Comment choisir le bon anti-aspergillaire?

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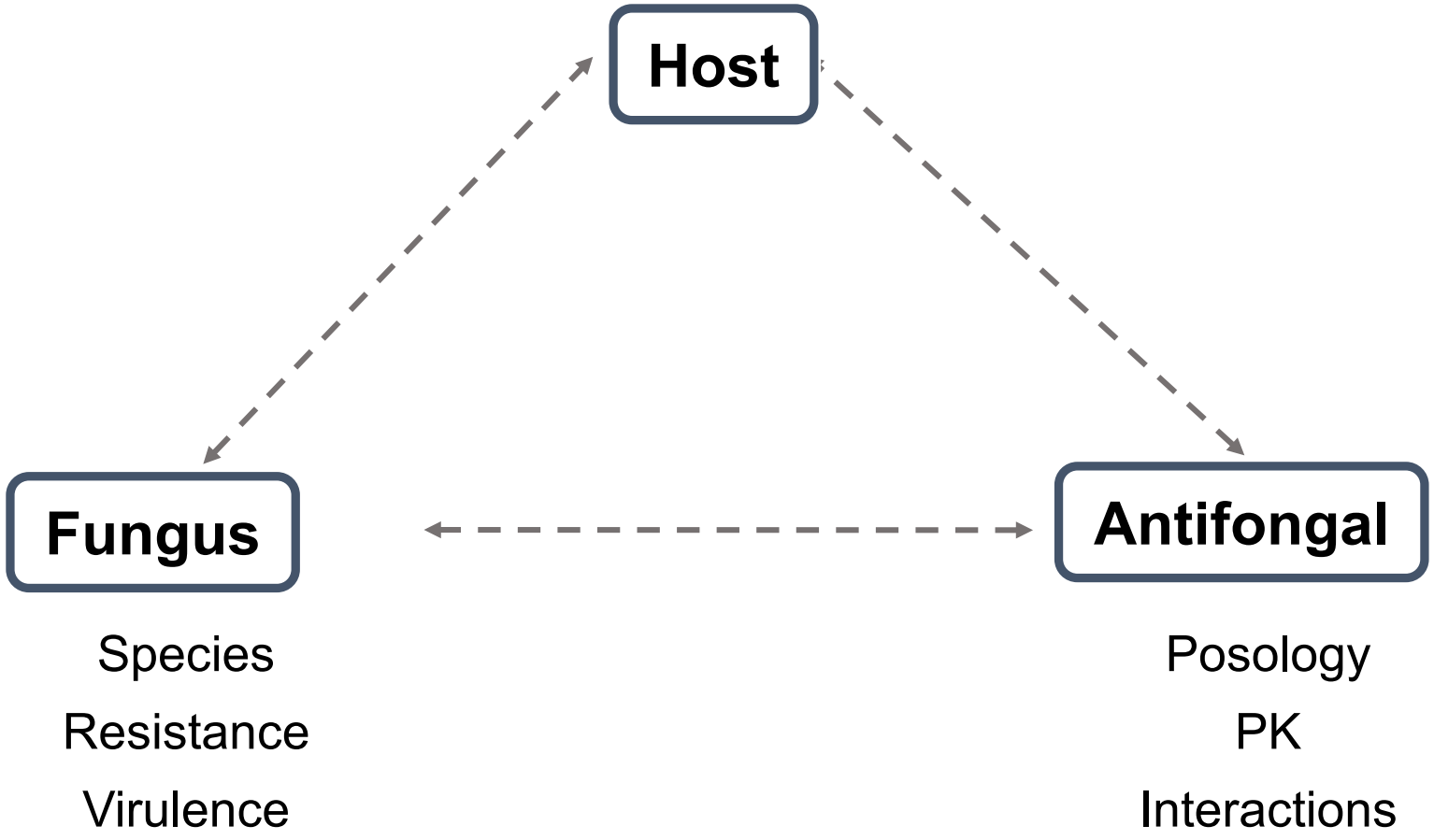
Conflits

- Gilead: travel, speaker bureau
- Basilea : travel, speaker bureau

Traitement de l’aspergillose

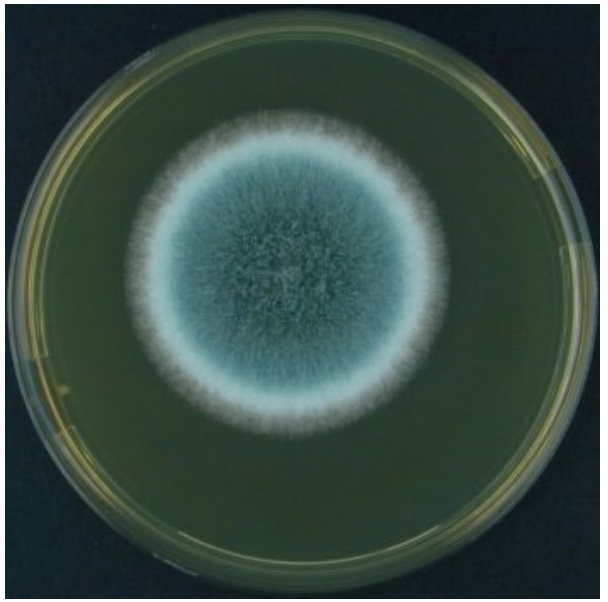


Surgery?

Polyène:
-Amphotéricine B liposomale
Triazolés:
-Itraconazole
-Voriconazole
-Posaconazole
-Isavuconazole
Echinocandines
-Caspofongine
-Micafongine

L'Aspergillus est il sensible?

- Dépend: espèce et antifongigramme
- Nécessité d'une culture



***Aspergillus* spp.**

EUCAST Antifungal Clinical Breakpoint Table v. 9.0 valid from 2018-02-12

MIC method (EUCAST standardised broth microdilution method)
Medium: RPMI1640-2% glucose, MOPS as buffer
Inoculum: Final 1x10(5) – 2.5x10(5) cfu/mL
Incubation: 48h
Reading: Visual, complete inhibition for amphotericin B and azoles (MIC), aberrant growth endpoint for echinocandins (MEC).
Quality control: *A. fumigatus* ATCC 204305, *A. flavus* ATCC 204304, *A. fumigatus* F 6919, *A. flavus* CM 1813, *C. parapsilosis* ATCC 22019 (read after 18-24 h) or *C. krusei* ATCC 6258 (read after 18-24 h).

L'Aspergillus est il sensible?

Antifungal agent	MIC breakpoint (mg/L)											
	A. flavus		*A. fumigatus*		*A. nidulans*		*A. niger*		*A. terreus*		Non-species related breakpoints[1]	
	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >
Amphotericin B	IE[2]	IE[2]	1	2	Note[3]	Note[3]	1	2	-	-	IE	IE
Anidulafungin	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE
Caspofungin	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE
Fluconazole	-	-	-	-	-	-	-	-	-	-	-	-
Isavuconazole	IE[2]	IE[2]	1	1	0.25	0.25	IE[2]	IE[2]	1	1	IE	IE
Itraconazole[4]	1	2	1	2	1	2	IE[2,5]	IE[2,5]	1	2	IE[5]	IE[5]
Micafungin	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE
Posaconazole[4]	IE[2]	IE[2]	0.125[6]	0.25[6]	IE[2]	IE[2]	IE[2]	IE[2]	0.125[6]	0.25[6]	IE	IE
Voriconazole[4]	IE[2]	IE[2]	1	2	IE	IE	IE[2]	IE[2]	IE[2]	IE[2]	IE	IE

Notes

L'Aspergillus est il sensible?

