffisance rénale; désordres électrolytiques
FDR: IR préexistante, coprescriptions néphrotoxiques, hypovolémie
prévenue par maintien volémie

Rare: cytopénies, hépatite

Yamazaki H *et al.* DMID 2018

Amphotéricine B: néphrotoxicité

Fréquent avec AmB déoxycholate: 28% Harbarth S *et al.* Am J Med 2001
Prédicteurs: ICU, cyclosporine, dose max > 60 mg/j



Elévation de créatinine:
Vers J4-5; réversible à l'arrêt

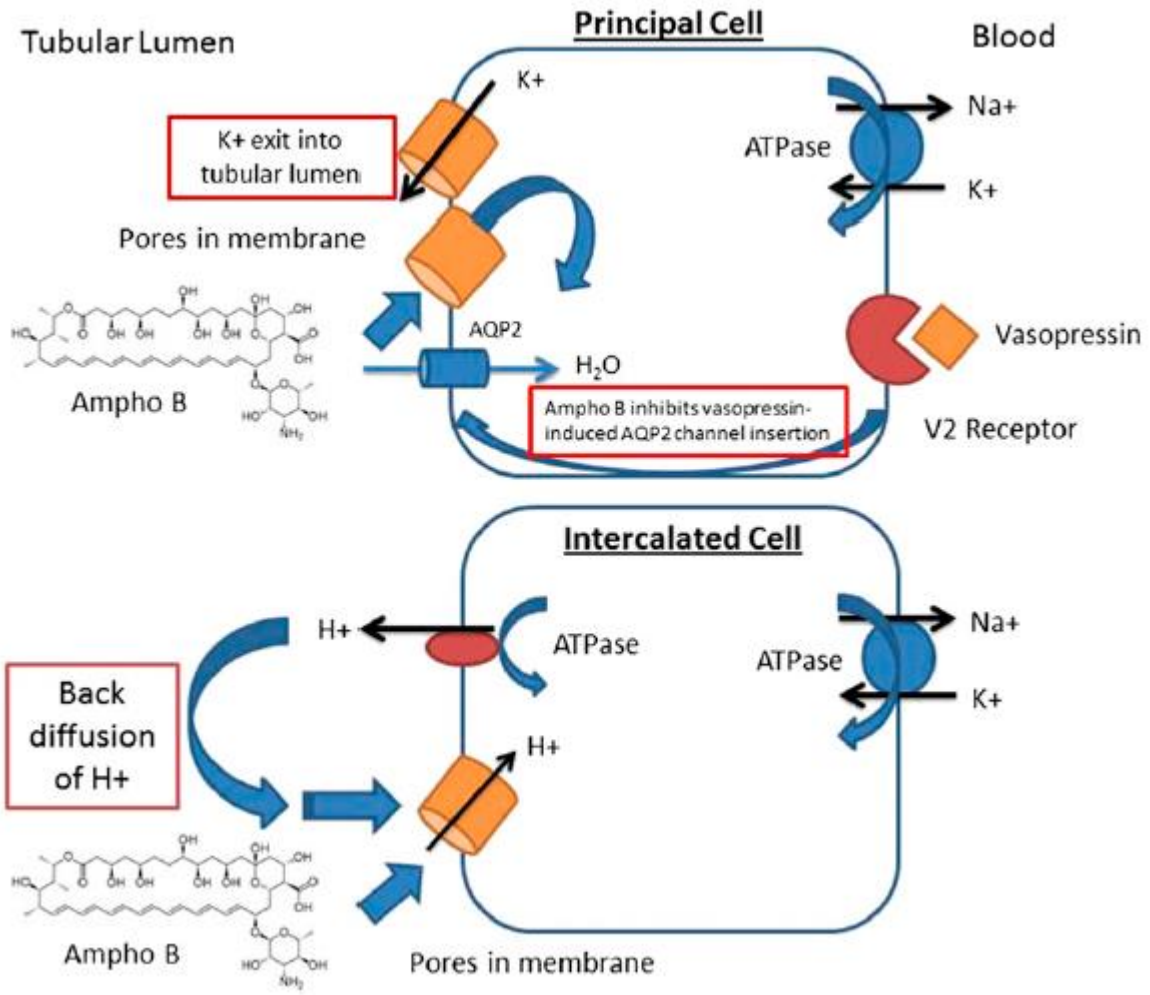
Troubles hydroélectrolytiques: hypoK, hypoMg, acidose tubulaire, Polyurie
par augmentation de la perméabilité des cellules tubulaires

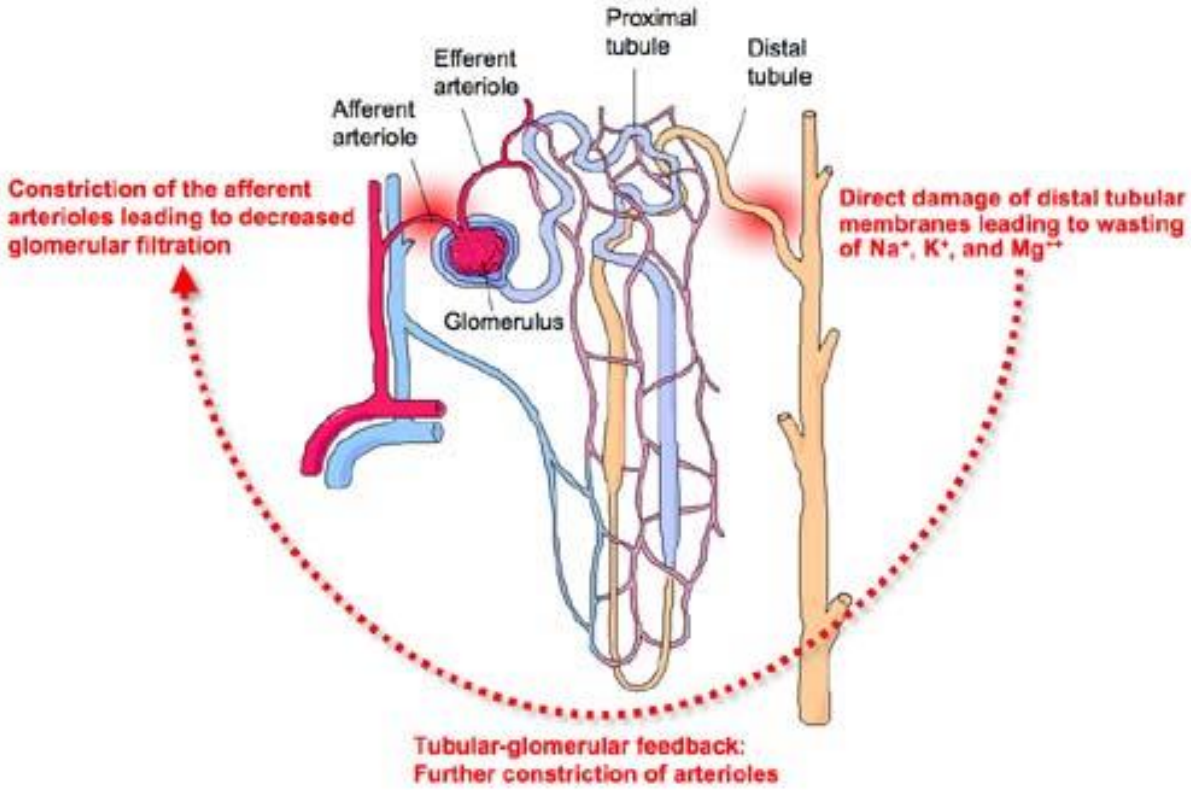
Vers J7-8

Prévention: « salt loading » Llanos A *et al.* Kidney Int 1991 pas d'effet sur tubulopathie
et formulations lipidiques: pas de déoxycholate, transfert direct to fungi via SRE

Traitement: arrêt AmB et supplémentation ionique

Néphrotoxicité de l'ampho B: mécanismes





Rosner M *et al.* CJASN 2017; doctorfungus.org

Formulations lipidiques de l'AmB: moins néphrotoxiques

Amphotericin B Liposomal X Amphotericin B in dextrose 5%

Studies	Jadad scale	N	Amphotericin B Liposomal Events/n	%	Amphotericin B in dextrose 5% Events/n	%	RR [IC 99%]	p	ARR (%)	Forest Plot
• Johnson PC. et al. Safety and efficacy of liposomal amphotericin B compared with conventional amphotericin B for induction therapy of histoplasmosis in patients with AIDS. Ann Inter Med. **2002**; 137(2):105-9.	**4**	77	5/53	9,4	9/24	37,5	0.25 [0.07, 0.91]	0,0042	28,1	
• Leenders ACAP. et al. Liposomal amphotericin B compared with amphotericin B deoxycholate in the treatment of documented and suspected neutropenia-associated invasive fungal infections. Br J Haematol **1998**; 103(1):205-12.	**2**	28	0/15	0	3/13	23,1	0.13 [0.00, 5.47]	0,003	23,1	
• Leenders ACAP. et al. Liposomal amphotericin B (AmBisome) compared with amphotericin and both followed by oral fluconazole in the treatment of AIDS-associated cryptococcal meningitis. AIDS **1997**; 11[6]:1463-71.	**3**	106	6/52	11,5	22/54	40,7	0.28 [0.10, 0.83]	0,0007	29,2	
• Prentice HG. et al. A randomized comparison of liposomal versus conventional amphotericin B for the treatment of pyrexia of unknown origin in neutropenic patients. Br J Haematol. **1997**; 98(3):711-8.	**2**	335	26/235	11,1	24/100	24,0	0.46 [0.24, 0.89]	0,002	12,9	
• Walsh T. et al. A randomized, double-blind trial of AmBisome (liposomal amphotericin B) versus Amphotericin B in the empirical treatment of persistently febrile neutropenic patients. Ann Hematol **1999**; 78 Suppl 1:S3	**5**	687	64/343	18,7	116/344	33,7	0.55 [0.39, 0.78]	<0.0001	15,1	
TOTAL		**1233**	**101/698**	**14,5**	**174/535**	**32,5**	**0.48 [0.36, 0.64]**	**<0.0001**	**18,1**	

Mistro S *et al.* CID 2012

AmB liposomale est moins néphrotoxique qu'ABLC

Variable	L Amph 3 mg/kg/d (n = 85)	L Amph 5 mg/kg/d (n = 81)	ABLC 5 mg/kg/d (n = 78)
Nephrotoxicity			
1.5 × Baseline creatinine value	25 (29.4)[a]	21 (25.9)[a]	49 (62.8)
2 × Baseline creatinine value	12 (14.1)[a]	12 (14.8)[a]	33 (42.3)
3 × Baseline creatinine value	5 (5.9)[b]	5 (6.2)[b]	21 (26.9)
Change, baseline-to-peak serum creatinine value (mg/dL)			
Mean ± SD	0.5 ± 0.8[c]	0.4 ± 0.4[c]	1.0 ± 1.0
Median (range)	0.3 (0–4.7)	0.2 (−0.1 to 2.1)	0.7 (0–5.3)
Peak creatinine value (mg/dL)			
Mean ± SD	1.3 ± 1.0[c]	1.2 ± 0.6[c]	1.8 ± 1.2
Median (range)	1.1 (0.3–6.3)	0.9 (0.3–3.3)	1.5 (0.5–6.0)
>1.5	22 (25.9)[d]	19 (23.5)[b]	38 (48.7)
>2.0	14 (16.5)	5 (6.2)[d]	19 (24.4)
>2.5	6 (7.1)	3 (3.7)[d]	14 (17.9)
>3.0	6 (7.1)	1 (1.2)[d]	10 (12.8)

NOTE. Data are no. (%) of patients unless otherwise indicated.

[a] $P \leq .001$, L Amph versus ABLC group; χ^2 test.

[b] $P \leq .001$, L Amph versus ABLC group; Fisher's exact test.

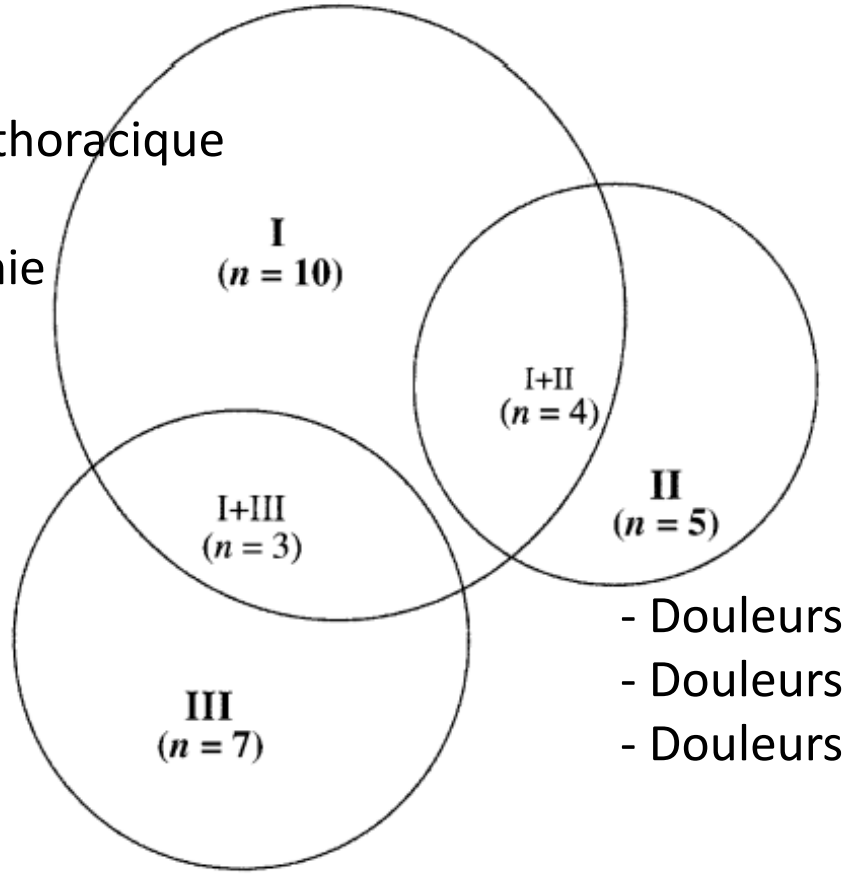
[c] $P \leq .001$, L Amph versus ABLC group; analysis of variance.

[d] $P \leq .01$, L Amph versus ABLC group; Fisher's exact test.

Wingard J *et al.* CID 2000

Formulations lipidiques de l'AmB: réactions à l'injection

- Douleur thoracique
- Dyspnée
- Hypoxémie



- Flushes
- Urticaire

- Douleurs lombaires
- Douleurs abdo
- Douleurs des MI

Management	
Diphenhydramine administration	27 (93)
Infusion interruption and resumption after diphenhydramine administration	27 (93)
Oxygen administration	6 (21)
Infusion permanently discontinued	4 (14)
Successful continuation of liposomal amphotericin B therapy upon rechallenge (*n* = 25)	25 (100)