	Valeurs des CMI50 / CMI90 (µg/ml) pour les antifongiques*						
Espèce (nombre d'isolats testés)	AMB	Itra	Vori	Posa	Caspo	Mica	Terbi
Aspergillus fumigatus (n=282)	0.25/0.5	0.25/≥8	0.25/4	0.12/0.5	0.5/0.5	0.01/0.03	2/4
Aspergillus flavus (n=116)	1/2	0.12/0.25	0.5/0.5	0.12/0.25	0.25/0.5	≤0.01/0.06	0.03/0.06
Aspergillus fischeri (n=5)	1/-	0.5/-	0.5/-	0.25/-	0.5/-	0.03/-	0.12/-
Aspergillus nidulans (n=32)	2/4	0.12/0.5	0.12/0.25	0.12/0.5	0.5/4	0.01/0.06	0.12/0.5
Aspergillus quadrilineatus (n=15)	0.5/1	0.12/0.5	0.12/0.25	0.12/0.25	2/2	≤0.01/0.03	0.12/0.12
Aspergillus sublatus (n=5)	1/-	0.25/-	0.12/-	0.12/-	1/-	≤0.01/-	0.06/-
Aspergillus section *Usti* (n=37)	0.5/1	4/≥8	4/8	≥8/≥8	2/≥8	0.25/1	0.25/0.5
Aspergillus section *Nigri* (n=26)	0.25/0.5	0.5/4	0.5/1	0.25/0.5	0.25/0.5	0.01/0.5	0.12/0.5
Aspergillus tubingensis (n=11)	0.25/0.25	0.5/2	1/2	0.25/0.25	0.12/0.25	≤0.01/≤0.01	0.12/0.25
Aspergillus terreus (n=37)	4/8	0.06/0.25	0.5/0.5	0.06/0.25	0.5/2	≤0.01/0.03	0.06/0.12
Aspergillus versicolor (n=9)	1/-	0.25/-	0.25/-	0.12/-	0.5/-	0.03/-	0.25/-
Aspergillus sydowii (n=5)	2/-	0.5/-	0.5/-	0.25/-	0.12/-	≤0.01/-	0.06/-

Polyène:
-Amphotéricine B liposomale

Triazolés:
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-Voriconazole
-Posaconazole
-Itraconazole

Echinocandines

Rapport CNRMA, unpublished data

L'Aspergillus est il sensible?

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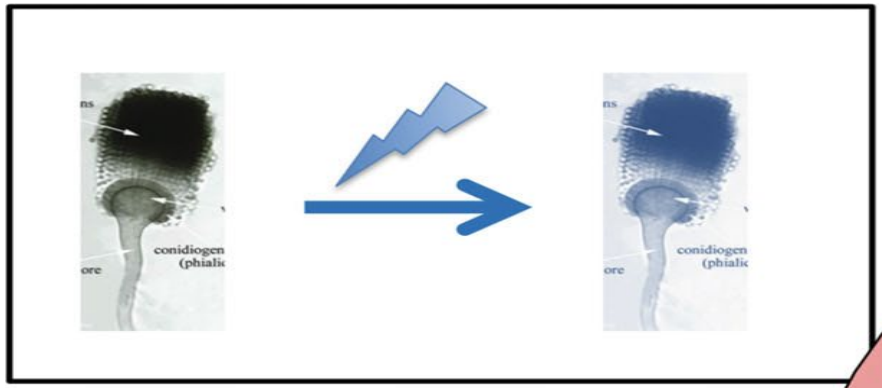
Echinocandines

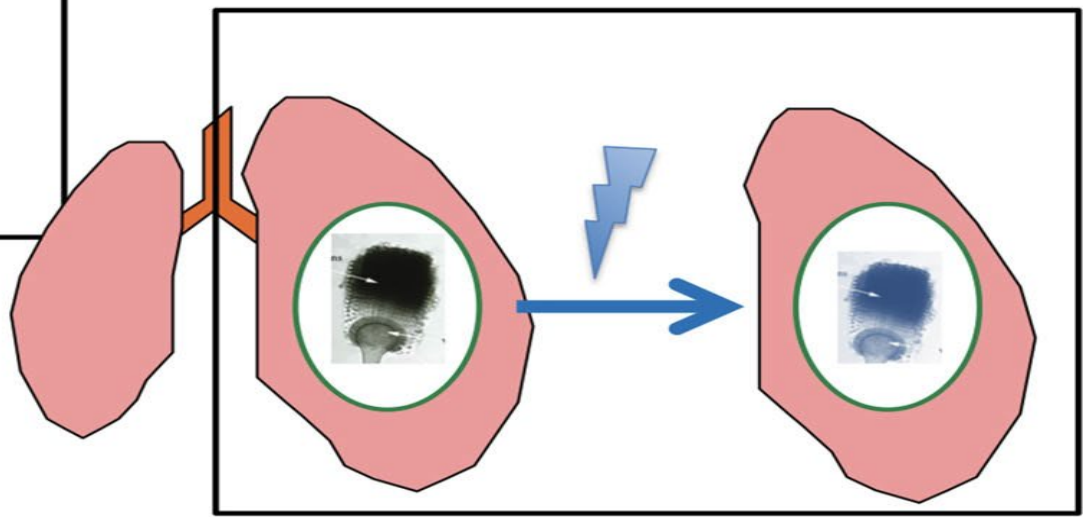
Rapport CNRMA, unpublished data

La résistance acquise d'*A. fumigatus* aux azolés

- Souches environnement (fongicides azolés)
- Duplication TR région promotrice et mutations ponctuelles
- Hyperexpression *cyp51A*
- TR34/L98H
- TR45/Y121F/T28*9A*
- Mortalité évelée

- Mutations ponctuelles *cyp51A*
- Pré exposition azolés
- Premières observations: patients avec cavités et infection chronique
- G54, M220, G138

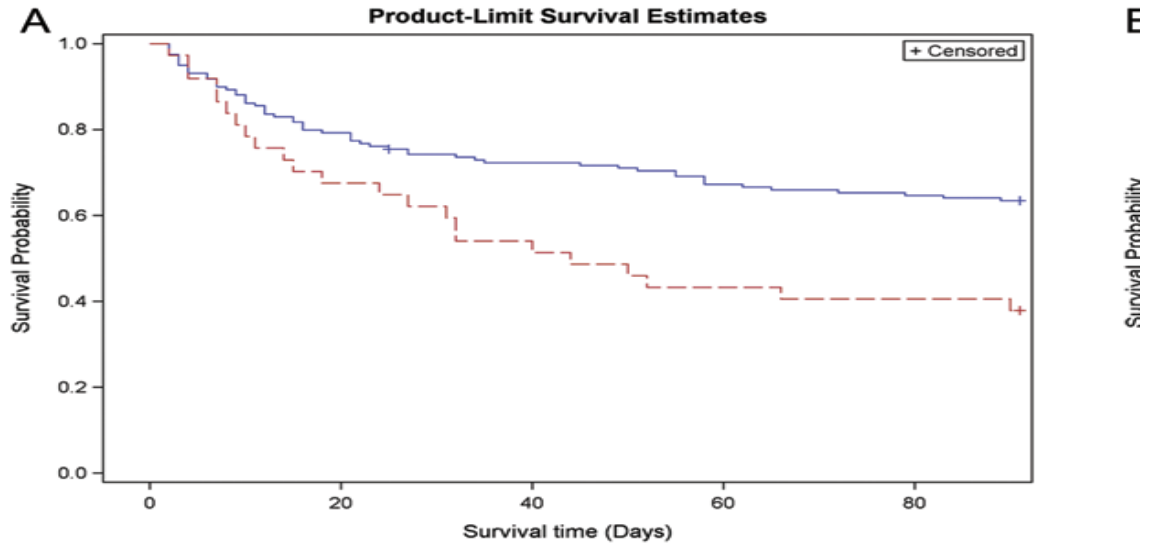




Meis J, Phil Trans B, 2016

Résistance au voriconazole et mortalité dans l'aspergillose invasive

- 2011-2015
- Netherlands
- 196 IA
- 19% vori R
- 53% HM
- 14 isolats testés isavu: R
- Mortalité patients *A. fumigatus* vori R
  - J42: 49% vs 28%
  - J90: 62% vs 3%

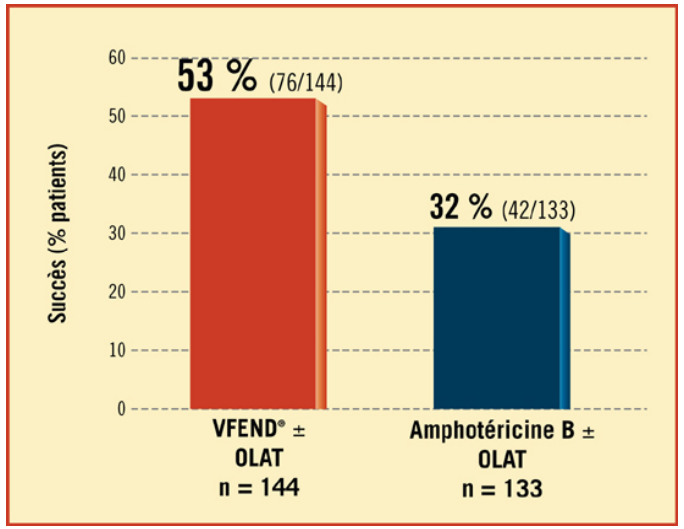


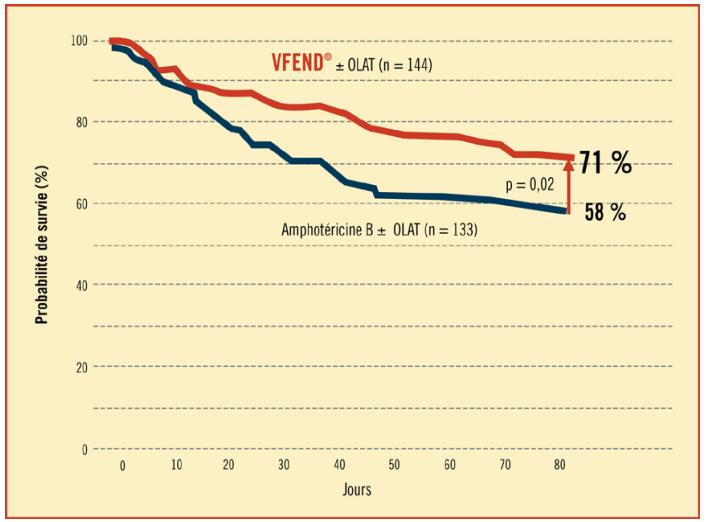
Lestrade, CID 2018

Voriconazole (1)

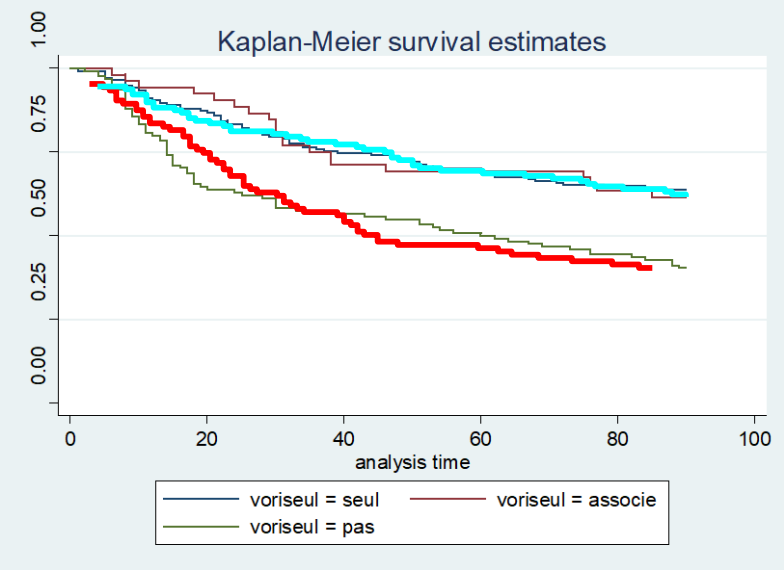
- Proven or probable AI, 1997-2000
- Voriconazole IV(n=144)
- Amphotericine B deoxycholate (n=133) 1-1,5 mg/kg/j
- S12 response

Herbrecht R, NEJM, 2002





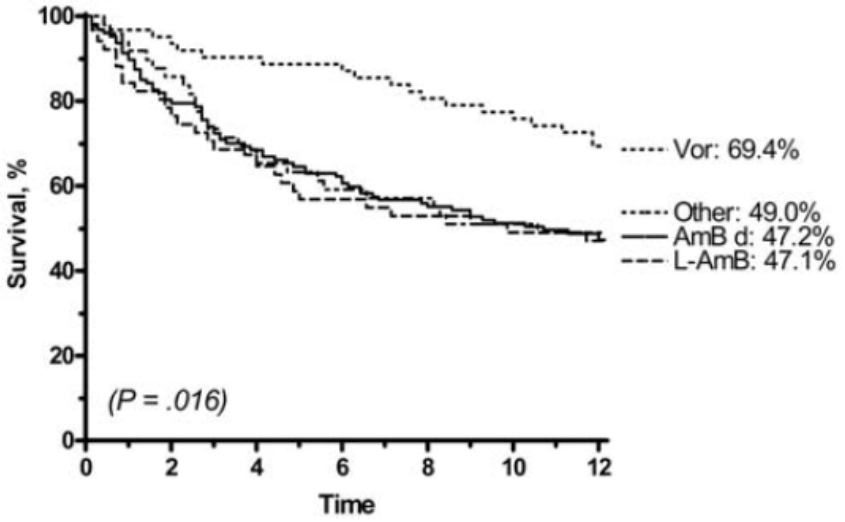
Voriconazole(2)



- **Vori +/- OLAT**
- **Ampho B +/- OLAT**

Lortholary CMI Dec 2011

- Strasbourg, retrospective
- 289 IA episodes
- Hemato-oncology
- 1997-2006



Nivoix. CID 2008

Voriconazole: suivi pharmacologique

- 52 patients with IFI
- ≤ 1 mg/L:
  - 13 (25%) patients
  - 6 (46%): failure
- > 5,5 mg/L:
  - 16 (31%)
  - 5 encephalopathy

Pascual A, CID 2008

Hépatotoxicité

Gestion de l'hepatotxicité:
-Prise en compte de la cytolyse
-Recherche autres hépatotoxiques
-Dosage
-Switch si cytolyse>3-5N