Pas de facteur de risque clairement identifié

Réactions croisées non systématiques

Farmakiotis D *et al.* CID 2013

Roden M *et al.* CID 2003

Nystatine

Exclusivement orale

Biodispo 0%

Indications: candidoses orales et génitales

Amphotéricine B

Spectre très large

Parentérale

Toxicité: réactions à l'injection, néphrologique

Formulations lipidiques prédominent

Indications principales: cryptococcose, mucormycose, histoplasmose

Azolés

Triazolés

Fluconazole

Itraconazole

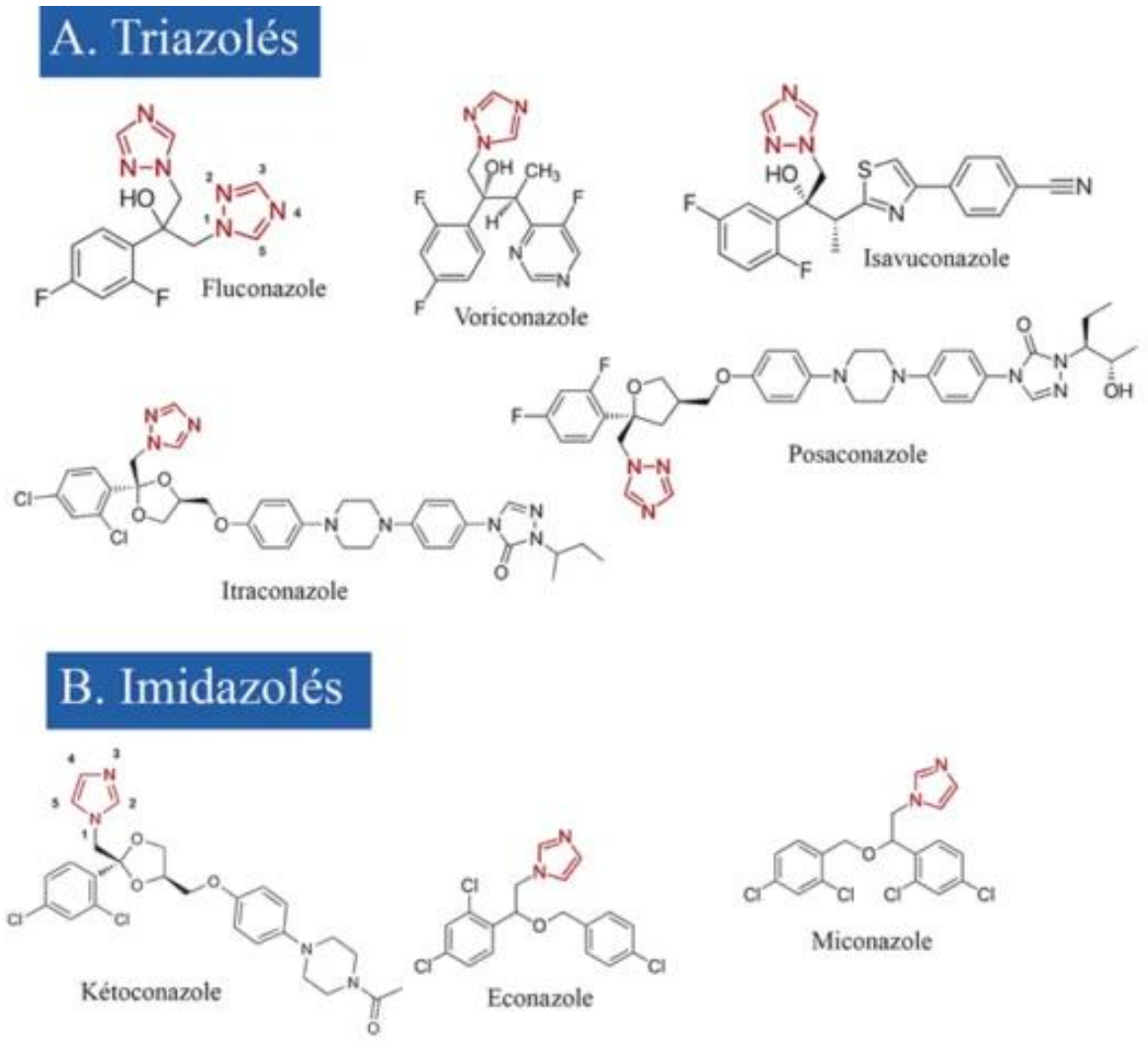
Voriconazole

Posaconazole

Isavuconazole

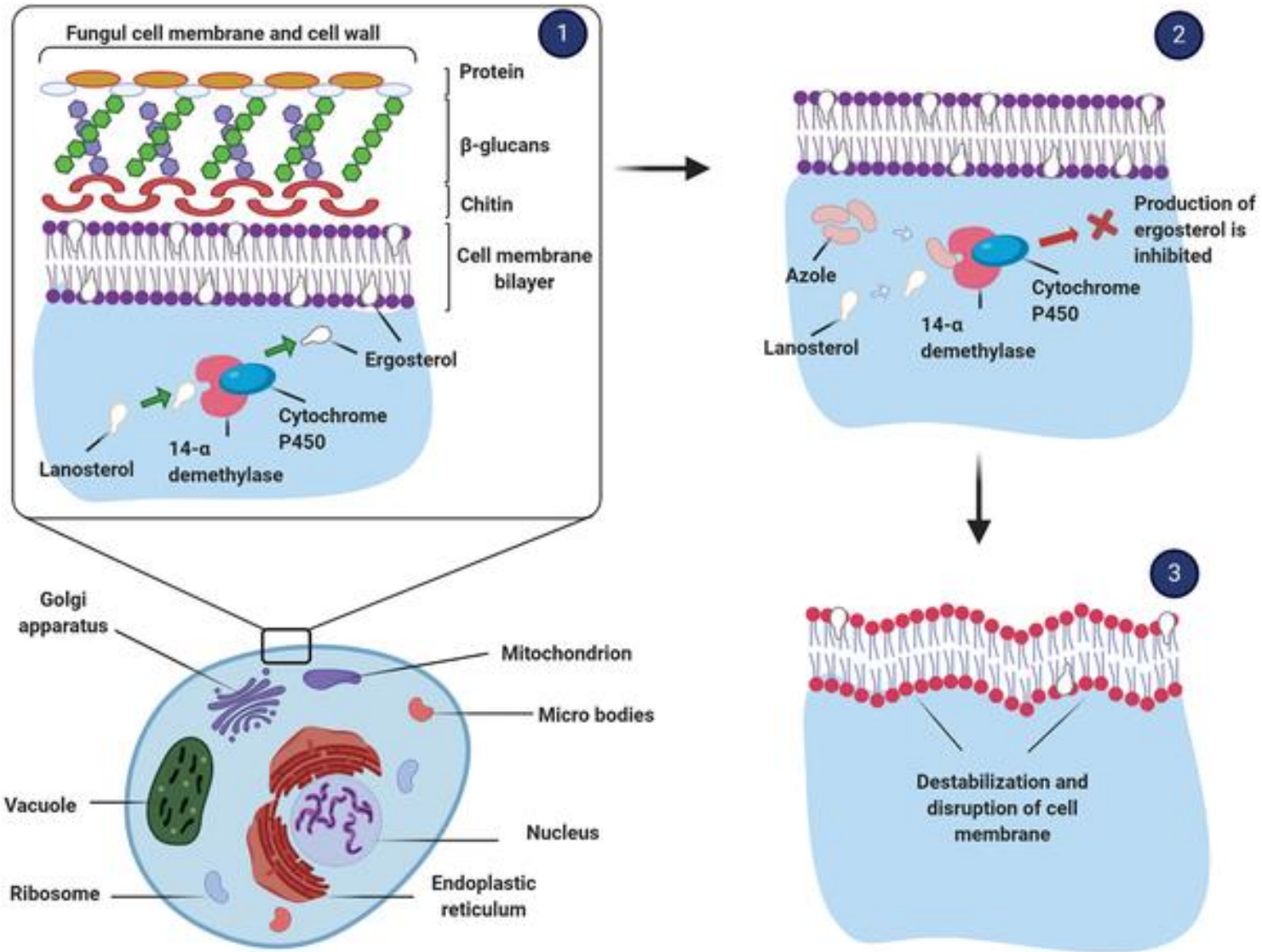
Imidazolés

Kétoconazole



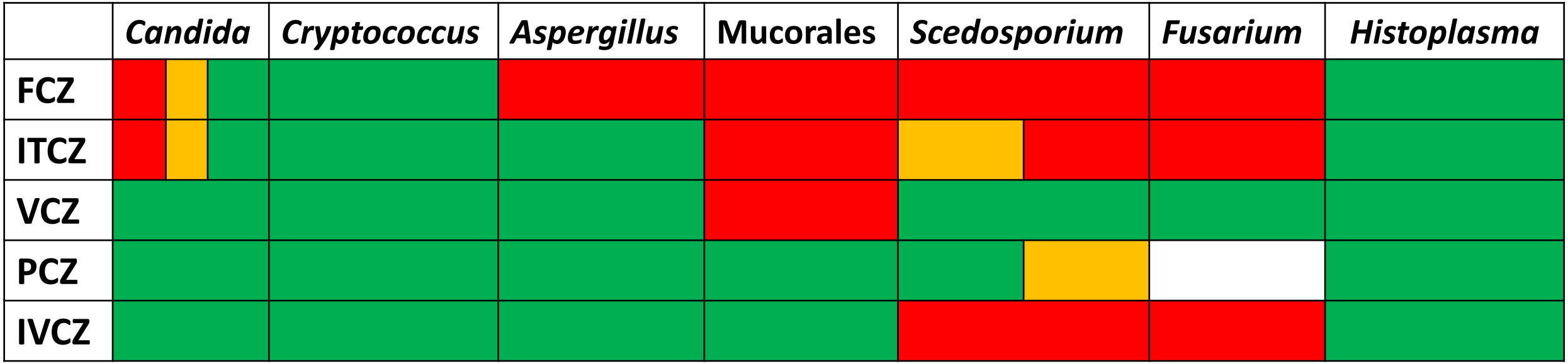
SFPT & CNPM: Pharmacologie des anti-infectieux, 2018

Azolés: mode d'action



Makvandi P *et al.* Adv Sci 2021

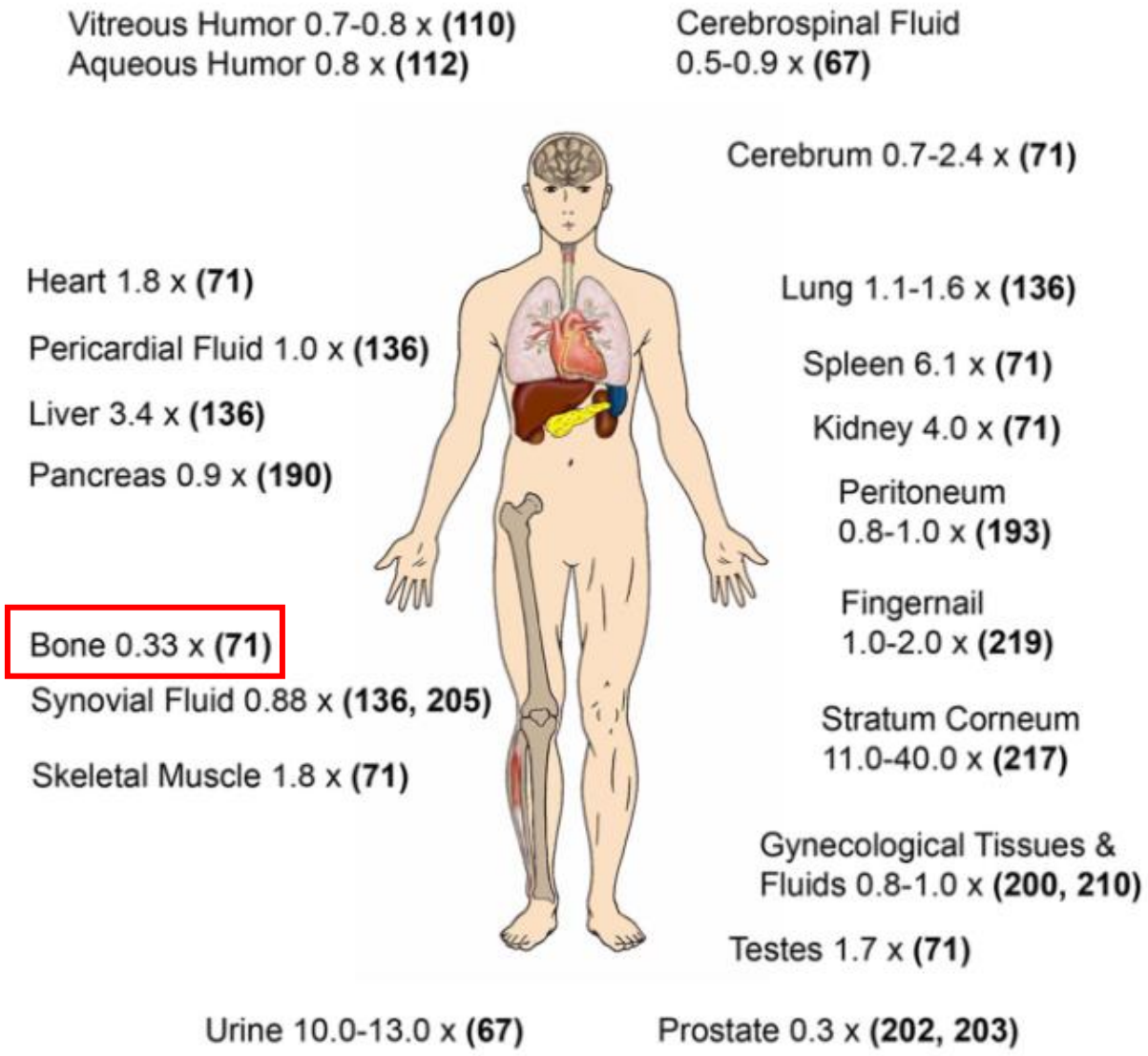
Azolés: spectre in vitro



Azolés: pharmacocinétique

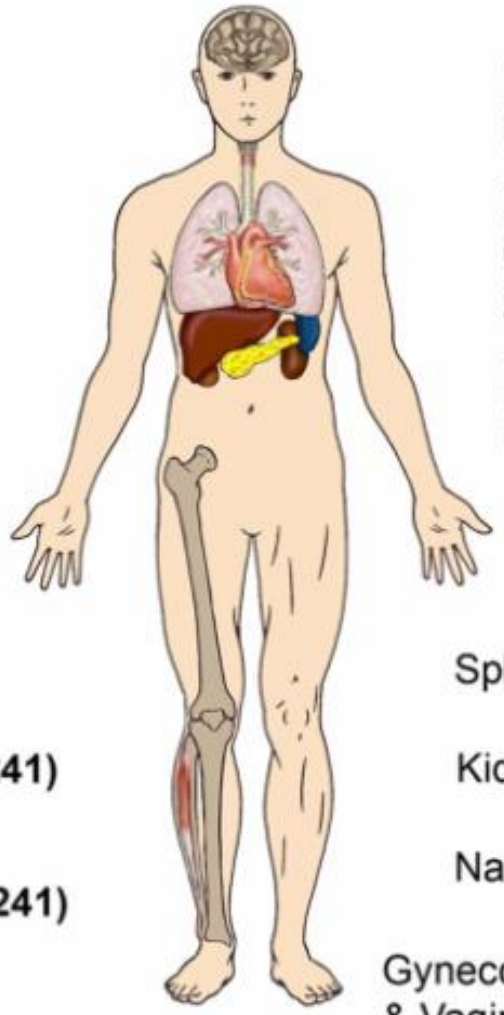
	FCZ	ITCZ	VCZ	PCZ	IVCZ
Biodisponibilité Orale	> 90%	55% (capsule) 75% (sol orale)	> 90%	54% (cp)	98%
Liaison protéique	10-12%	99%	58%	> 98%	> 99%
Volume de distribution (l/kg)	0.7	11	4.6	7-25	450 litres
Demi-vie (h)	24-30h	25-50h	Variable (6)	26-31h (cp) 27h (IV)	130h
Métabolisme	Hépatique 11%	Hépatique	Hépatique	Hépatique	Hépatique
Elimination	Urinaire 90%	Urinaire 20% Fécale (inactifs)	Urinaire 80% (inactif)	Fécale 77%	Urinaire 46%