Table 6. Summary of meta-analyses for incidence of adverse events

Cut-off value (mg/L)	RR (95% CI)	No. of studies	No. of participants in experimental group	No. of participants in control group	I^2 %	*P*
Hepatotoxicity						
≤3.0 versus >3.0	0.37 (0.16, 0.83)	5	150	90	40	0.02
≤4.0 versus >4.0	0.32 (0.14, 0.74)	7	225	83	64	0.007
≤5.0 versus >5.0	0.40 (0.16, 1.03)	5	203	37	69	0.06
≤5.5 versus >5.5	0.44 (0.28, 0.70)	8	396	91	16	<0.001
≤6.0 versus >6.0	0.41 (0.28, 0.62)	7	336	51	0	<0.001
Neurotoxicity						
≤3.0 versus >3.0	0.52 (0.13, 2.01)	2	24	25	0	0.34
≤4.0 versus >4.0	0.20 (0.05, 0.74)	2	32	17	0	0.02
≤5.0 versus >5.0	0.19 (0.01, 4.14)	1	15	8	NA	0.29
≤5.5 versus >5.5	0.37 (0.21, 0.65)	4	223	68	1	<0.001
≤6.0 versus >6.0	0.40 (0.05, 3.57)	2	35	13	0	0.41
Visual disorder						
≤3.0 versus >3.0	1.64 (0.54, 5.01)	2	24	7	0	0.38
≤4.0 versus >4.0	3.88 (0.64, 23.32)	2	26	5	0	0.14
≤5.0 versus >5.0	2.93 (0.50, 17.11)	2	28	3	0	0.23
≤5.5 versus >5.5	2.64 (0.59, 11.83)	3	120	19	0	0.21
≤6.0 versus >6.0	2.93 (0.50, 4.25)	2	28	3	0	0.76

Jin H, JAC 2016

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for *CYP2C19* and Voriconazole Therapy

B Moriyama[1], A Owusu Obeng[2,3,4], J Barbarino[5], SR Penzak[6], SA Henning[1], SA Scott[2,7], JAG Agúndez[8], JR Wingard[9], HL McLeod[10], TE Klein[5], SJ Cross[11,12], KE Caudle[11] and TJ Walsh[13]

Table 1 Assignment of likely CYP2C19 phenotypes based on genotypes

Likely phenotype	Genotypes[a]	Examples of *CYP2C19* diplotypes
CYP2C19 ultrarapid metabolizer (~2–5% of patients)[b]	An individual carrying two increased function alleles	*17/*17
CYP2C19 rapid metabolizer (~2–30% of patients)[b]	An individual carrying one normal function allele and one increased function allele	*1/*17
CYP2C19 normal metabolizer[c] (~35–50% of patients)[b]	An individual carrying two normal function alleles	*1/*1
CYP2C19 intermediate metabolizer (~18–45% of patients)[b]	An individual carrying one normal function allele and one no function allele or one no function allele and one increased function allele	*1/*2, *1/*3, *2/*17[d]
CYP2C19 poor metabolizer (~2–15% of patients)[b]	An individual carrying two no function alleles	*2/*2, *2/*3, *3/*3

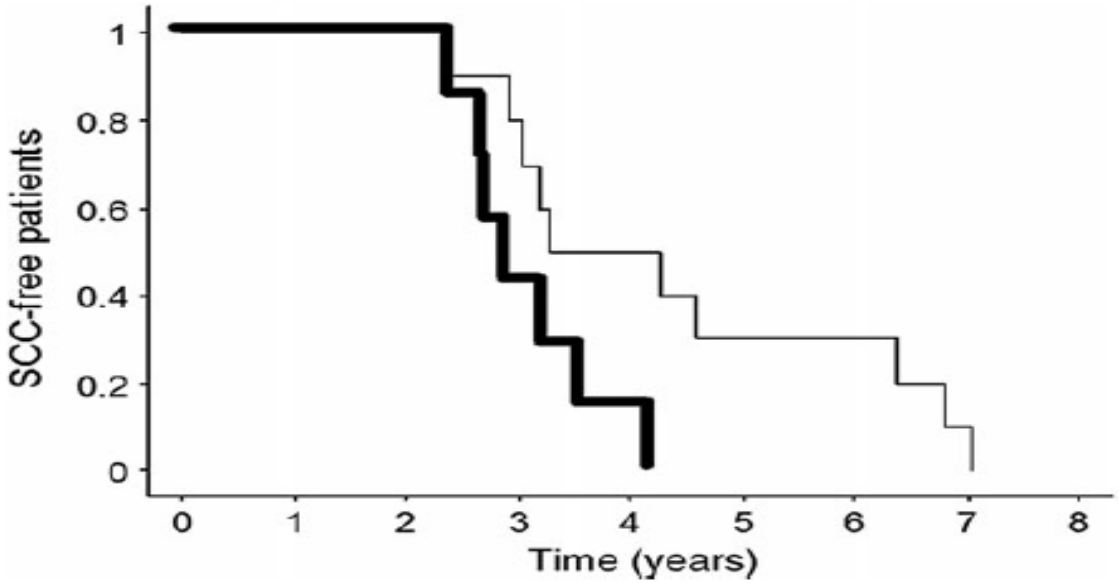
Table 2 Dosing recommendations for voriconazole treatment based on CYP2C19 phenotype for adult patients

CYP2C19 phenotype	Implications for voriconazole pharmacologic measures	Therapeutic recommendations	Classification of recommendations[a]
CYP2C19 ultrarapid metabolizer (*17/*17)	In patients for whom an ultrarapid metabolizer genotype (*17/*17) is identified, the probability of attainment of therapeutic voriconazole concentrations is small with standard dosing	Choose an alternative agent that is not dependent on CYP2C19 metabolism as primary therapy in lieu of voriconazole. Such agents include isavuconazole, liposomal amphotericin B, and posaconazole.[b]	Moderate[c]
CYP2C19 rapid metabolizer (*1/*17)	In patients for whom a rapid metabolizer genotype (*1/*17) is identified, the probability of attainment of therapeutic concentrations is modest with standard dosing	Choose an alternative agent that is not dependent on CYP2C19 metabolism as primary therapy in lieu of voriconazole. Such agents include isavuconazole, liposomal amphotericin B, and posaconazole.[b]	Moderate
CYP2C19 normal metabolizer	Normal voriconazole metabolism	Initiate therapy with recommended standard of care dosing[b]	Strong

Clinical Pharmacology and therapeutics, 2017

Complications dermatologiques

- 2002-2012
- 19 squamous cell carcinoma
- 35 months after treatment start
- 1st year: phototoxicity
- 2nd year: actinic keratosis
- 3rd year: squamous cell carcinoma



Transplantés

Dermatological surveillance

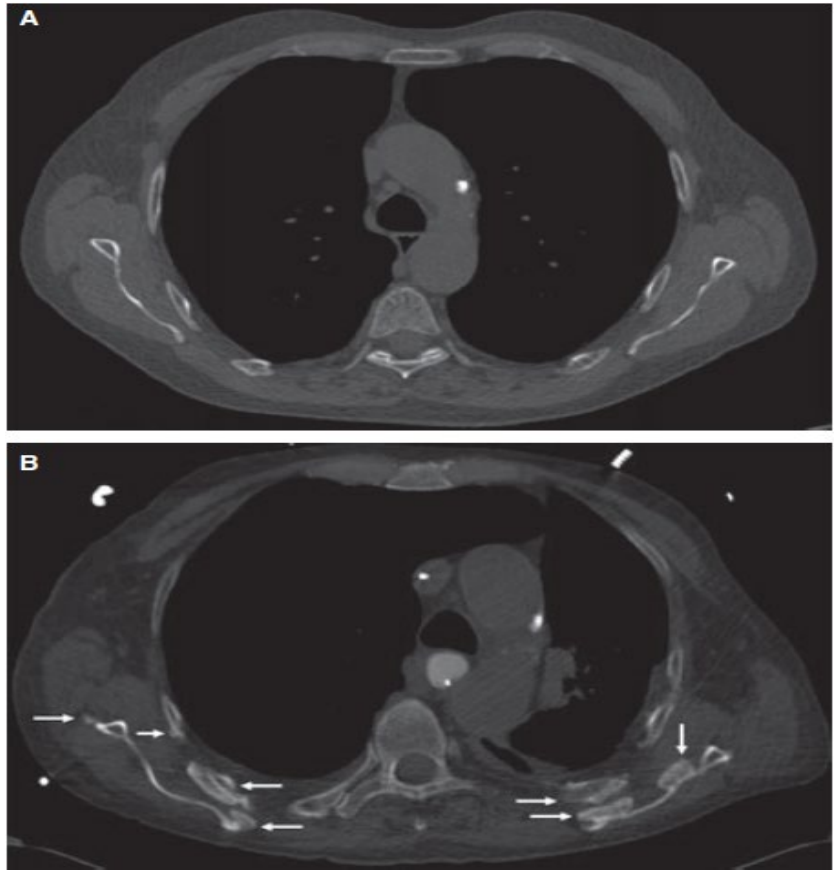
Epaulard O, CID 2013

Neuropathies

- 220 patients traited with azoles
- 10% neuropathy
- M4
- 9% under voriconazole
- 3% under posaconazole
- 2 non reversible episodes
    - Baxter, JAC 2011

Periostitis and voriconazole

- Voriconazole: trifluoré
- Pain
- High PA and fluor
- Periostitis (scinti)



Tedja R, TID, 2013, Moon W, CID 2014

Isavuconazole

- Large spectrum azole
- IV and PO
- No cyclodextrine
- In vitro activity: Candida, Aspergillus, Mucorales
- 200mg X 3/d J1-J2 then 200mg/d
- Biodisponibility 98%

Table 2
Total numbers and MIC distributions for *Aspergillus* species

	n (%)	Isavuconazole MIC (mg/L)				Voriconazole (mg/L)			
		MIC range	MIC_{50}	ECOFF	MIC > ECOFF (%)	MIC range	MIC_{50}	ECOFF	MIC > ECOFF (%)
A. fumigatus sensu stricto	211 (69.0)	≤0.125–>16	1	2	13.7	≤0.125–>16	0.5	1	15.2

Miceli, CID 2015, Astvad, CMI 2017

Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by *Aspergillus* and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial

Johan A Maertens, Issam I Raad, Kieren A Marr, Thomas F Patterson, Dimitrios P Kontoyiannis, Oliver A Cornely, Eric J Bow, Galia Rahav, Dionysios Neofytos, Mickael Aoun, John W Baddley, Michael Giladi, Werner J Heinz, Raoul Herbrecht, William Hope, Meinolf Karthaus, Dong-Gun Lee, Olivier Lortholary, Vicki A Morrison, Ilana Oren, Dominik Selleslag, Shmuel Shoham, George R Thompson III, Misun Lee, Rochelle M Maher, Anne-Hortense Schmitt-Hoffmann, Bernhardt Zeiher, Andrew J Ullmann

Maertens J, Lancet 2016

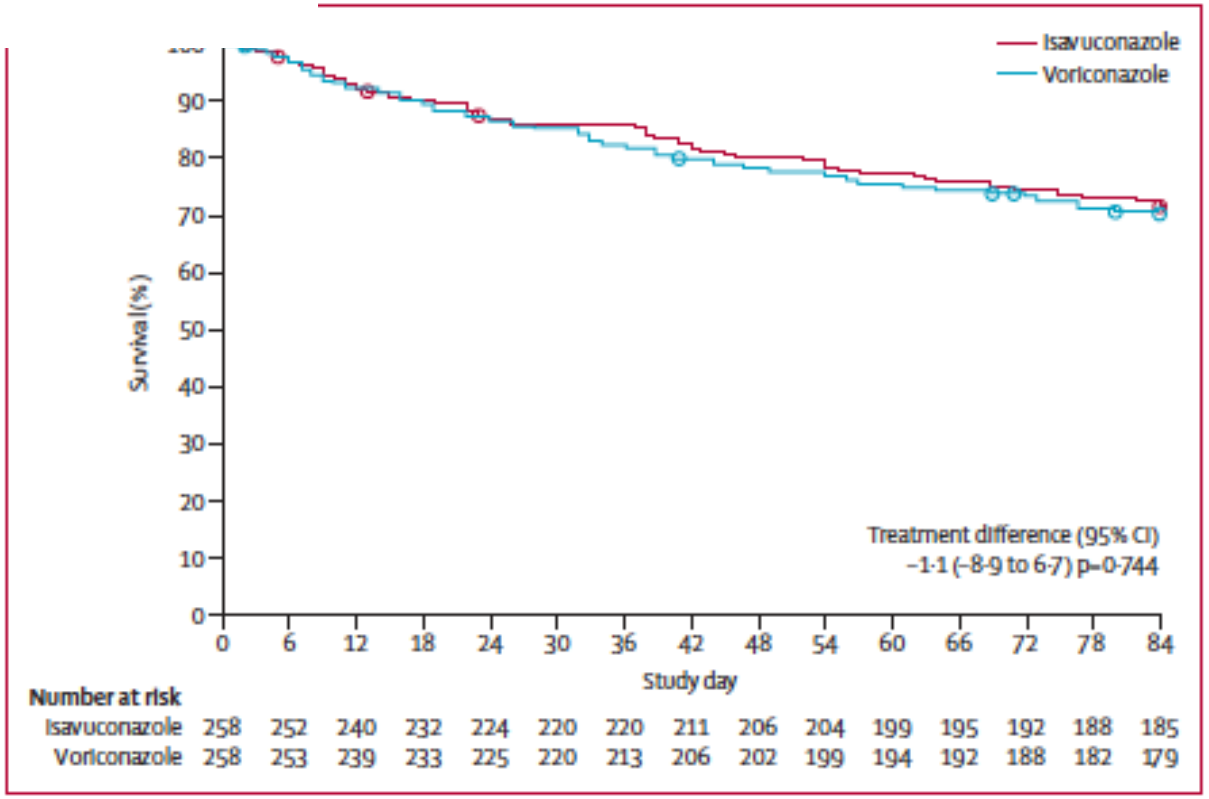


Figure 2: **Survival from first dose of study drug to day 84**
Patients were censored on the day of their last known survival status, represented by the circles. Figure shows data for ITT population. ITT=intention to treat; all randomised patients who received study drug.