Diffusion tissulaire du fluconazole



Felton T *et al.* Clin Microbiol Rev 2014

Diffusion tissulaire de l'itraconazole



Cerebrospinal Fluid
<0.002-12.0 x **(73, 74)**

Lung Tissue
0.9-7.0 x **(73, 139)**

Epithelial Lining Fluid
0.33 x & Alveolar Cells
2.0-4.0 x **(56)**

Bronchial Tissue
0.001 x **(140)**

Esophagus 3.0 x **(160)**

Liver 3.5 x **(73)**

Bone 4.7 x **(73)**

Muscle 1.5-2.4 x **(73, 241)**

Skin 0.5-8 x **(73, 239, 241)**

Spleen 1.0-3.1 x **(73, 241)**

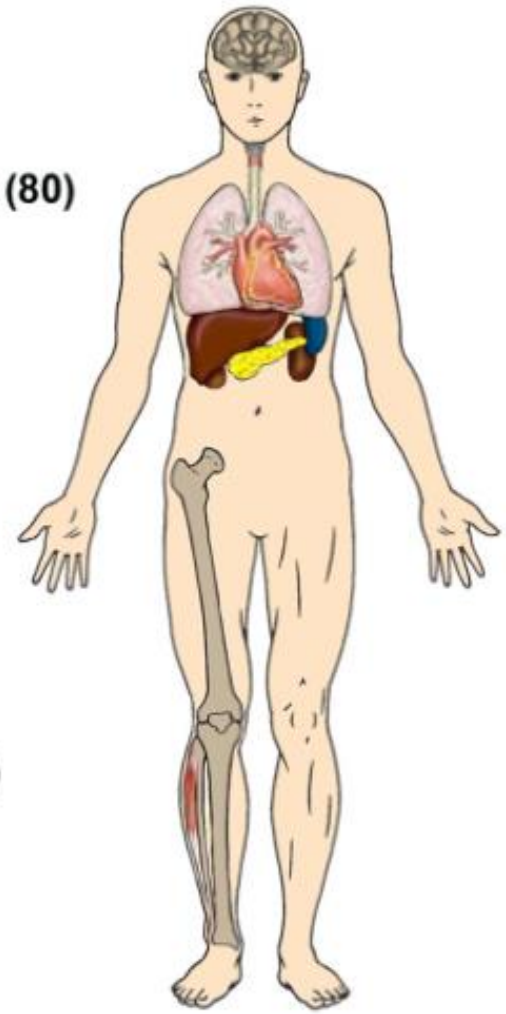
Kidney 1.5 x **(73)**

Nails 0.6 x **(122)**

Gynecological Tissues 1.6-20 x
& Vaginal Fluids 0.1-0.5 x **(73)**

Felton T *et al.* Clin Microbiol Rev 2014

Diffusion tissulaire du voriconazole



Brain Abscess 1.0-2.3 x **(243)**

Cerebrospinal Fluid
0.2-1.0 x **(83)**

*Lung Tissue
0.3-3.2 x **(80)**

*Myocardium 0.4-4.6 x **(80)**

Epithelial Lining Fluid
2-1.1 x **(58, 142)**

*Liver 1.1-7.4 x **(80)**

Pleura
0.7-1.0 x **(153, 154)**

Bone 5 x **(208)**

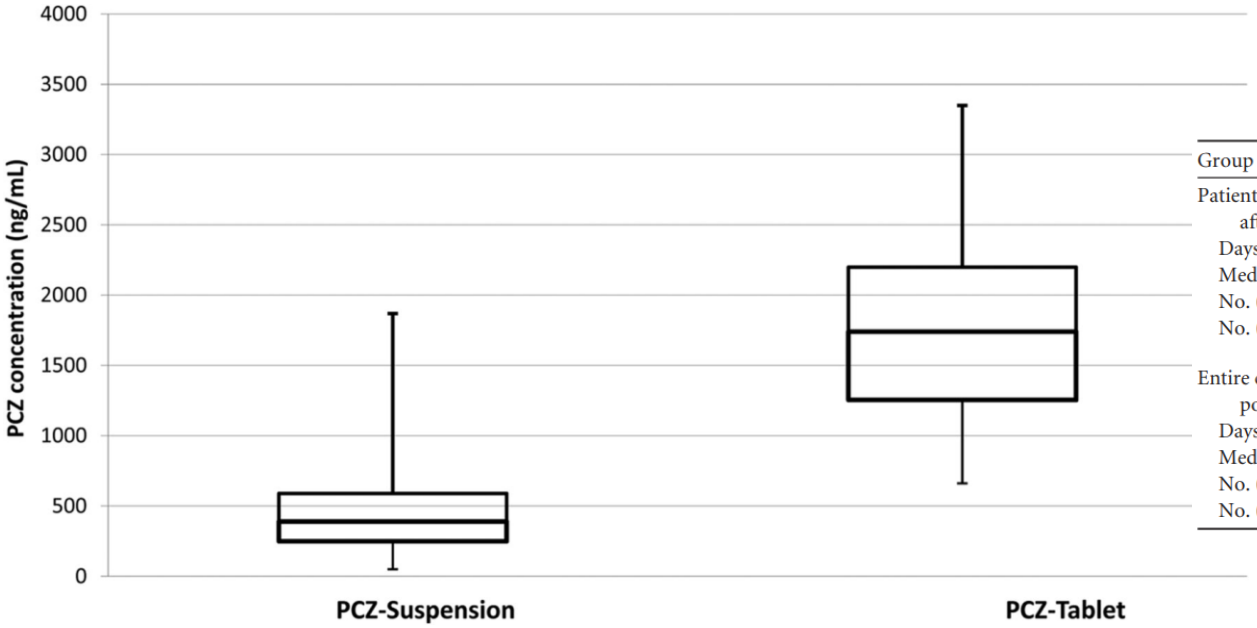
*Spleen 0.4-3.5 x **(80)**

Synovium 0.25 x **(208)**

*Kidney 0.6-2.7 x **(80)**

Felton T *et al.* Clin Microbiol Rev 2014

Posaconazole: préférer les comprimés



Group and parameter	DR tablet	Suspension	P^b
Patients with initial levels determined 5 to 14 days after posaconazole administration	$n = 20$	$n = 43$	
Days from initiation to first level (IQR)	10 (6–13)	8 (6–12)	0.424
Median level (IQR)	1,655 (1,080–2250)	798 (572–1,500)	0.004
No. (%) >700 ng/ml	18 (90)	25 (58)	0.011
No. (%) >1,250 ng/ml	15 (75)	14 (32.6)	0.002
Entire cohort regardless of when initial posaconazole levels were drawn	$n = 32$	$n = 61$	
Days from initiation to first level (IQR)	11.5 (7–19)	8 (7–15)	0.303
Median level (IQR)	1,620 (957–2,258)	967 (590–1,420)	<0.001
No. (%) >700 ng/ml	29 (90.6)	37 (60.7)	0.003
No. (%) >1,250 ng/ml	20 (62.5)	19 (31.1)	0.004

Cumpston A *et al.* AAC 2015; Durani U *et al.* AAC 2015

Azolés: prescrire en pratique

	FCZ	ITCZ	VCZ	PCZ	IVCZ
Voie	Orale IV	Capsule: avec alim & pH acide Sol orale: à jeun	Orale (à jeun) IV	Orale IV	Orale IV
Rythme d'administration	1 à 2/j	1 à 2/j	2/j	1/j	1/j
Dose (mg/j)	50 à 800	200 à ...	200 à 800	300	200/8h, 2 j 200/jour
Diluant	NaCl/G5%	NaCl	NaCl/G5%	NaCl/G5%	NaCl/G5%
Adaptation si insuffisance rénale	Oui	CI si DFG < 30	Non (sauf IV)	Non	Non
Adaptation si dysfonction hépatique	Non	Oui	Oui	Non	Oui?
Adaptation si obésité	Poids réel	?	Poids ajusté	Non	Non
Grossesse	Eviter*	Non	Non (sauf...)	Non (sauf...)	Non
Allaitement	Si besoin	Eviter	Eviter	Eviter	Non

Azolés: toxicité hépatique

2 à 12% (arrêt <1 à 8%)

Profil: cytolytique, cholestatique, mixte

Délai: variable (1 mois)

Formes **graves** décrites

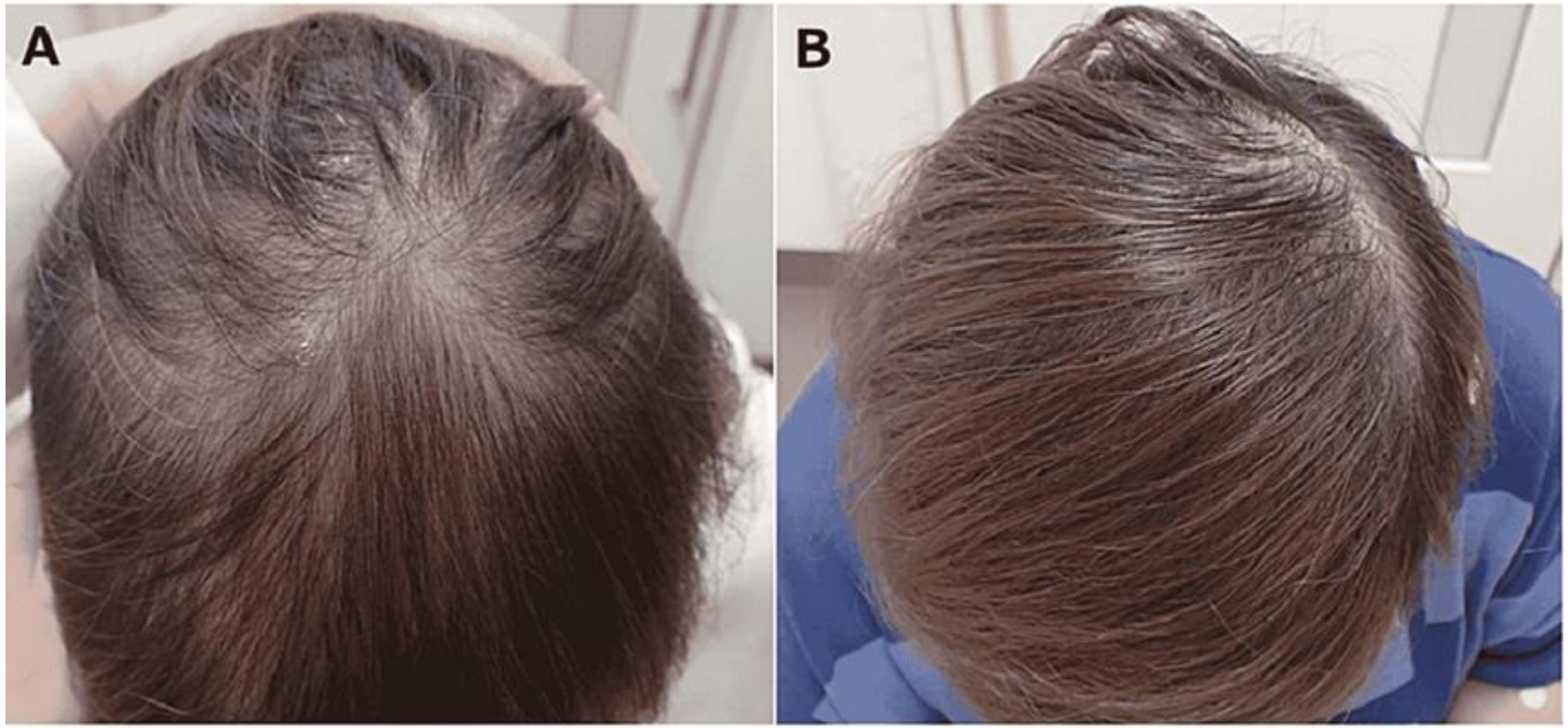
Azole	Pattern of hepatic injury	Approximate incidence of elevations in LFTs (%)	Toxicity requiring discontinuation of drug
Ketoconazole	Hepatocellular[a]	3–17.5	~1 in 1000–3000 patients experience LFT elevations serious enough to warrant discontinuation of drug
Itraconazole	Cholestatic[b]	1–17.4	~1.5% of patients experience LFT elevations serious enough to warrant discontinuation of drug
Fluconazole	Cholestatic	1–10	~0.7% of patients experience LFT elevations serious enough to warrant discontinuation of drug
Voriconazole	Mixed[c] hepatocellular and cholestatic	12–19	Fulminant hepatic failure rare
Posaconazole	Hepatocellular	1–10	LFT elevations serious enough to warrant discontinuation of drug are rare
Isavuconazole	Varied	<5	Limited data

Pas de franc lien avec les **doses ni de FDR**

Pas de réactions croisées Spellberg B et al. CID 2003; Foo H et al. CID 2007; Heinz W et al. Mycoses 2013; Pinto A et al. AAC 2009; DiPippo A et al. Mycoses 2019; Martinez-Casanova J et al. Infect Drug Resist 2018

Benitez L *et al.* Drugs 2019

Fluconazole: toxicités spécifiques (rares)



Pappas P *et al.* Ann Intern Med 1995; Yoshihara H *et al.* Cureus 2022

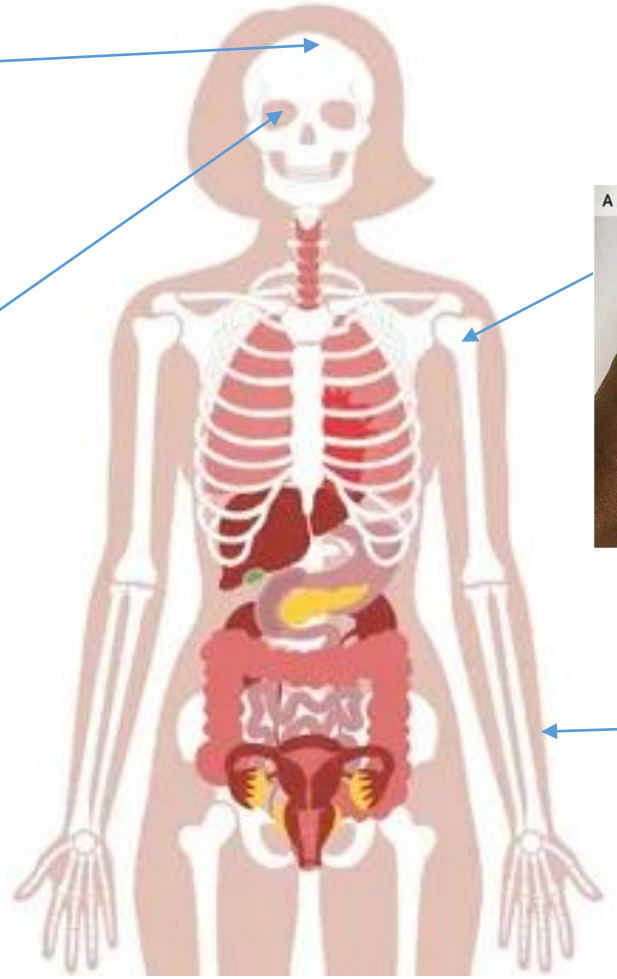
Voriconazole: toxicités spécifiques

Neurototoxicité
Hallucinations v>a
Confusion, agitation
Association T0 > 5.5

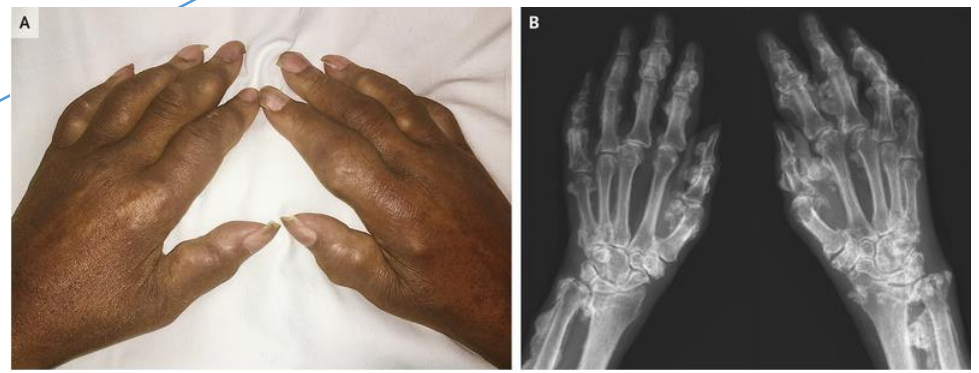
Neuropathie périph.
Rare
SOT sous tacrolimus

Ophtalmotoxicité
Photopsies/flashes 19%
Photophobie 2%
Dyschromatopsies 1%

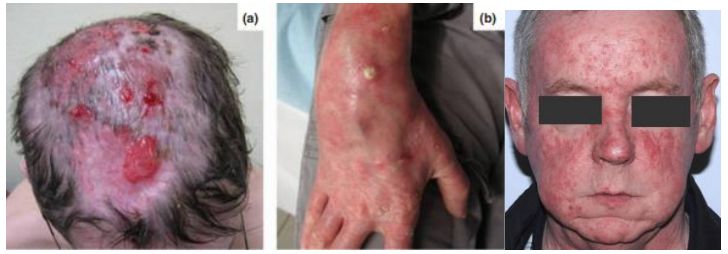
Début de ttt
Durée 30-60 min
Transitoires



Fluoroses osseuses
Périostéites



Toxicité cutanée
Photodermatoses
Carcinomes cutanés



Epaulard O *et al.* CMI 2010; Denning D *et al.* Clin Exp Dermatol 2001; Hedrick J *et al.* NEJM 2019; Boussaud V et al. JHLT 2008