Isavuconazole: tolerance

	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

Pas de TDM du voriconazole

Maertens J, Lancet 2016

Gestion des triazolés

	Isavuconazole	Voriconazole	Posaconazole (cp)
/d	1/j	2/j	/j
Food	Indifférent	A jeun	Indiffèrent
Renal failure	Pas d'ajustement de dose	Pas d'ajustement de dose Forme IV Creat >250	Pas d'ajustement de dose
Liver failure	Pas d'ajustement de dose	Ajustement	Ajustement
Through level	2-5 mg/L	1-5 mg/L	1-2.5mg/L
QT	Shortened	Prolonged	Prolonged

Townsend RW Eur J Clin Pharmacol 2017, Desai A, AAC, 2016

Interactions

	Voriconazole	Isavuconazole	Posaconazole cp
Tacrolimus	Diminution du tacro de 60%	Diminution de 30% ou suivi rapproché	Diminution du tacro de 50%
Sirolimus	Contre indiqué	Diminution de 30% ou suivi rapproché	Pas de données suffisante

⊖ : rifampicine, statines, AVK

Groll A, Clinical Pharmacology in Drug Development, 2017
KieuV, TID, 2018
Collins J, 2019

Amphotéricine B liposomale

- Ambiload study
- Probable or proven IFD (95% AI)

- L-AmB 10 mg/kg vs 3 mg/kg 2S then 3 mg/kg
- 10 mg/kg (n=94), response =46%
- 3 mg/kg (n=107), response= 50%
- More nephrotoxicity and hypokaliemia in 10 mg/kg

Cornely OA, CID 2007

Caspofungine

Caspofungin first-line therapy for invasive aspergillosis in allogeneic hematopoietic stem cell transplant patients: an European Organisation for Research and Treatment of Cancer study

R Herbrecht[1], J Maertens[2], L Baila[3], M Aoun[4], W Heinz[5], R Martino[6], S Schwartz[7], AJ Ullmann[8], L Meert[3], M Paesmans[3], O Marchetti[9], H Akan[10], L Ameye[4], M Shivaprakash[11] and C Viscoli[12], for the Infectious Diseases Group of the EORTC

Table 2 Response rates at the end of therapy in the modified intent-to-treat patient population ($n = 24$)

Response	*End of caspofungin therapy* n *(%)*	*At week 12* n *(%)*
Success		
Complete response	0	4 (17)
Partial response	10 (42)	4 (17)
Failure		
Stable disease	1 (4)	1 (4)
Disease progression	12 (50)	2 (8)
Not done	1 (4)	1 (4)
Death before assessment	—	12 (50)

-IA allogenic HSCT
-Caspofungin: 1st line
-N=24 patients
-Median treatment duration 24 days

-Survival: W6: 79% W12: 50% (underlying condition)

-Response: evaluated with stringent criteria: 50% nodule regression EOT

-Comparaison:
LamB: 47% favorable outcome
Vori: 32% favorable outcome

BMT 2010

Annals of Internal Medicine

ORIGINAL RESEARCH

Combination Antifungal Therapy for Invasive Aspergillosis

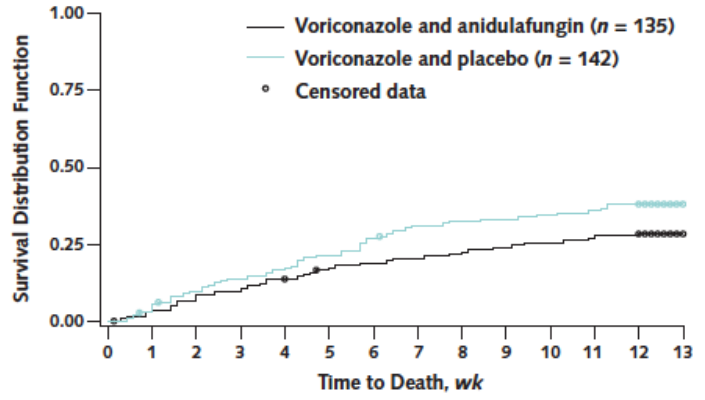
A Randomized Trial

Kieren A. Marr, MD; Haran T. Schlamm, MD; Raoul Herbrecht, MD; Scott T. Rottinghaus, MD; Eric J. Bow, MD, MSc; Oliver A. Cornely, MD; Werner J. Heinz, MD; Shyla Jagannatha, PhD; Liang Piu Koh, MBBS; Dimitrios P. Kontoyiannis, MD; Dong-Gun Lee, MD; Marcio Nucci, MD; Peter G. Pappas, MD; Monica A. Slavin, MD; Flavio Queiroz-Telles, MD, PhD; Dominik Selleslag, MD; Thomas J. Walsh, MD; John R. Wingard, MD; and Johan A. Maertens, MD, PhD

Ann Intern Med. 2015;162:81-89.

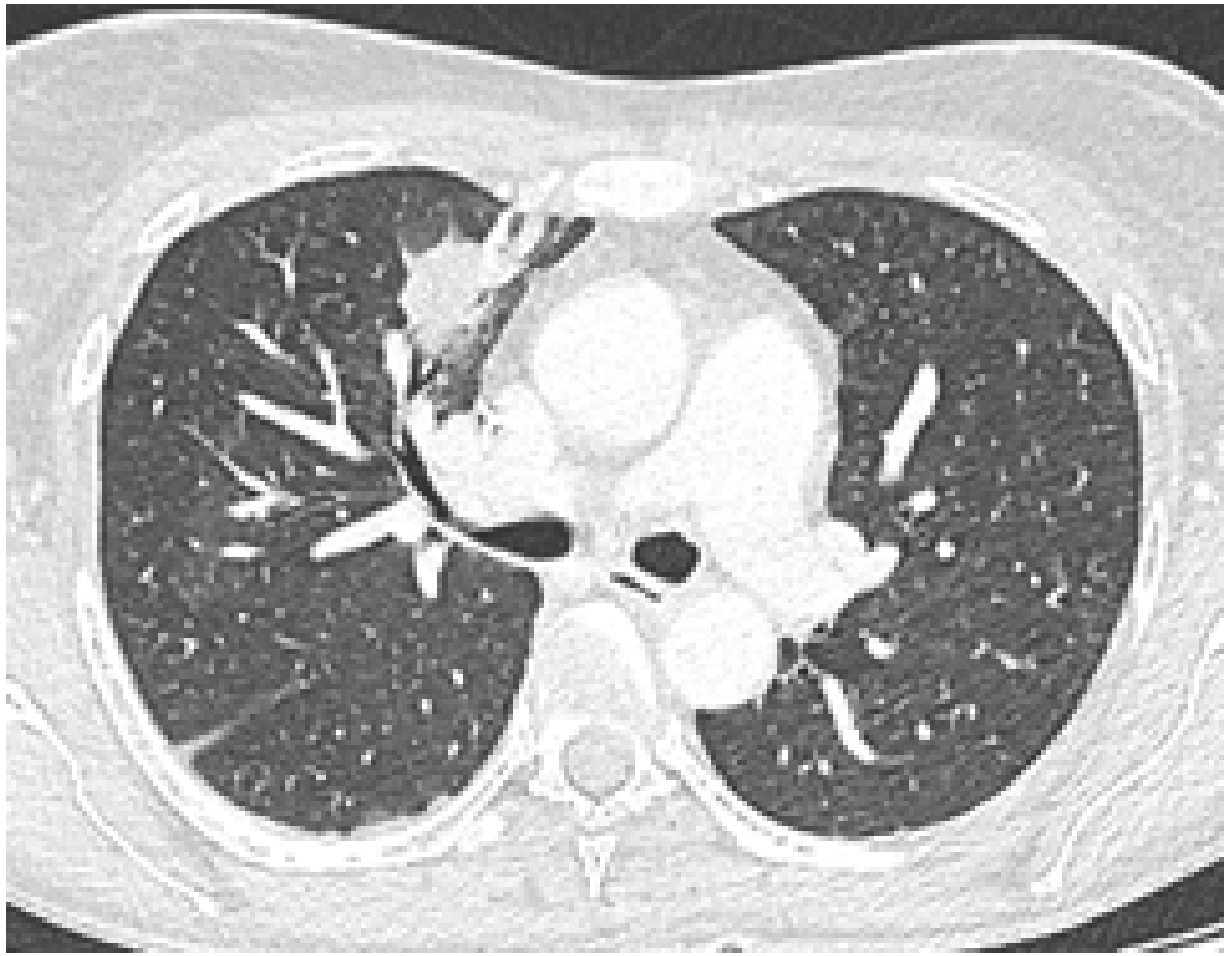
- Randomized, double-blind, placebo-controlled multicenter trial.
- voriconazole and anidulafungin vs voriconazole monotherapy for treatment of IA.
- 454 patients with HM or HCT suspected or documented IA
- Primary analysis: MITT 277 patients in whom IA was confirmed
- Mortality W6 : combination: 19.3% vs monotherapy 27.5% (P = 0.087)
- 78.7% had IA diagnosis established by CT + GM : W6 mortality combination: 15.7% vs. 27.3% (P = 0.037).

Figure 2. Cumulative incidence of death in the modified intention-to-treat population.



Log-rank, $P = 0.086$.

Quel traitement de première ligne pour l'aspergillose pulmonaire invasive?



ECIL-6 recommandations for first-line treatment of invasive aspergillosis

	Grade	Comments
Voriconazole[a]	A I	Daily dose: 2x6 mg/kg on day 1 then 2x4 mg/kg (initiation with oral therapy: C III)
Isavuconazole	A I	As effective as voriconazole and better tolerated
Liposomal amphotericin B	B I	Daily dose: 3 mg/kg
Amphotericin B lipid complex	B II	Daily dose: 5 mg/kg
Amphotericin B colloidal dispersion	C I	Not more effective than d-AmB but less nephrotoxic
Caspofungin	C II	
Itraconazole	C III	
Combination voriconazole[a] + anidulafungin	C I	
Other combinations	C III	
Recommendation against use		
Amphotericin B deoxycholate	A I	Less effective and more toxic

[a]Monitoring of serum levels is indicated. In the absence of sufficient data for first-line monotherapy, anidulafungin, micafungin and posaconazole have

Tissot F, Haematologica 2017;102:433-444

ESCMID-ECMM-ERS guidelines for first line targeted therapy of pulmonary disease

Intervention	SoR	QoE	Comment
Isavuconazole	**A**	**I**	**DIII if mould active azole prophylaxis** **Fewer adverse events than voriconazole**
Voriconazole	**A**	**I**	**DIII if mould active azole prophylaxis**
L-AmB	B	II	
Combination of voriconazole + anidulafungin	C	I	No significant difference compared to voriconazole In GM-positive (subgroup) better survival
Itraconazole	C	III	DIII if mould active azole prophylaxis
Caspofungin	C	II	
ABLC	C	III	
Micafungin	C	III	
ABCD	D	I	
Conventional AmB	D	I	
Other combination	D	III	

Ullmann A, CMI 2018. Suppl 1: e1-e38

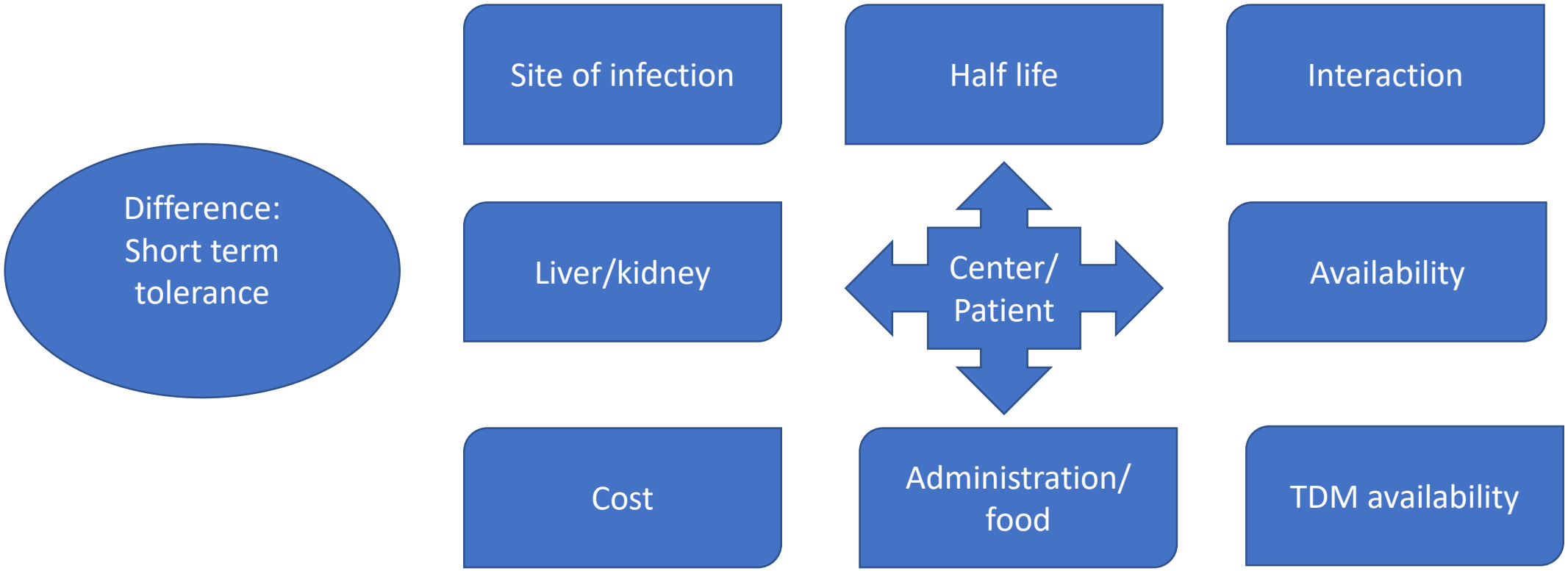
IDSA recommendations for Invasive pulmonary aspergillosis treatment

		Strength of recommandation	Quality
Primary therapy	**Voriconazole**	**Strong**	**High**
Alternative	L-AmB	Strong	Moderate
	Isavuconazole	**Strong**	**Moderate**
	Other lipid formulation	Week	Low
Selected patients with documented IPA	Voriconazole and en echinocandin	Weak	Moderate
Not recommended	Echinocandin	Strong	Moderate

Patterson T. Clin Infect Dis 2016;63:433-42.

Quel azolé choisir?

Out of the context of azole antimould prophylaxis



Voriconazole dose et formulation

Guidelines		
ECIL-6	2 x 6 mg/kg on day 1 then 2 X 4 mg/kg	Initiation with oral therapy CIII
ESCMID/ECMM/ERS	2 x 6mg/kg IV (oral 400 mg bid) D1 then 2 x 4 mg/kg IV (oral 200-300mg) bid	Initiation with oral therapy CIII Consider switching to oral therapy in stable and pharmacokinetically reliable patients.
IDSA	2 x 6 mg/kg IV on day 1 Then 2 x 4 mg/kg IV oral therapy can be used at 200–300 mg bid or weight based dosing on a mg/kg basis	

Start with voriconazole IV
D1 6mg/kg bid then 4 mg/kg bid
When oral therapy 4 mg/kg bid

Tissot F, Haematologica 2017;102:433-444, Patterson T. Clin Infect Dis 2016;63:433-42, Ullmann A, CMI 2018. Suppl 1: e1-e38

Salvage therapy?