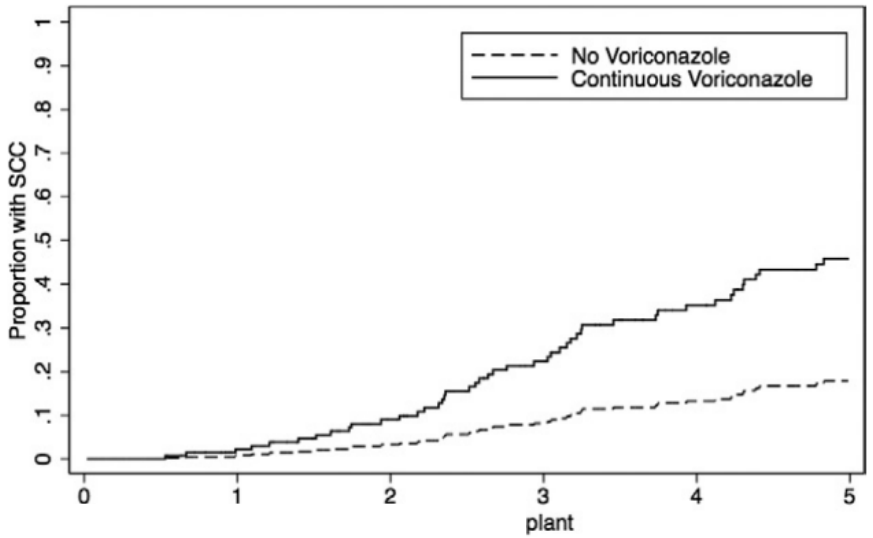
Toxicité cutanée du voriconazole

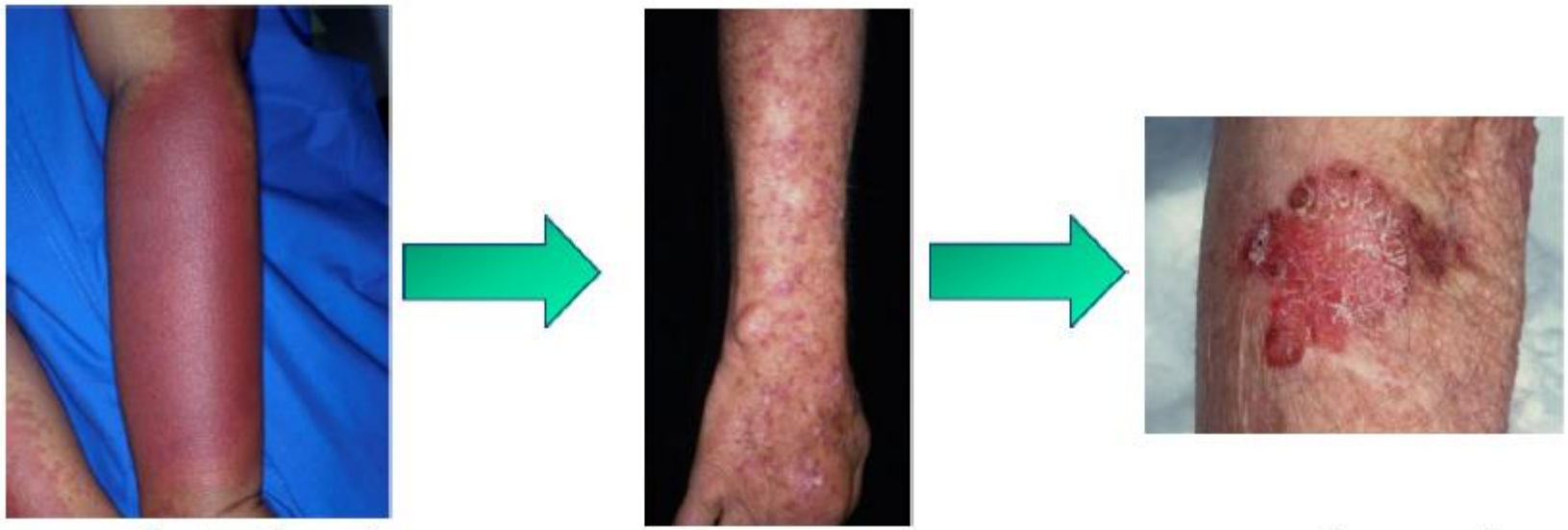
Plus fréquente chez SOT

Etapes: photodermatose→KA →CE

Médiane SCC 39 mois

FDR chez SOT: dose cumulée et exposition solaire





Chronic erythema of sun-exposed area

Actinic keratosis in same areas

Squamous cell carcinoma

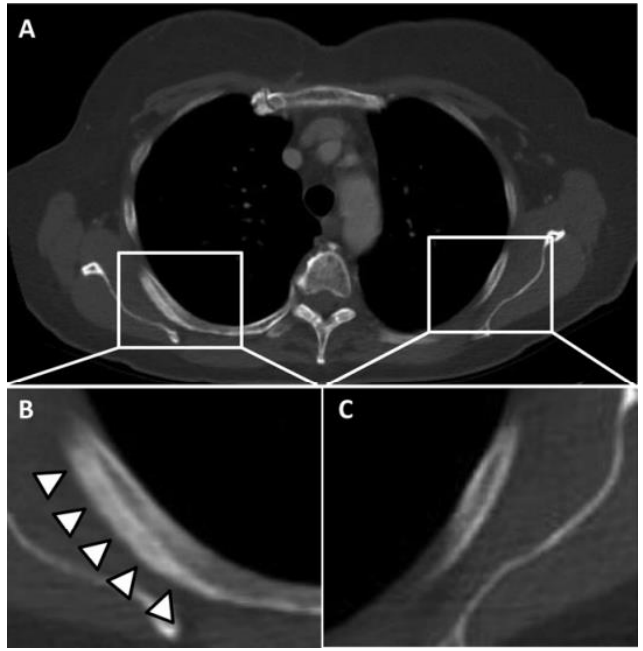
Epaulard O et al. CID 2013; Cowen E *et al.* JAAD 2010; Singer J et al. JHLT 2012; Hamandi B et al. AJT 2018; Benitez L *et al.* Drugs 2019

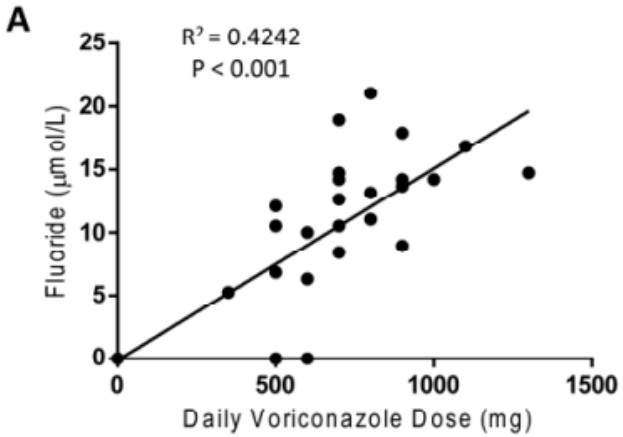
Périostites sous voriconazole

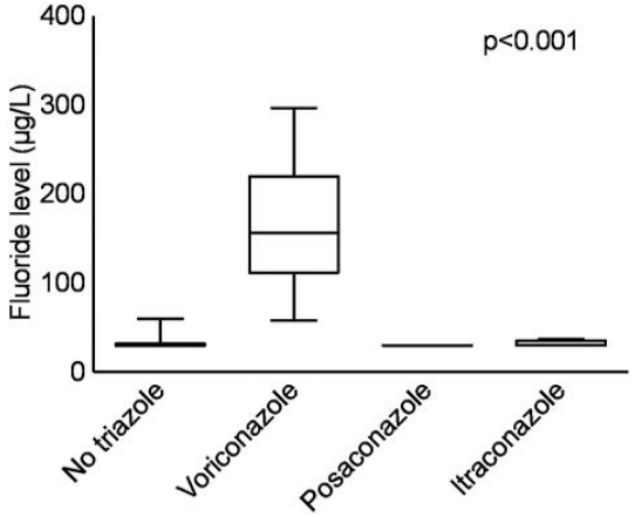
Douleurs osseuses bilatérales
Elévation des PAL

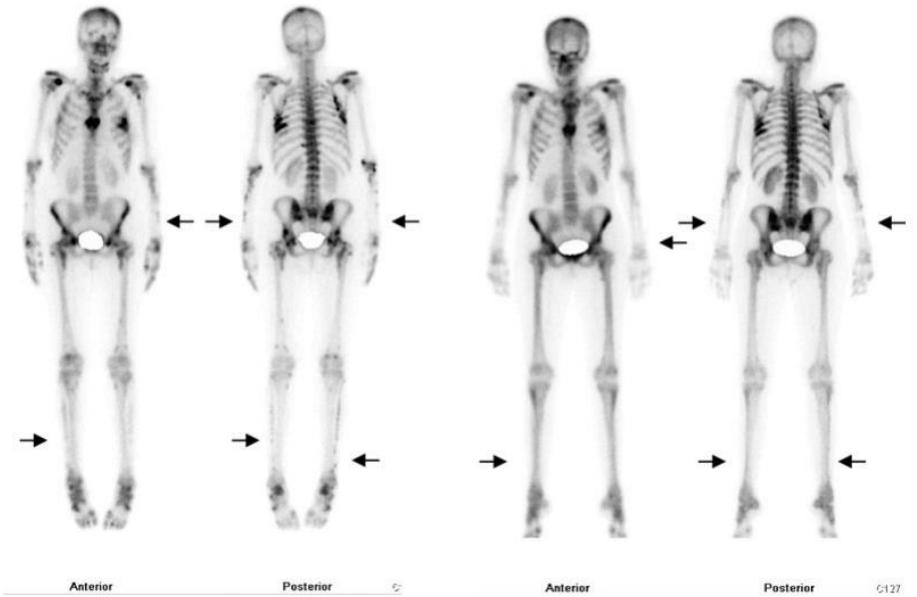
Fluor sérique élevé

Réversible à l'arrêt









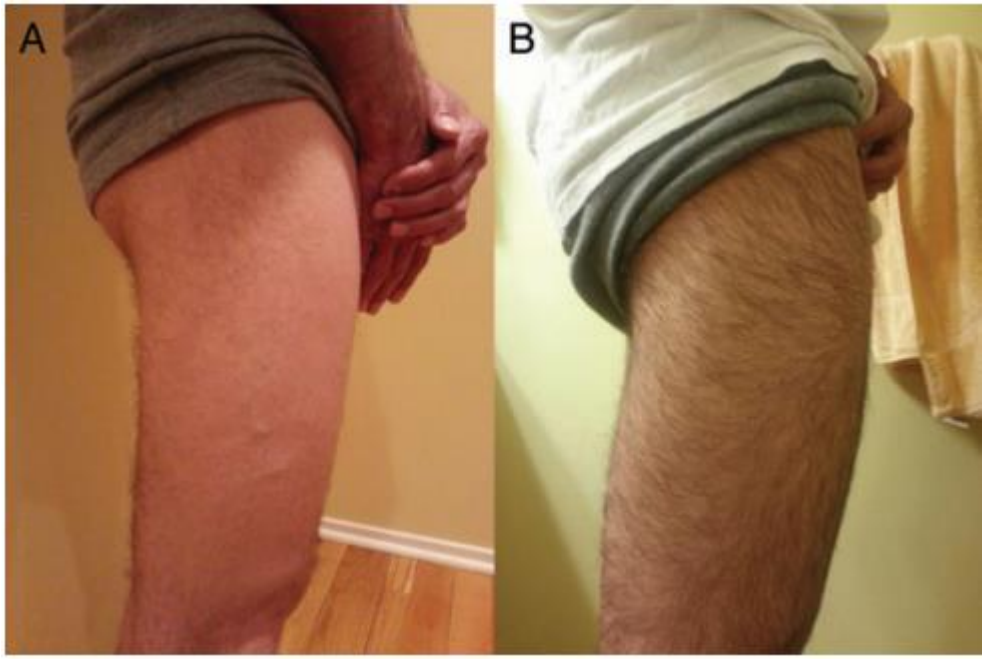
Wang T et al. AJT 2009; Wermers R et al. CID 2011; Gerber B et al. Blood 2012; Moon W *et al.* CID 2014

Voriconazole: autres toxicités

Allongement du QTc

Anomalie des phanères

Characteristic	Number (%) (n = 152)
Age, mean (range), y	64.7 (29–90)
Female sex	96 (63)
White	150 (99)
Body mass index ≥ 35	38 (25)
Chronic renal insufficiency	7 (5)
Coronary artery disease	21 (14)
Diabetes mellitus	28 (18)
Hypertension	64 (42)
Hyperlipidemia	52 (34)
Immunosuppression[a]	12 (8)
Osteoarthritis	22 (15)

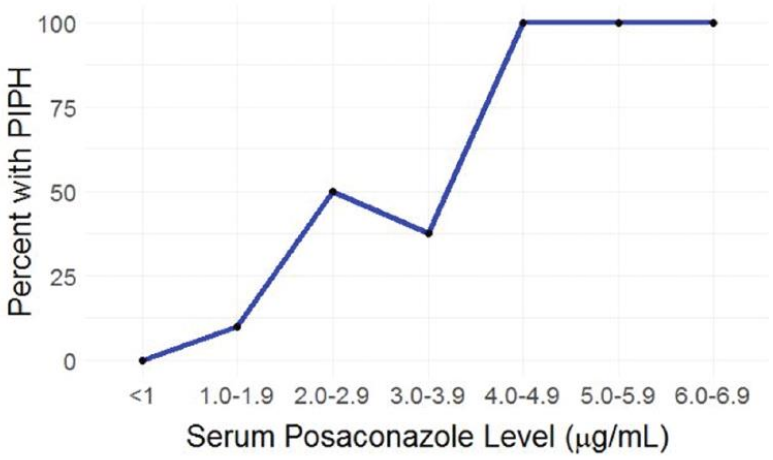


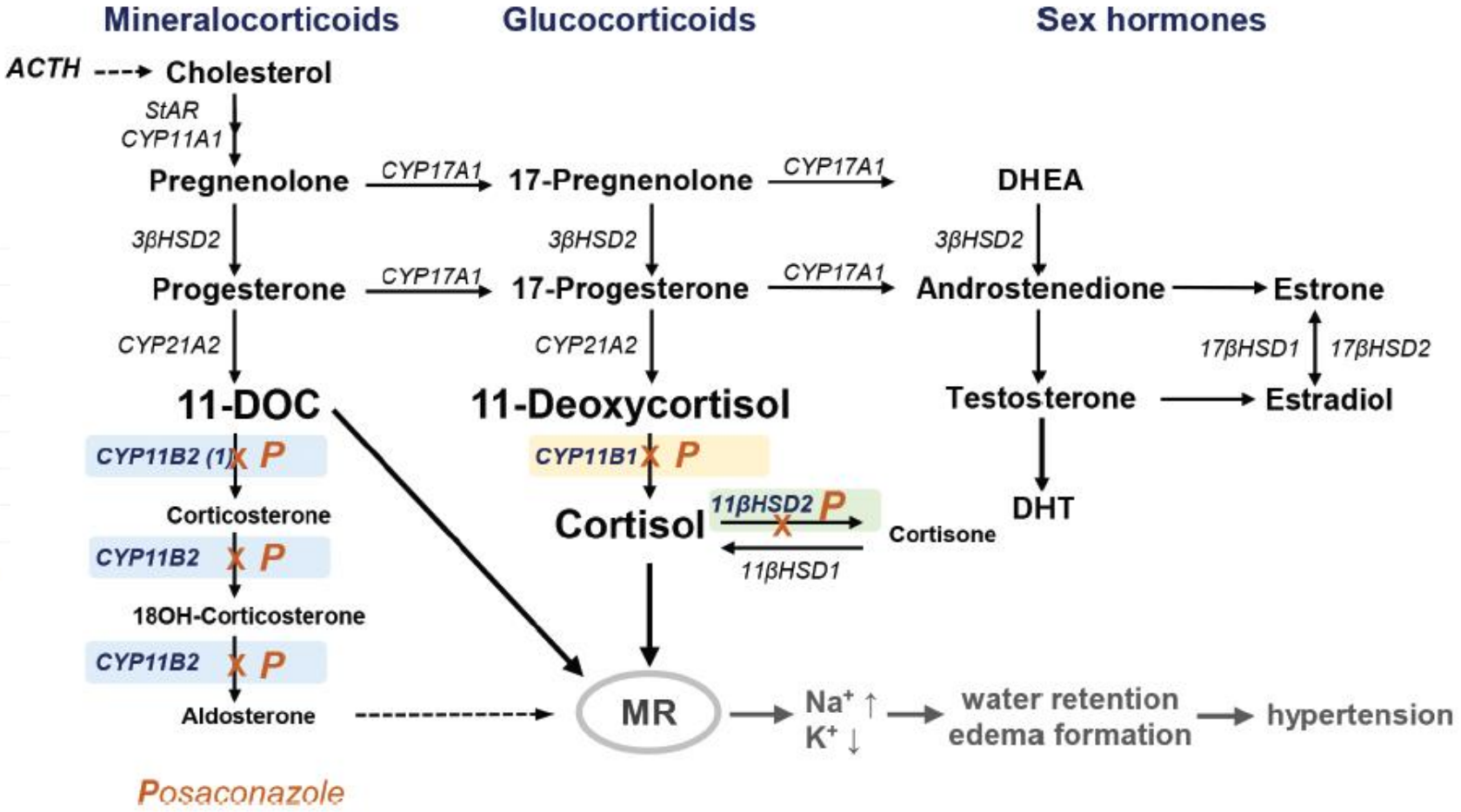
Malani A *et al.* CID 2014

Posaconazole: toxicités spécifiques

Allongement du **QTc**: rare (1%)

Effets **endocriniens**:





Nguyen M *et al.* CID 2020

Isavuconazole: tolérance

	Isavuconazole (n=257)	Voriconazole (n=259)	p value
Overall	247 (96%)	255 (98%)	0·122
Gastrointestinal disorders	174 (68%)	180 (69%)	0·705
Infections and infestations	152 (59%)	158 (61%)	0·719
General disorders and administrative site conditions	148 (58%)	144 (56%)	0·658
Respiratory, thoracic, and mediastinal disorders	143 (56%)	147 (57%)	0·859
Metabolism and nutrition disorders	108 (42%)	121 (47%)	0·289
Nervous system disorders	95 (37%)	89 (34%)	0·582
Skin and subcutaneous tissue disorders*	86 (33%)	110 (42%)	0·037¶
Investigations (abnormal laboratory tests)	85 (33%)	96 (37%)	0·357
Blood and lymphatic system disorders	77 (30%)	82 (32%)	0·703
Psychiatric disorders†	70 (27%)	86 (33%)	0·151
Musculoskeletal and connective tissue disorders	69 (27%)	77 (30%)	0·495
Vascular disorders	67 (26%)	77 (30%)	0·378
Renal and urinary disorders	55 (21%)	58 (22%)	0·832
Cardiac disorders	43 (17%)	57 (22%)	0·148
Eye disorders‡	39 (15%)	69 (27%)	0·002¶
Injury, poisoning, and procedural complications	33 (13%)	39 (15%)	0·526
Hepatobiliary disorders§	23 (9%)	42 (16%)	0·016¶
Immune system disorders	20 (8%)	25 (10%)	0·533
Neoplasms benign, malignant and unspecified	19 (7%)	31 (12%)	0·101
Ear and labyrinth disorders	14 (5%)	13 (5%)	0·846
Reproductive system and breast disorders	8 (3%)	13 (5%)	0·373
Endocrine disorders	5 (2%)	3 (1%)	0·503
Congenital, familial, and genetic disorders	3 (1%)	2 (1%)	0·685
Social circumstances	0	1 (<1%)	>0·999

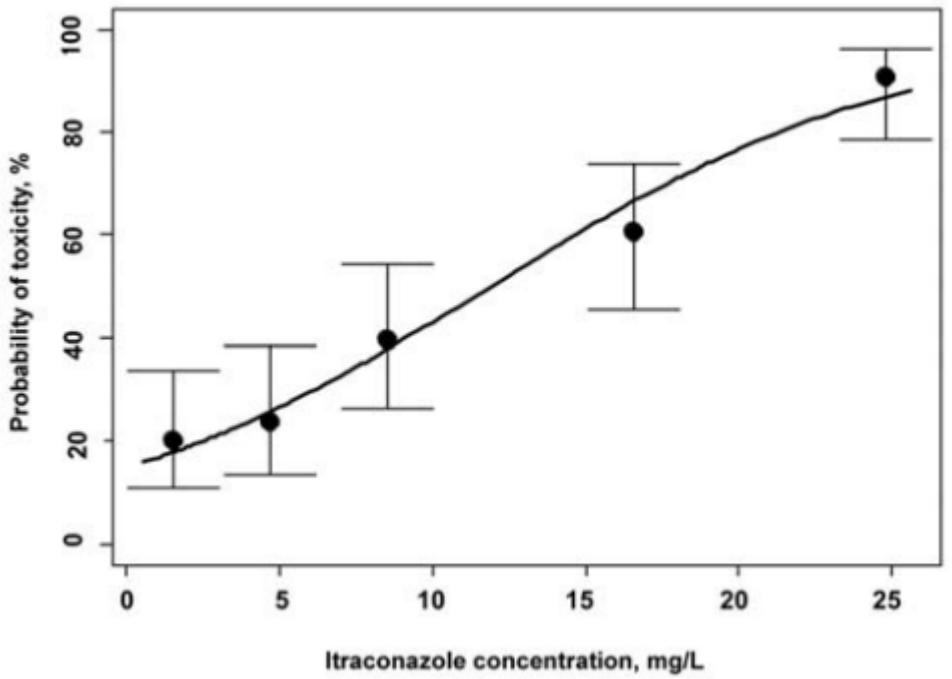
Maertens J *et al.* Lancet 2016

Monitoring plasmatique de l'itraconazole

A faire à J14

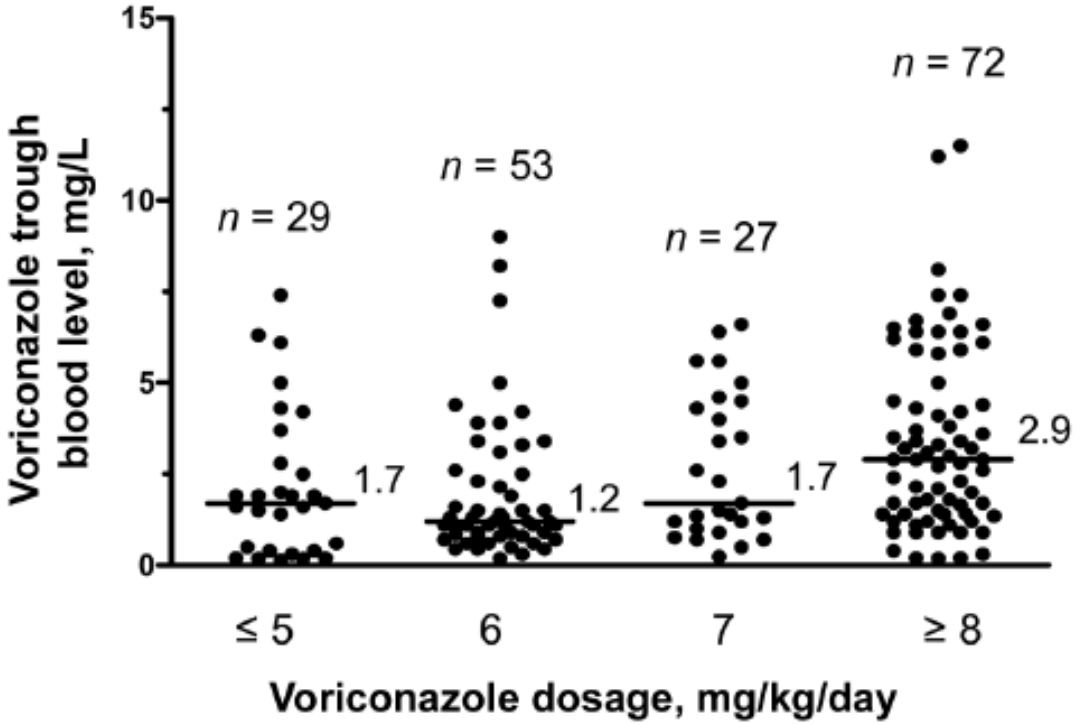
Any moment

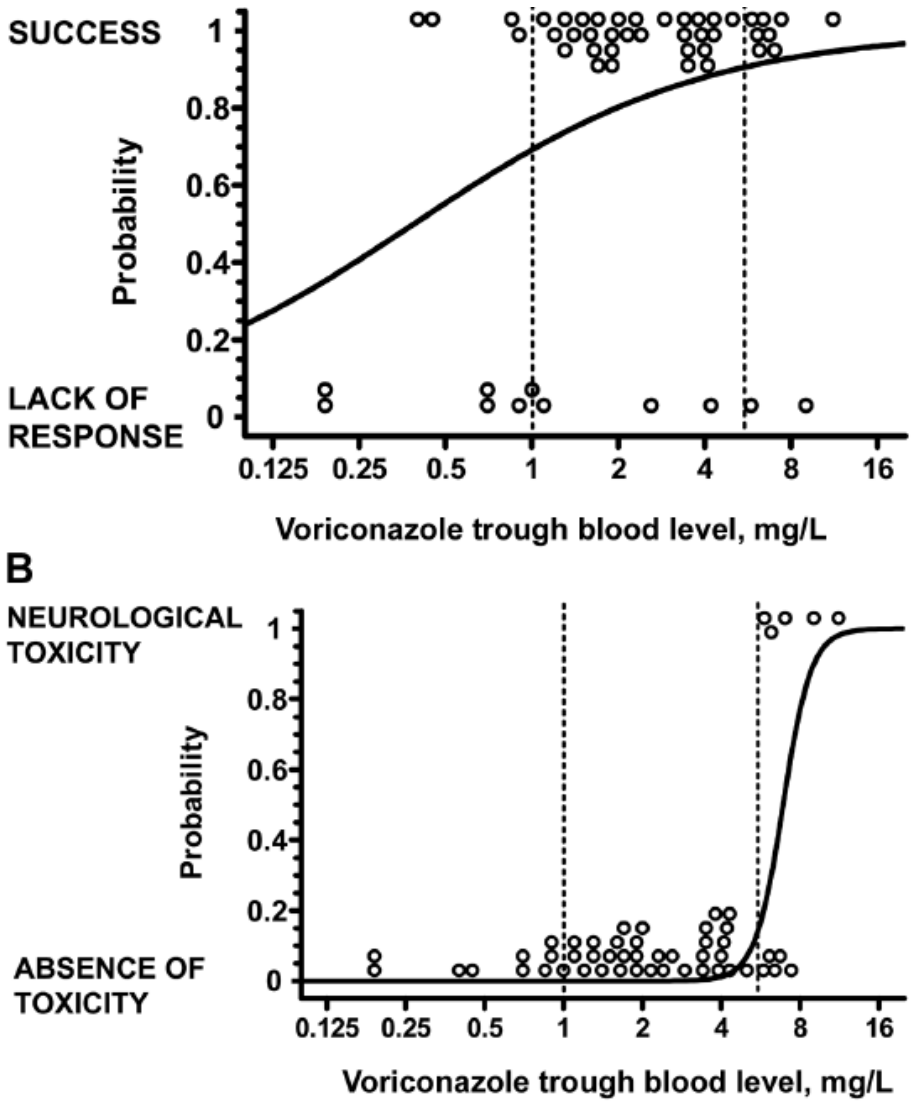
HPLC: 1 mg/l (ITCZ + OH-ITCZ)
Dosage **biologique**: 3 mg/l



Lestner J *et al.* CID 2009

Taux plasmatiques de voriconazole: intérêt

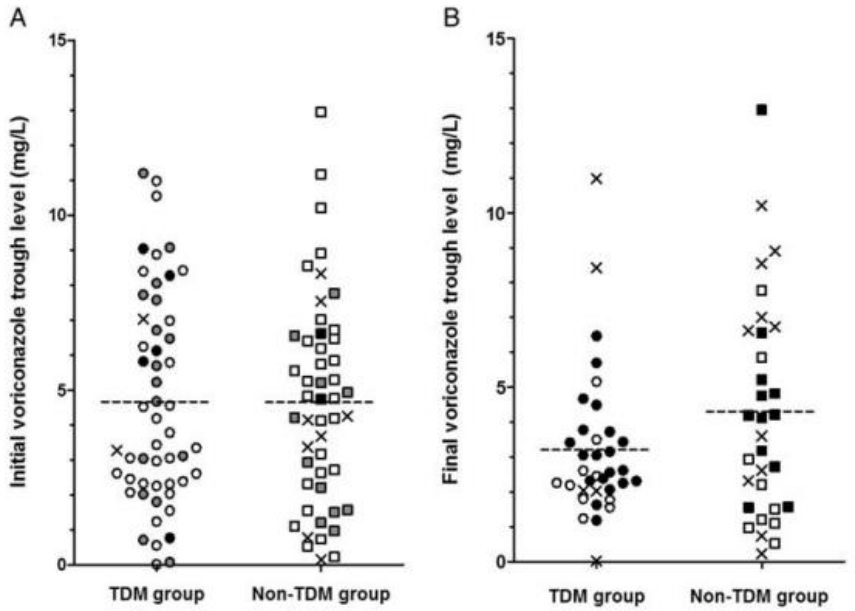




Pascual A et al. CID 2008

TDM du voriconazole: RCT

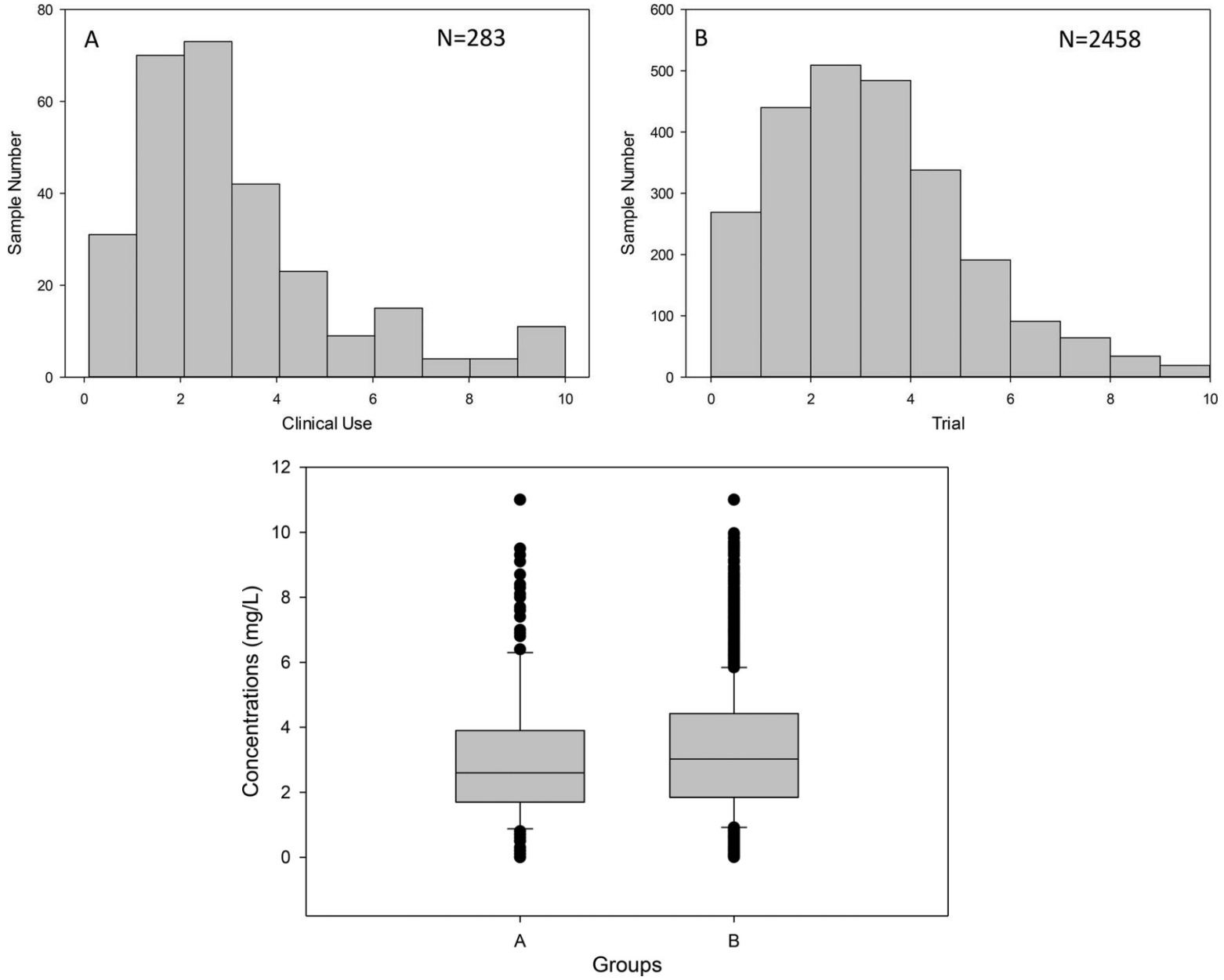
	TDM (n = 55)	Non-TDM (n = 53)	*P* Value
Possible or stronger relationship			
All events	23 (42)	22 (42)	.97[a]
Elevation of hepatic enzymes	15 (27)	14 (26)	.92[a]
Encephalopathy[b]	8 (15)	7 (13)	.84[a]
Others[c]	5 (9)	8 (15)	.34[a]
Severe events	7 (13)	5 (9)	.586[a]
Elevation of hepatic enzymes	4 (7)	3 (6)	>.99[d]
Encephalopathy	2 (4)	0	.49[d]
Others	2 (4)	2 (4)	>.99[d]
Probable or likely relationship			
All events	12 (22)	9 (17)	.53[a]
Elevation of hepatic enzymes	3 (6)	4 (8)	.71[d]
Encephalopathy	6 (11)	5 (9)	.80[a]
Others	3 (6)	2 (4)	>.99[d]
Severe events	2 (4)	2 (4)	>.99[d]
Elevation of hepatic enzymes	0	1 (2)	.49[d]
Encephalopathy	1 (2)	0	>.99[d]
Others	1 (2)	1 (2)	>.99[d]
Drug discontinuation due to adverse events	2 (4)	9 (17)	.02[a]



	TDM (n = 37)	Non-TDM (n = 34)	*P* Value
Treatment success	30 (81)	20 (59)	.04
Complete response	21 (57)	13 (38)	.12
Partial response	9 (24)	7 (21)	.71
Stable response	1 (3)	2 (6)	.60
Treatment failure	6 (16)	12 (35)	.07

Park W *et al.* CID 2012

TDM de l'isavuconazole: pas en routine



Andes D *et al.* AAC 2018

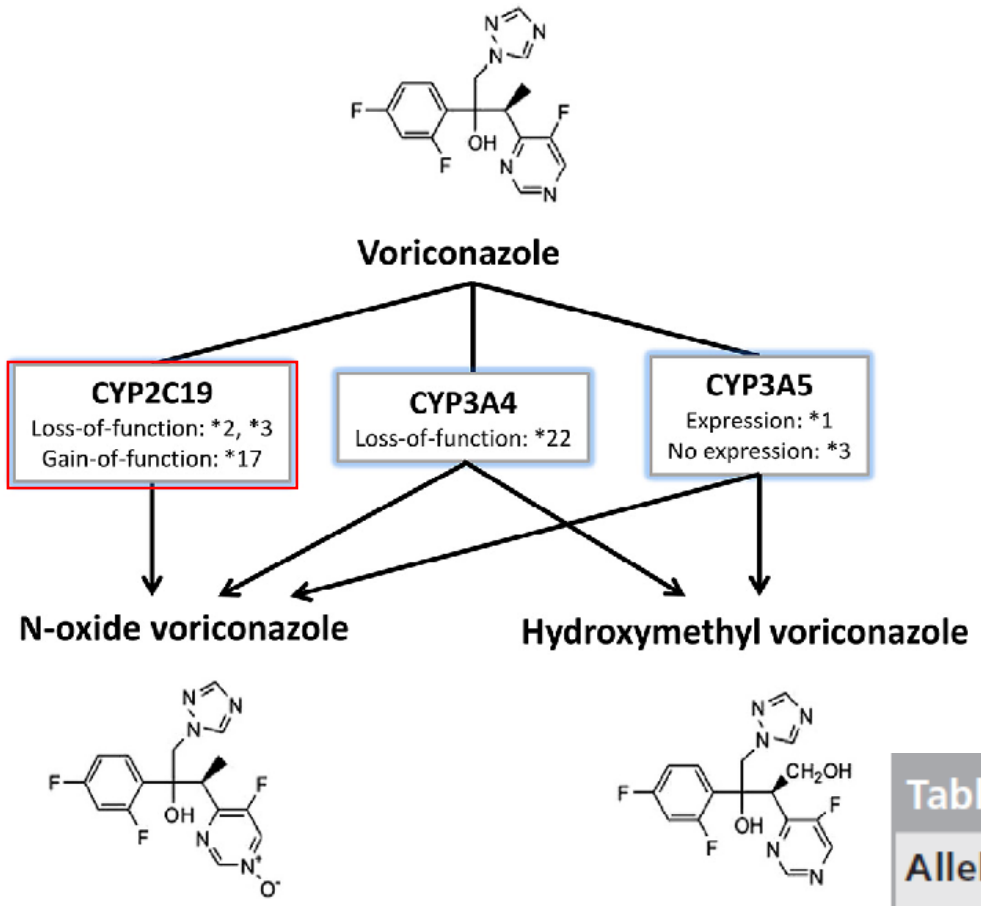
Surveillance des taux plasmatiques des azolés

	FCZ	ITCZ	VCZ	PCZ	IVCZ
PK variable	O	O	O	O	O
Index thérapeutique étroit	N	O	O	?	?
Recommandé par	N	O ESCMID/IDSA	O ESCMID/IDSA	IDSA/ESCMID	N
Pour efficacité	N	O	O	O	?
Pour tolérance	N	O	O	?	?
Objectif traitement	NA	1-4 HPLC	1-5.5	> 1	?
Objectif prophylaxie	NA	0.5-4 HPLC	1-5	> 0.7	?