- Failure definition:
  - Documentation: coinfection?
  - CT progression in not synonymous to failure
  - GM monitoring
  - Host status
  - Azoles trough level
  - Aspergillus MIC
- Rule:
  - Switch to another drug class

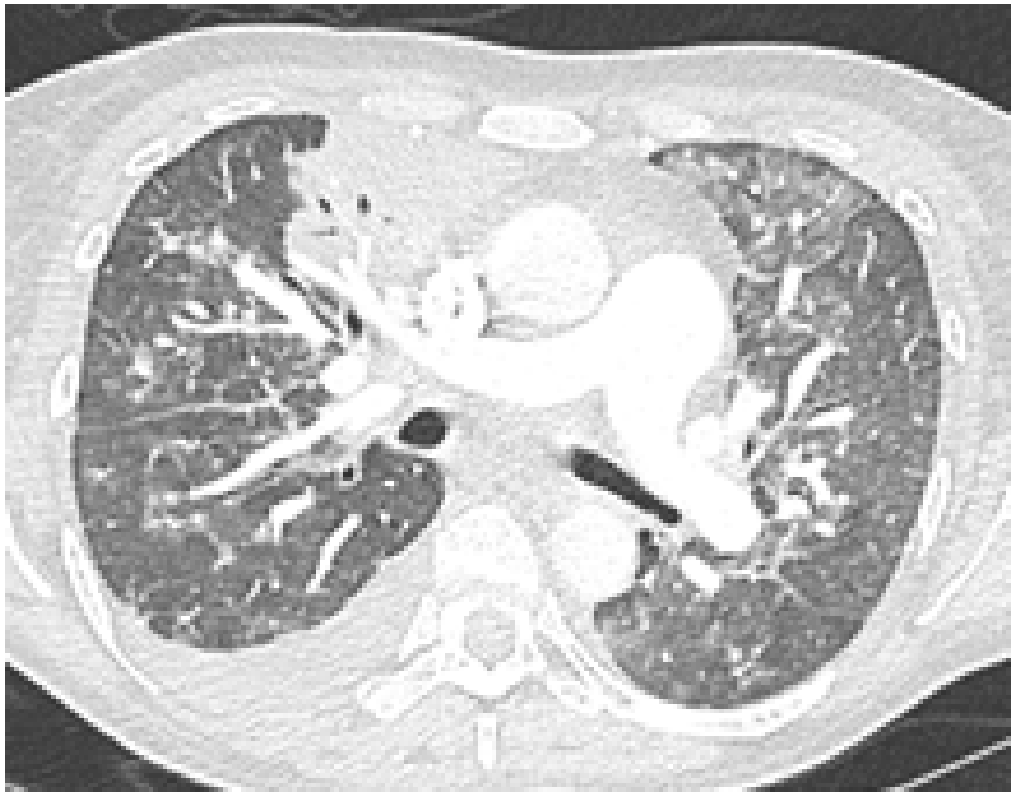


Table 8. ECIL-6 recommendations for salvage therapy of invasive aspergillosis.

	Grade	Comments
Liposomal amphotericin B	B II	No data on voriconazole failure
Amphotericin B lipid complex	B II	No data on voriconazole failure
Caspofungin	B II	No data on voriconazole failure
Itraconazole	C III	Insufficient data
Posaconazole[a]	B II	No data on voriconazole failure
Voriconazole[a]	B II	If not used in first-line
Combination	B II	Various studies and conflicting results

[a]Monitoring of serum levels is indicated, especially if posaconazole oral suspension is used.

Tissot F, Haematologica 2017;102:433-444, Patterson T. Clin Infect Dis 2016;63:433-42, Ullmann A, CMI 2018. Suppl 1: e1-e38

Extra pulmonary aspergillosis

Location		AF	SoR	QoE	Surgery
CNS	IDSA	Vori	Strong	Moderate	
	IDSA	Alternative: L AmB	Strong	Moderate	
	ESCMID/ECMM/ERS	Vori	A	II	
	ESCMID/ECMM/ERS	AmB lipid formulation	B	III	
	ESCMID/ECMM/ERS	Posa, itra, echino	D	III	
Endophthalmitis	IDSA	Systemic vori + intravitreal vori or AmB	Strong	Low	
	ESCMID/ECMM/ERS	Vori L-AmB	A A	II II	
Invasive sinusitis	IDSA	Vori or L-AmB	Strong	Moderate	
Endocarditis	IDSA	Vori or L-AmB	Strong	Low	+ Surgery
Osteomyelitis or arthritis	IDSA	Voriconazole	Strong	Moderate	+ Surgery

Patterson T. Clin Infect Dis 2016;63:433-42, Ullmann A, CMI 2018. Suppl 1: e1-e38

Posaconazole comprimés et aspergillose chronique

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doi:10.1093/jac/dky539 Advance Access publication 26 December 2018

Journal of Antimicrobial Chemotherapy

Therapeutic drug monitoring and adverse events of delayed-release posaconazole tablets in patients with chronic pulmonary aspergillosis

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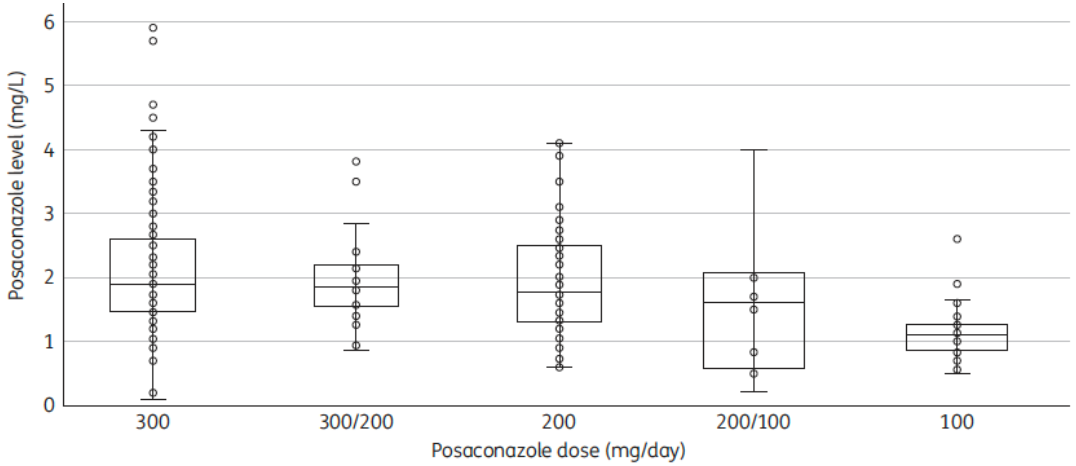

Table 2. Risk factors for developing AEs (grade ≥2) on posaconazole tablets

Risk factor	AEs	No AEs, *n* (%)	*P* (univariate)	*P* (multivariate)
Dose (mg), *n* (%)				
300	69 (34.3)	132 (65.7)	reference	reference
300/200[a]	0 (0)	30 (100)	0.998	0.998
200	19 (16.2)	98 (83.8)	0.001	**0.006**
200/100[b]	2 (25)	6 (75)	0.594	0.987
100	12 (27.9)	31 (72.1)	0.43	0.837

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ORIGINAL ARTICLE

WILEY mycoses

Isavuconazole et aspergillose chronique

Isavuconazole and voriconazole for the treatment of chronic pulmonary aspergillosis: A retrospective comparison of rates of adverse events

Felix Bongomin[1,2] | Niamh Maguire[3] | Caroline B. Moore[3] | Timothy Felton[2,4] | Riina Rautemaa-Richardson[2,3,5]

Mycoses 2019

- CPA
- 21 patients with voriconazole
  - 86% AE
- 20 patients with isavuconazole
  - 60% AE

Conclusion

- Voriconazole et isavuconazole en première ligne dans les localisations pulmonaires
- Voriconazole si localisation cérébrale
- Dosages à répéter
- Pharmacogénétique
- Toxicité à court et long terme
- Interactions
- Limiter les traitements prolongés par voriconazole (switch)
- Nouvelles molécules en cours d’étude