VCZ: les taux plasmatiques ne prédisent pas la tox hépatique chez les caucasiens
prédisent la tox neurologique

Lewis R *et al.* ECIL 6 guidelines

Pharmacogénétique du voriconazole



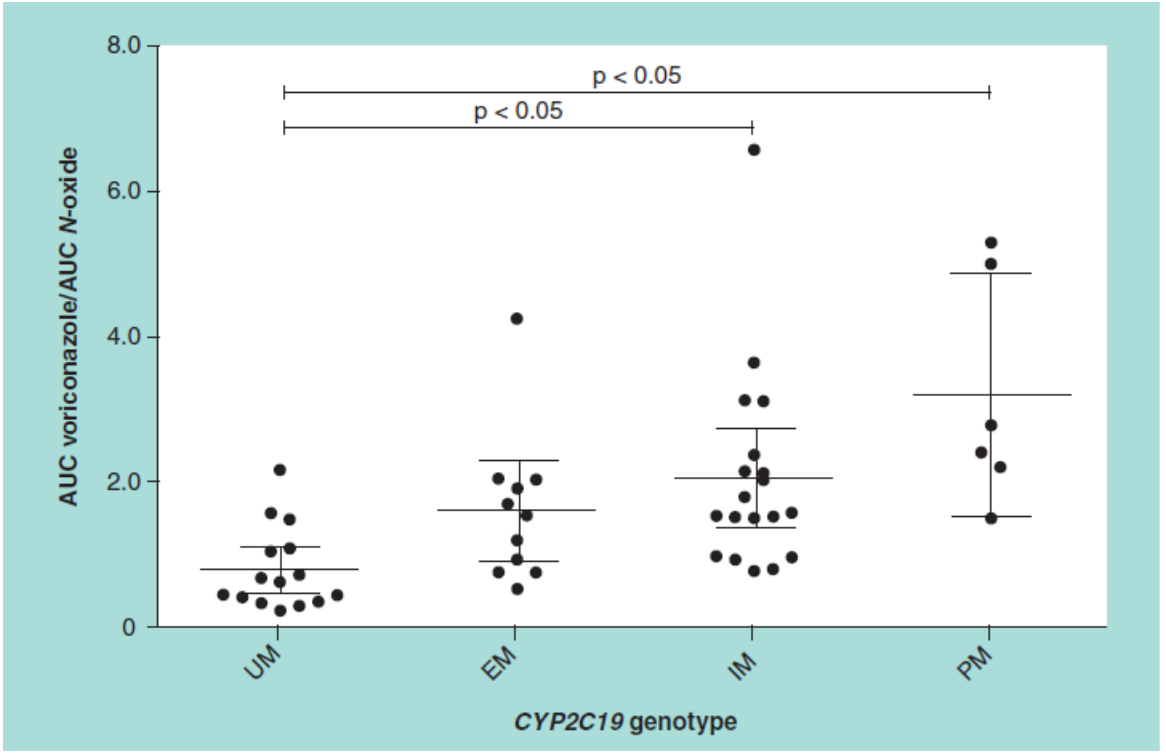


Table 1. Most important variant alleles of *CYP2C19*.

Allele	Effect on protein	Effect on activity	Variant allele frequency		
			Europeans	*Asians*	*Africans*
*2	Splicing defect	No activity	0.15	0.30	0.17
*3	Stop codon	No activity	0.004	0.05	0.004
*4	Initiation codon	No activity	0.006	0.004	Unknown
*17	Increased transcription	Increased activity	0.18–0.22	0.01–0.4	0.17–0.18

Gautier-Veyret E *et al.* IJAA 2016

Mikus G *et al.* Pharmacogenomics 2011

Métabolisme des triazolés

	Fluconazole	Voriconazole	Itraconazole	Posaconazole	Isavuconazole
Inhibitor					
CYP2C19	Strong	Moderate			
CYP2C9	Moderate	Weak			
CYP3A4	Moderate	Strong	Strong	Strong	Moderate
Substrate					
CYP2C19		Major			
CYP2C9		Major			
CYP3A4		Minor	Major		Major

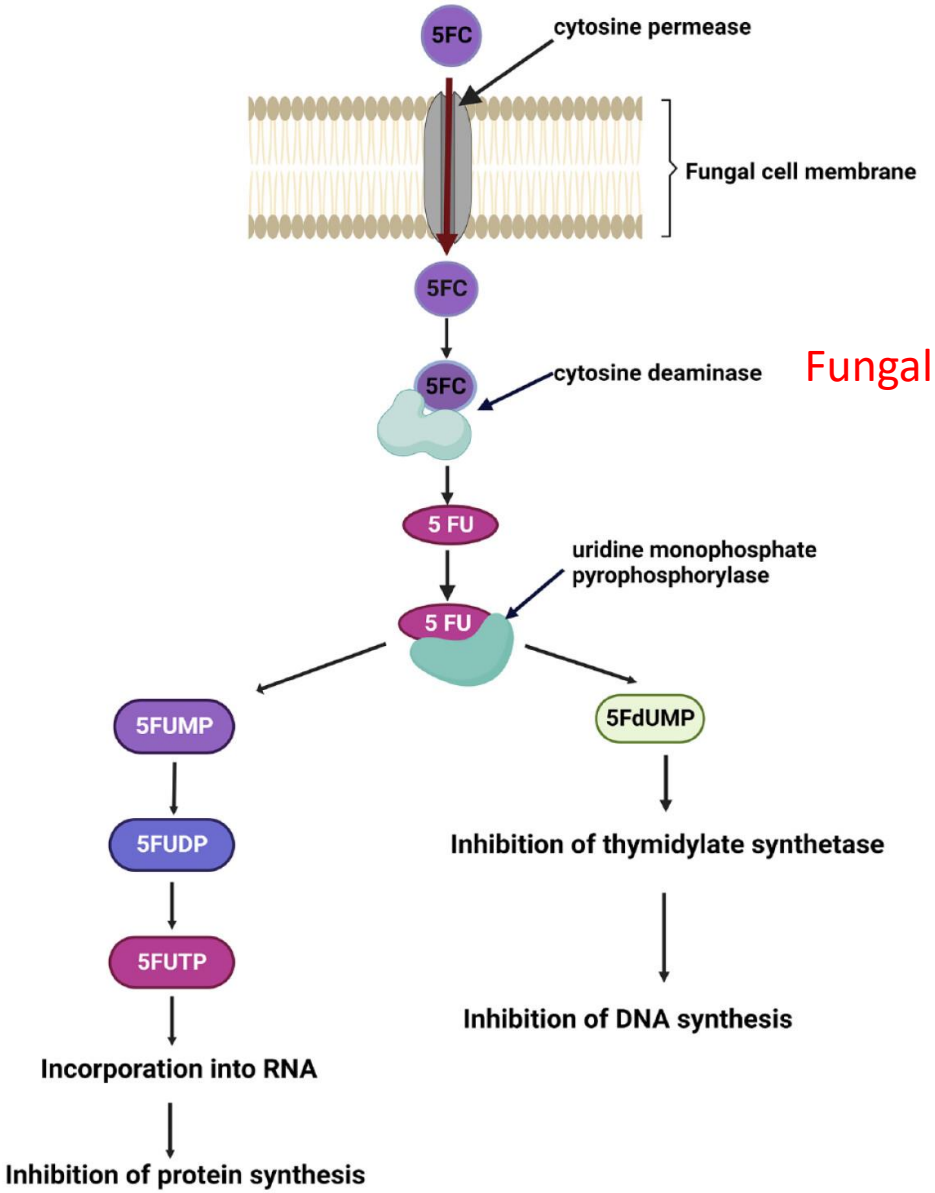
Shah S, idstewardship.com

Interactions et triazolés

Inhibition du métabolisme de la molécule co-prescrite	**Induction du métabolisme de l'azolé**	**Inhibition du métabolisme de l'azolé**
CNI	Rifamycines	Clarithromycine
Inhibiteurs de mTOR	Carbamazépine	Cobicistat
NACO	Phenytoïne	Ritonavir
Vincristine		
Statines (certaines)		

L'induction enzymatique peut être retardée

Flucytosine: mode d'action



Sigera L *et al.* Ther Adv Infect Dis 2023

Flucytosine : spectre

Levures	Filamenteux	Dimorphiques	*Pneumocystis*
Candida *Cryptococcus*	*Aspergillus* Mucorales Dermatophytes *Scedosporium* *Fusarium*	*Histoplasma* *Coccidioides* *Blastomyces* *Sporothrix*	

Candida krusei

Flucytosine: pharmacocinétique

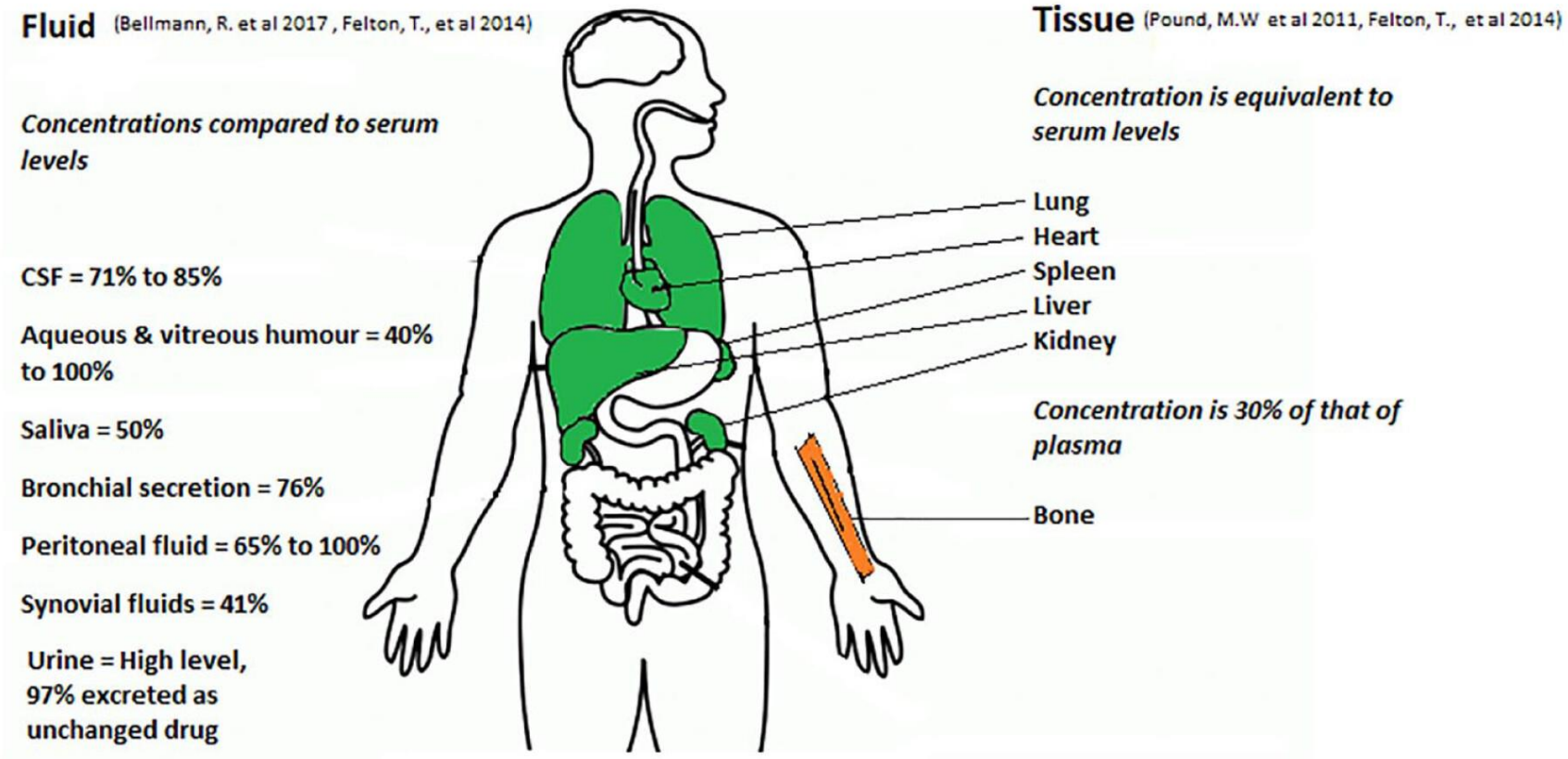
Biodisponibilité orale: 76-89% (attention Al, Mg)

Liaison protéique: 2-4%

Vd: 0.6-0.9 l/kg

T ½: 3-4h

Elimination rénale

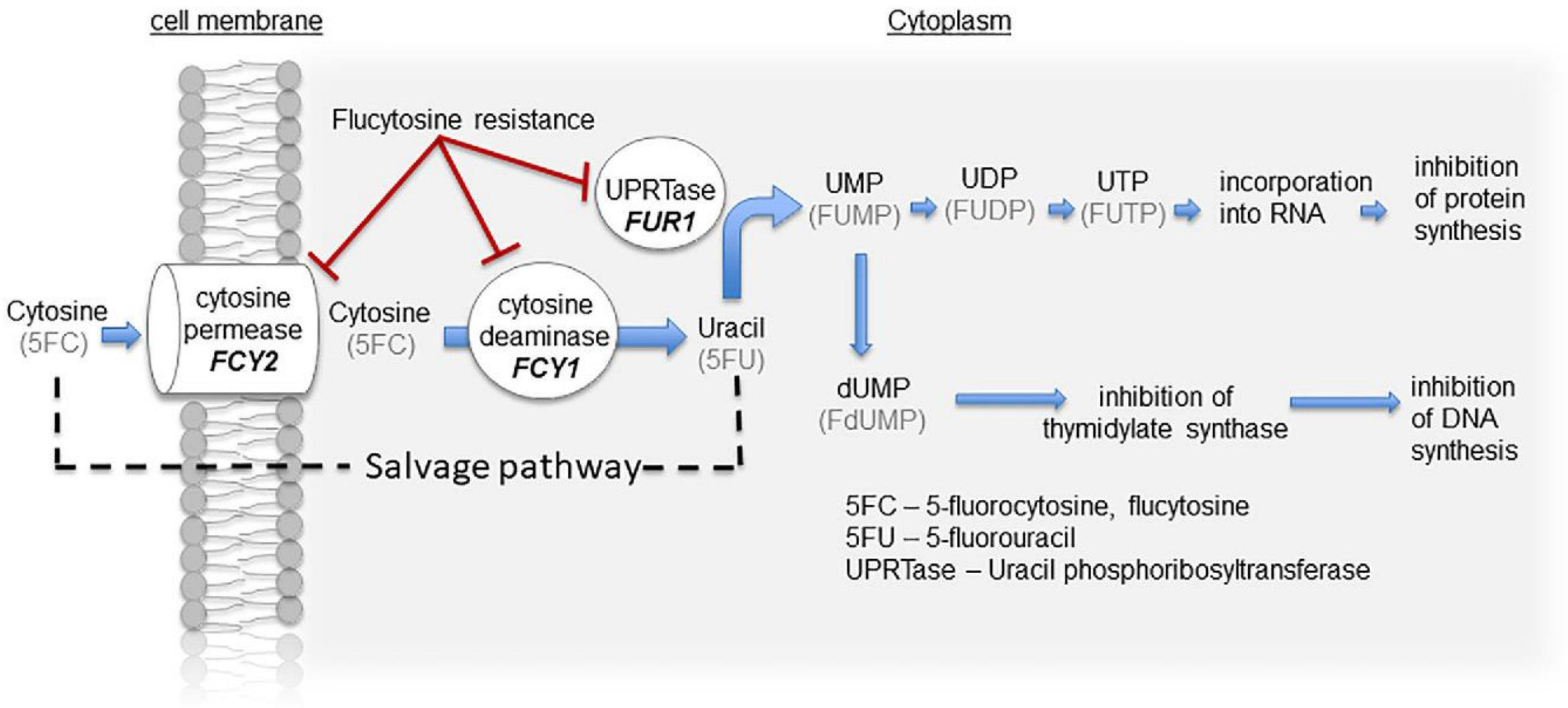


Sigera L *et al.* Ther Adv Infect Dis 2023

Flucytosine : prescrire en pratique

	FC
Voie d'administration	Orale/IV
Rythme d'administration	4/jour
Dose (mg/kg/j)	100
Durée de perfusion	1 h
Diluant	G5%
Adaptation si insuffisance rénale	Oui
Adaptation si dysfonction hépatique	Non
Adaptation si obésité	Selon poids idéal
Grossesse	Contre-indiqué

Flucytosine : le problème de la résistance acquise



Vu K *et al.* Med Mycol 2018

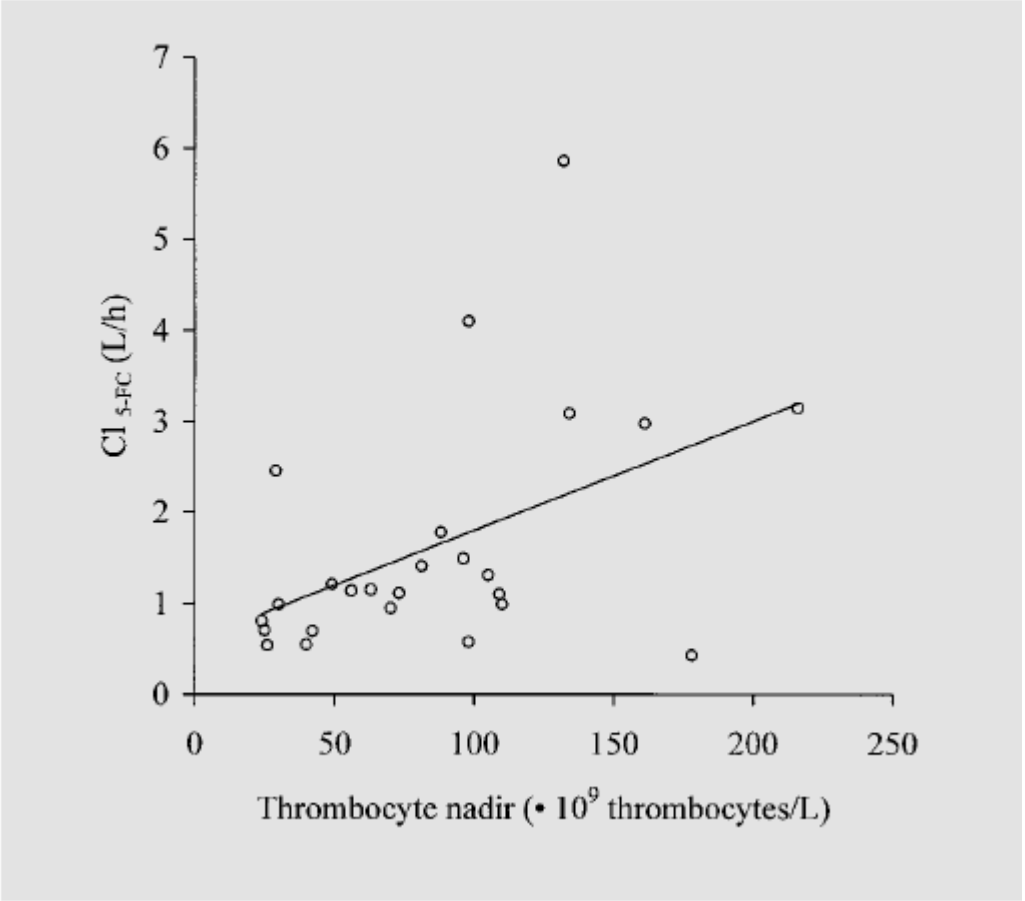
Flucytosine: toxicités

Cytopénies corrélées aux taux sériques

Nausées/vomissements (6%)

Hépatites (5%)

Exanthèmes



Vermes A *et al.* Chemotherapy 2000

Flucytosine: TDM

Surtout pour toxicité

Prudence si I Rénale

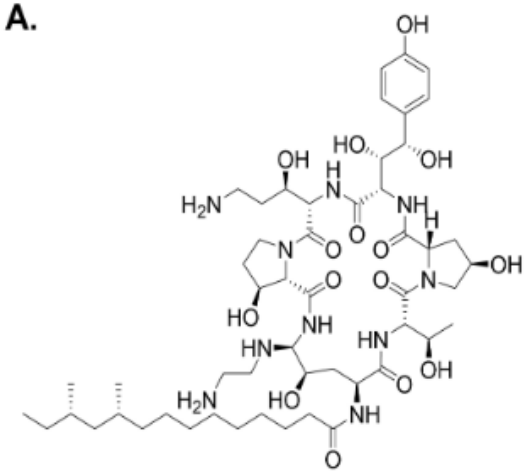
Quand? Après 3 à 5 doses, pic H+2h

Diminuer la dose si pic > 100

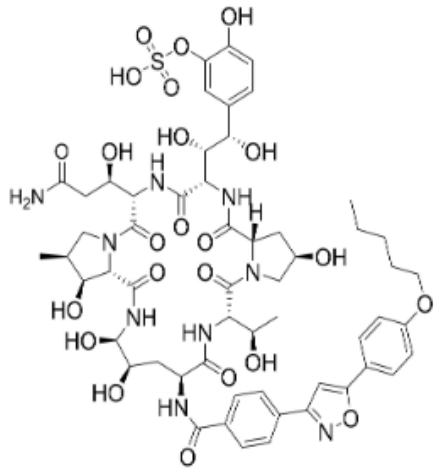
Concentration cible (mg/L)	**Flucytosine**
Résiduelle Adulte Néonatalogie	 30 à 40 20 à 40
Pic Adulte Néonatalogie	 40 à 80 50 à 80
Toxicité	Cmax> 100 mg/L Hématologique, gastro-intestinale, hépatique, rash cutané

Echinocandines

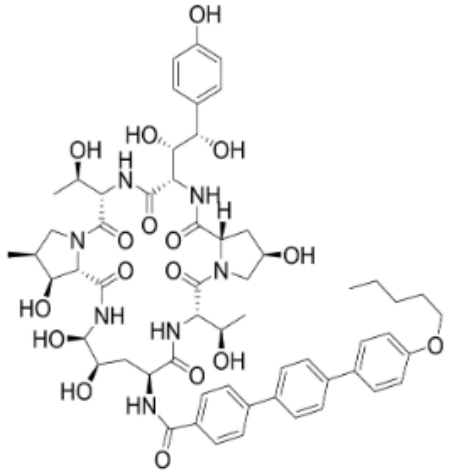
A.



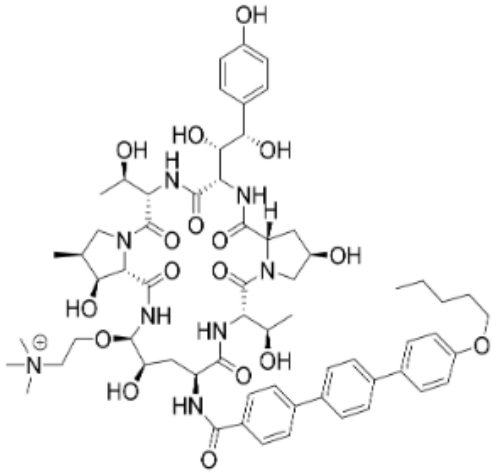
Caspofungin
FDA approved: 2001



Micafungin
FDA approved: 2005



Anidulafungin
FDA approved: 2006



Rezafungin
FDA approved: 2023

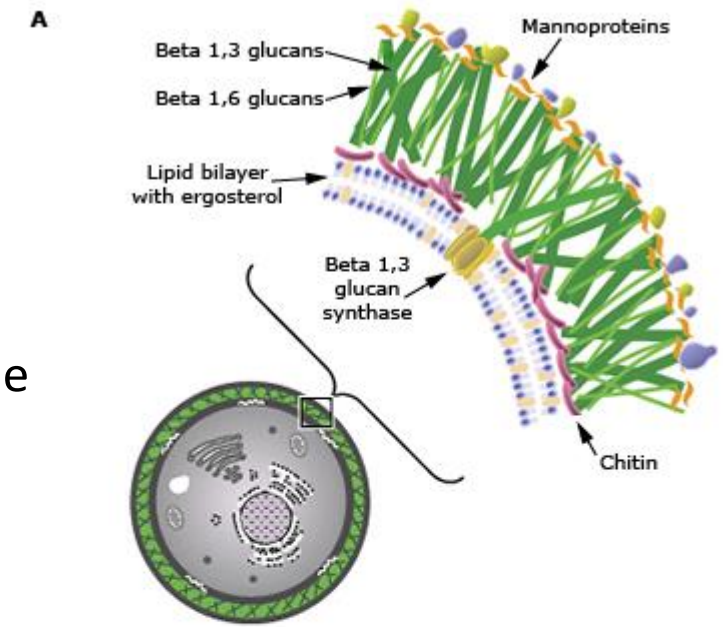
Jospe-Kaufman M *et al.* Angew Chem Int Ed 2024

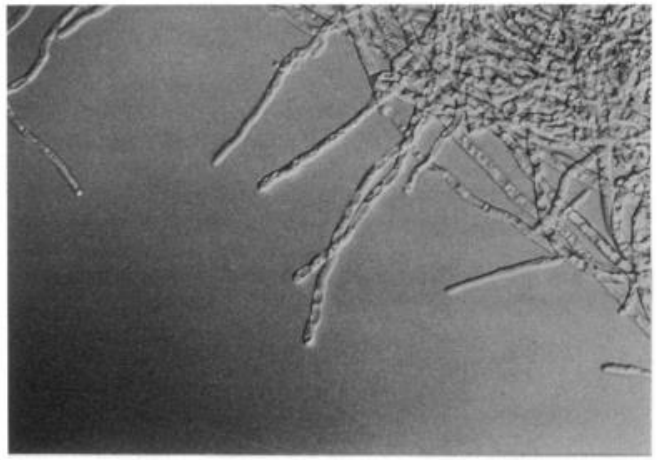
Echinocandines: mode d'action

Fongicides sur *Candida*

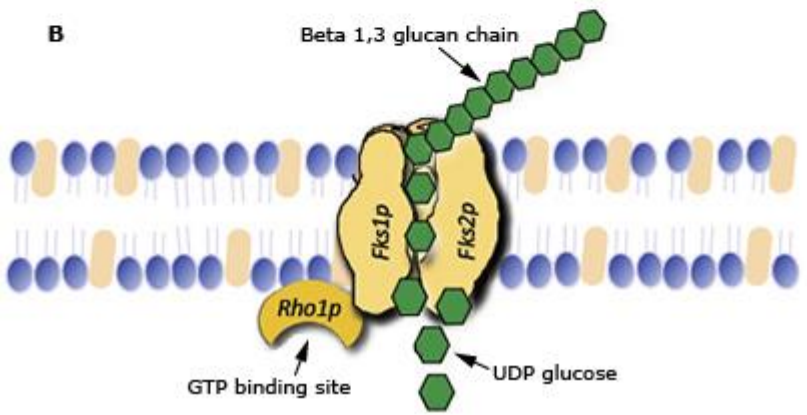
Fongistatiques sur *Aspergillus*

Pas de cible « collatérale » humaine

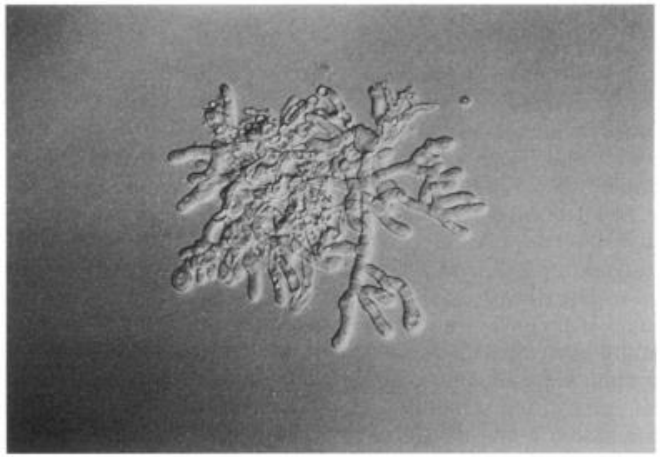




A. fumigatus



B



Dr R. Lewis, U Bologna; Kurtz M et al. AAC 1994

Echinocandines : spectre

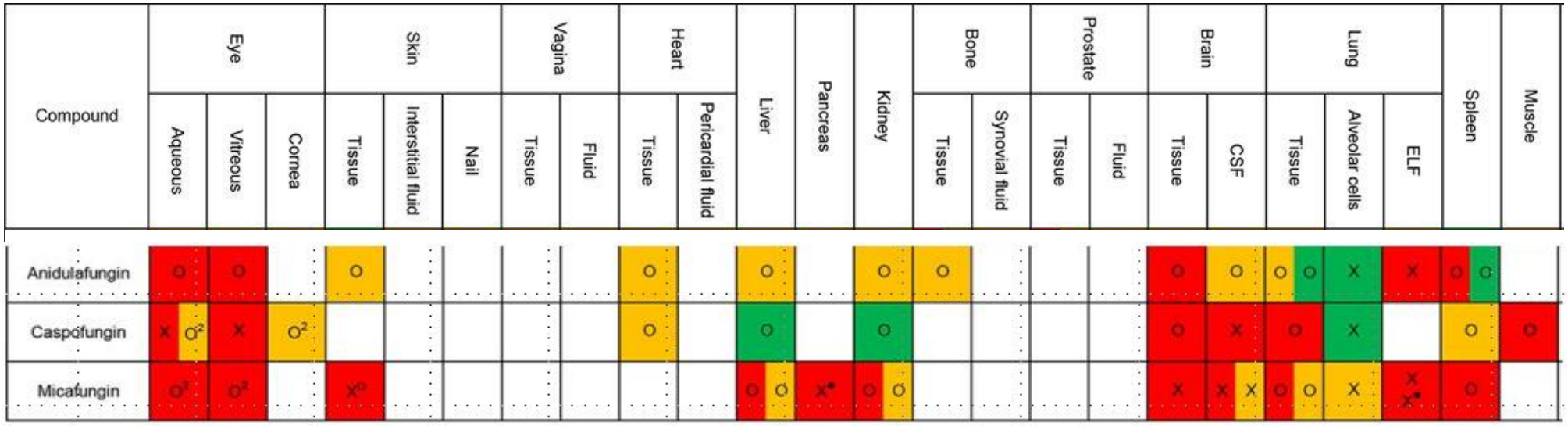
Levures	Filamenteux	Dimorphiques	*Pneumocystis*
Candida *Cryptococcus*	*Aspergillus* Mucorales Dermatophytes *Scedosporium* *Fusarium*	*Histoplasma* *Coccidioides* *Blastomyces* *Sporothrix*	

Candida glabrata
Candida guilliermondii
(Candida parapsilosis)

Echinocandines: pharmacocinétique

	Caspofungine	Micafungine	Anidulafungine	Rezafungine
Biodisponibilité Orale	0%	0%	0%	0%
Liaison protéique	96-97%	99.8%	99%	
Volume de distribution (l/kg)	0.14	0.39	0.50	
Demi-vie (h)	27-50	14-17.2	40-50	
Métabolisme	Hépatique	Hépatique	Aucun	Minime
Elimination	Urines 41 (1)% Fécale 35%	Urines 0.7% Fécale 40%	Urines < 1%	Fécal

Echinocandines : diffusion tissulaire

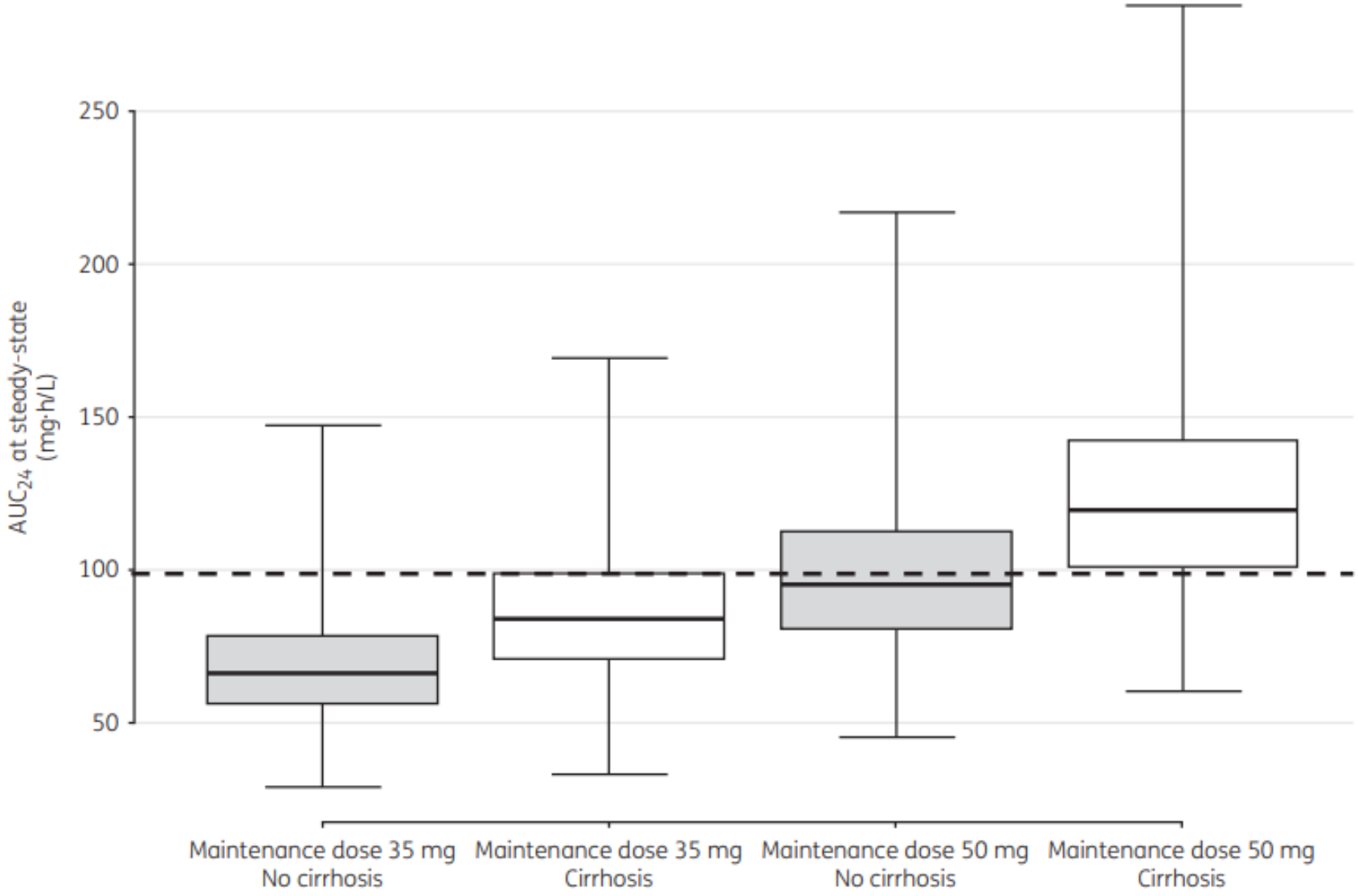


Felton T *et al.* CMR 2014

Echinocandines: prescrire en pratique

	Caspofungine	Micafungine	Anidulafungine	Rezafungine
Voie	IV	IV	IV	IV
Rythme d'administration	1/j	1/j	1/j	1/sem
Dose (mg/j)	70 mg Puis 50 mg/j	50 à 100		400 mg Puis 200 mg/sem
Diluant	NaCl	NaCl/G5%	NaCl/G5%	NaCl/G5%
Adaptation si insuffisance rénale	Non	Non	Non	Non
Adaptation si dysfonction hépatique	Oui?	Oui?	Non	Non
Adaptation si obésité	Poids réel (100)	Si > 125 kg	Si > 140 kg	A priori non
Grossesse	Non	Non	Non	?
ECMO	A priori pas de changement			

Caspofungine et cirrhose décompensée



Gustot T *et al.* JAC 2018

Echinocandines: toxicité

Hépatique: cytolyse 7-14%
élévation des PAL 4-12%

Histaminolibération: si > 1.1 mg/min (MRGPRX2)

Fièvre: surtout caspofungine

Douleur à l'injection: ralentir et diluer (4%)

Signes digestifs: 1-3%

Très rare: cytopénies, IC

Gustot T *et al.* JAC 2018

Echinocandines: toxicité

Table 2 Adverse effects of echinocandins (Sable et al 2002; Carver 2004; Raasch 2004; Krause, Reinhardt, et al 2004; Cancidas PI 2005; Groll et al 2005; Mycamine PI 2005; Eraxis PI 2006)

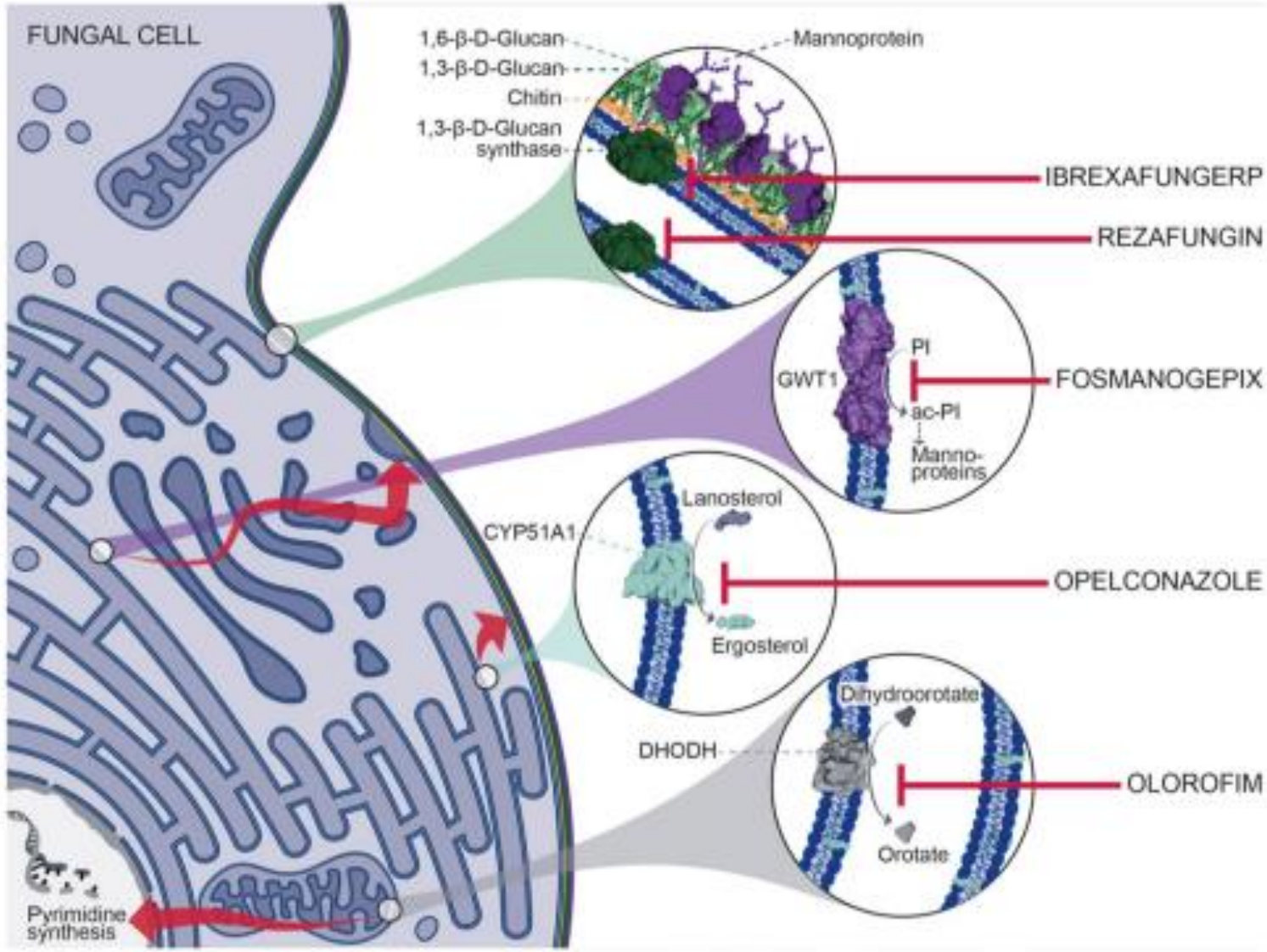
Parameter		Caspofungin	Micafungin	Anidulafungin
Hematologic	Neutropenia		1.2%	1.0%
	Leukopenia		0.9%	0.7%
	Eosinophilia	3%	Rarely related to infusion	
	Thrombocytopenia	<4%		
	Leukopenia	<4%		
	Decreased Hgb, Hct	3%–12%		
Gastrointestinal	Nausea	<3%	2.4%	1.0%
	Diarrhea		2.1%	
	Vomiting	<3%		0.7%
	Dyspepsia			0.3%
Miscellaneous	Hyperbilirubinemia		3.3%	
	Increased GGT			<1%
	Elevated AST/ALT	Do not exceed 5X ULN, transient, reversible. ~14%, <2%, 11%–24%	Rare, and generally insignificant	<1%
	Hypokalemia	11% after 70 mg dose; <4% with 50 mg dose	1.8%	2.4%–3.1%
	Rash			<1%
	Pyrexia	12%–26%, 3.6% (depending on comparator)		0.7%
	Headache	<3%		1.3%
	Flushing	<3%		
	Phlebitis/thrombophlebitis	3.5%, 12%–18%	Rare	1.3%
	Infusion related reactions/ Histamine release	2%	Rare	1 pt "flushing" with infusion

Eschenauer G *et al.* Ther Clin Risk Manag 2007

Echinocandines: interactions

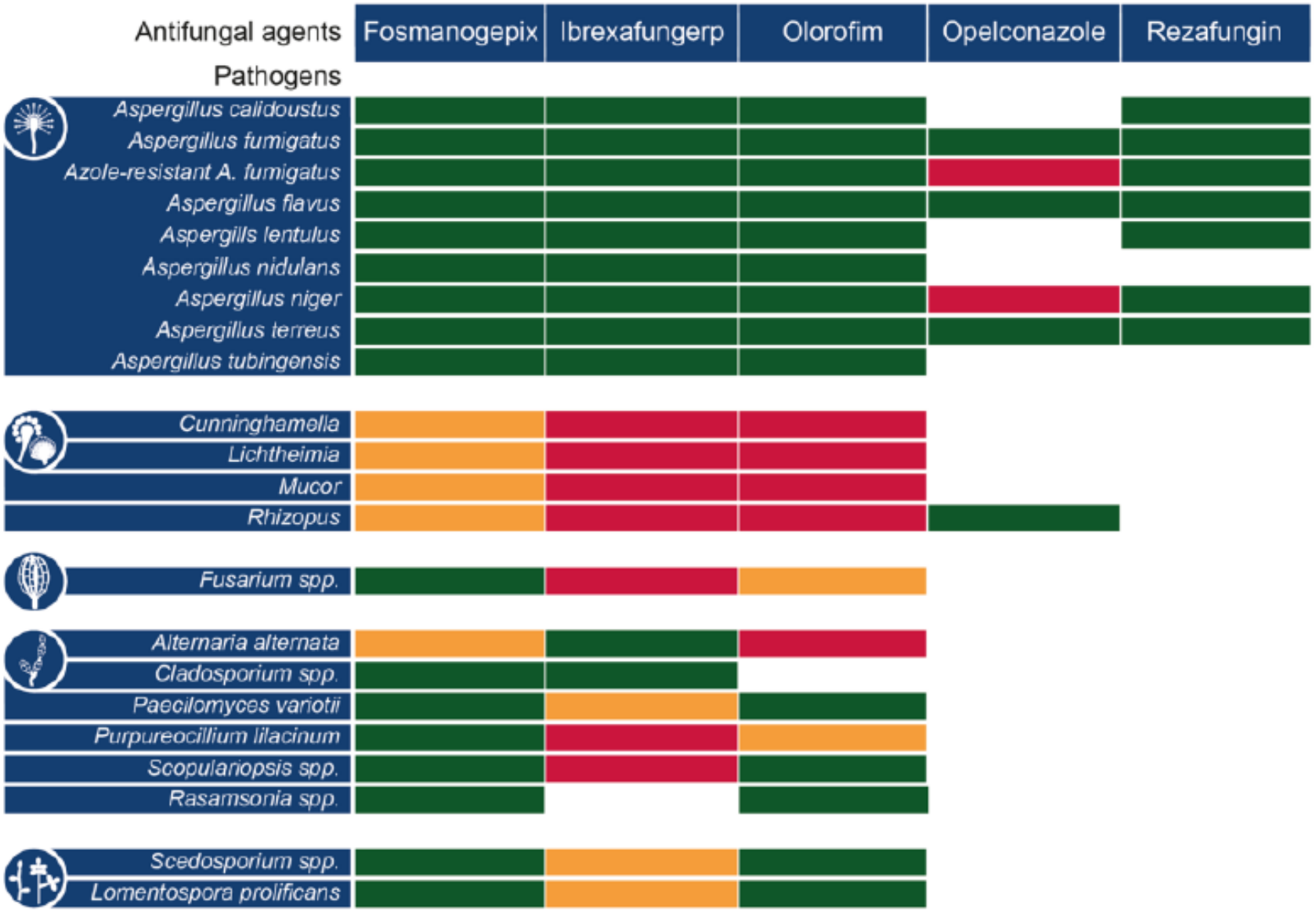
Caspofungine	**Micafungine**	**Anidulafungine**
Cyclosporine: ↑ AUC caspo Surveiller BH	*Cyclosporine*: ↑ exposition Impact minime...	
Tacrolimus: ↓ T0 20% Surveiller résiduelles	*Nifedipine*: ↑ exposition Surveiller PA	
Rifampicine: ↓ expo caspo Maintenir 70 mg/j		
Autres inducteurs: idem		

Nouveaux antifongiques



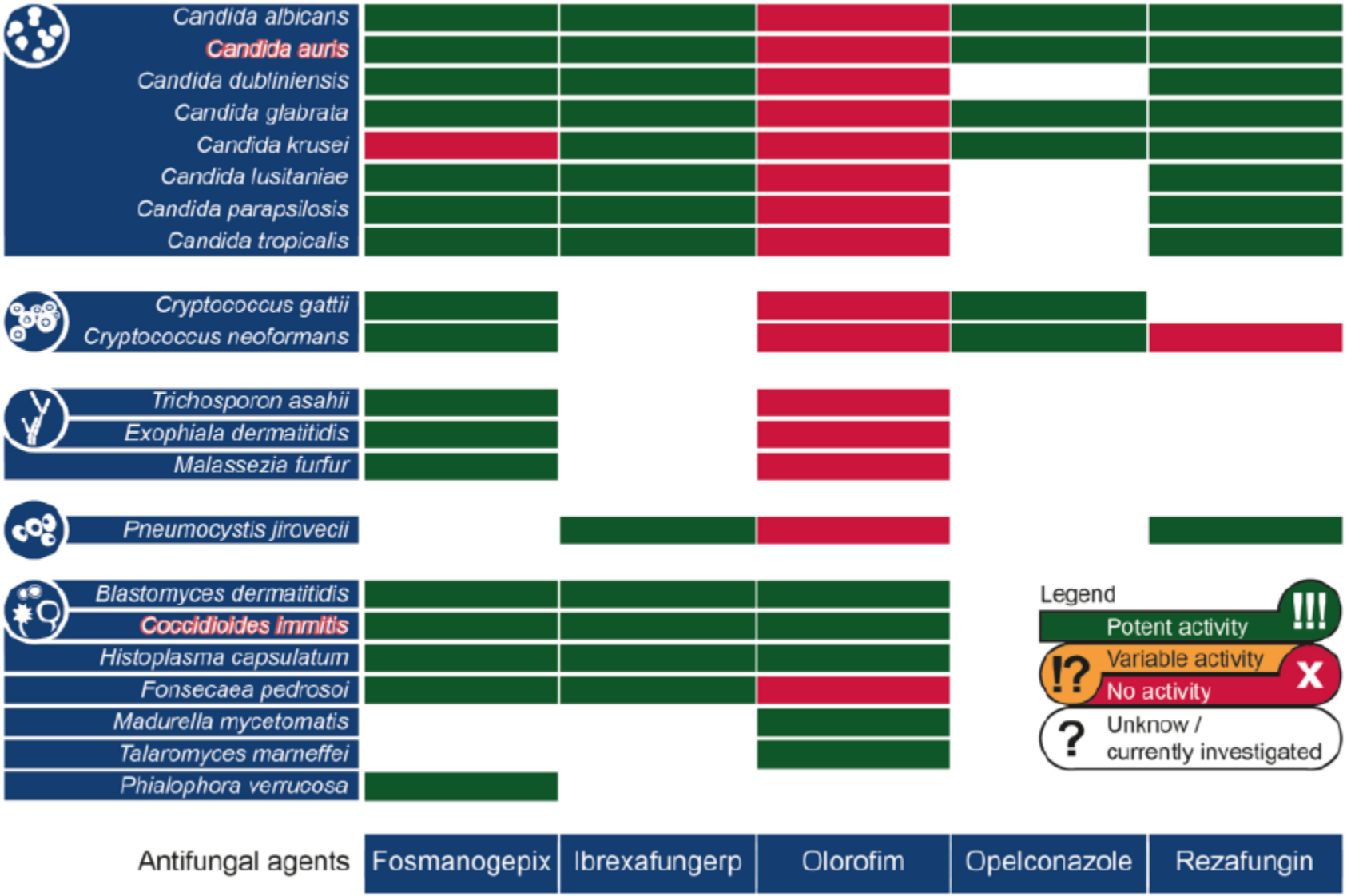
Hoenigl M *et al.* Drugs 2021

Nouveaux antifongiques: spectre



Hoenigl M *et al.* Drugs 2021

Nouveaux antifongiques: spectre



Hoenigl M *et al.* Drugs 2021

Conclusions

Polyenes: ampho B liposomale surtout
spectre très large, peu de R acquise
néphrotoxicité

Azolés: les plus utilisés
PK à connaître
nombreuses interactions
surveillance hépatique
dosages parfois

Echinocandines: surtout *Candida*
uniquement IV mais bien tolérés

Flucytosine: cryptococcose & certaines candidoses
hématotoxicité, pas de monothérapie

Nouvelles molécules prometteuses

Merci!