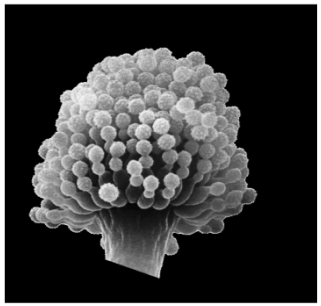
27ème JRPI - Session Champignons
12 octobre 2021

Bithérapie anti-aspergillaire
Quand et laquelle ?

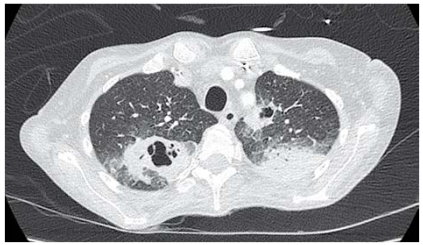


Dr. Fanny Vuotto

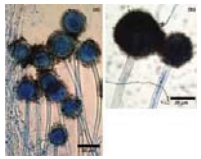
Service de Maladies infectieuses
Centre Hospitalier Universitaire de Lille
fanny.vuotto@chru-lille.fr

Bithérapie ?

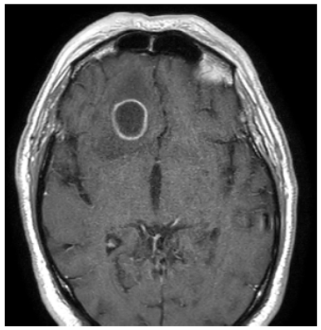
Gravité ?



Résistance aux AF ?



Terrain ?



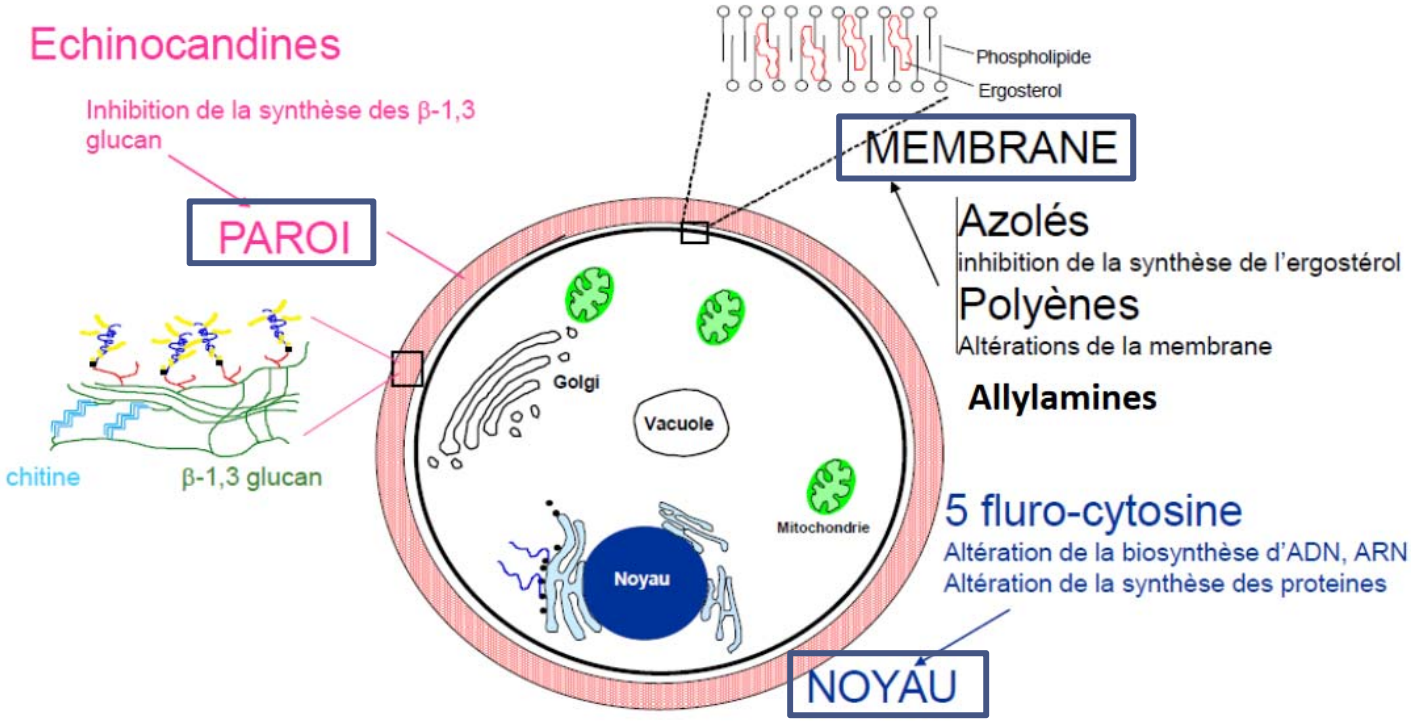
Site d'accès difficile ?

Preuve de la supériorité d'une association dans le traitement initial ?

Echec du traitement par monothérapie ?

Rationnel

Associer 2 molécules avec cibles différentes ➡ effet additif/synergique



ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 2005, p. 3572–3574
0066-4804/05/$08.00+0 doi:10.1128/AAC.49.8.3572–3574.2005

In Vitro Synergy Testing of Anidulafungin with Itraconazole, Voriconazole, and Amphotericin B against *Aspergillus* spp. and *Fusarium* spp.

Annie Philip, Zekaver Odabasi, Jose Rodriguez, Victor L. Paetznick, Enuo Chen, John H. Rex,† and Luis Ostrosky-Zeichner*

Vol. 49, No. 8

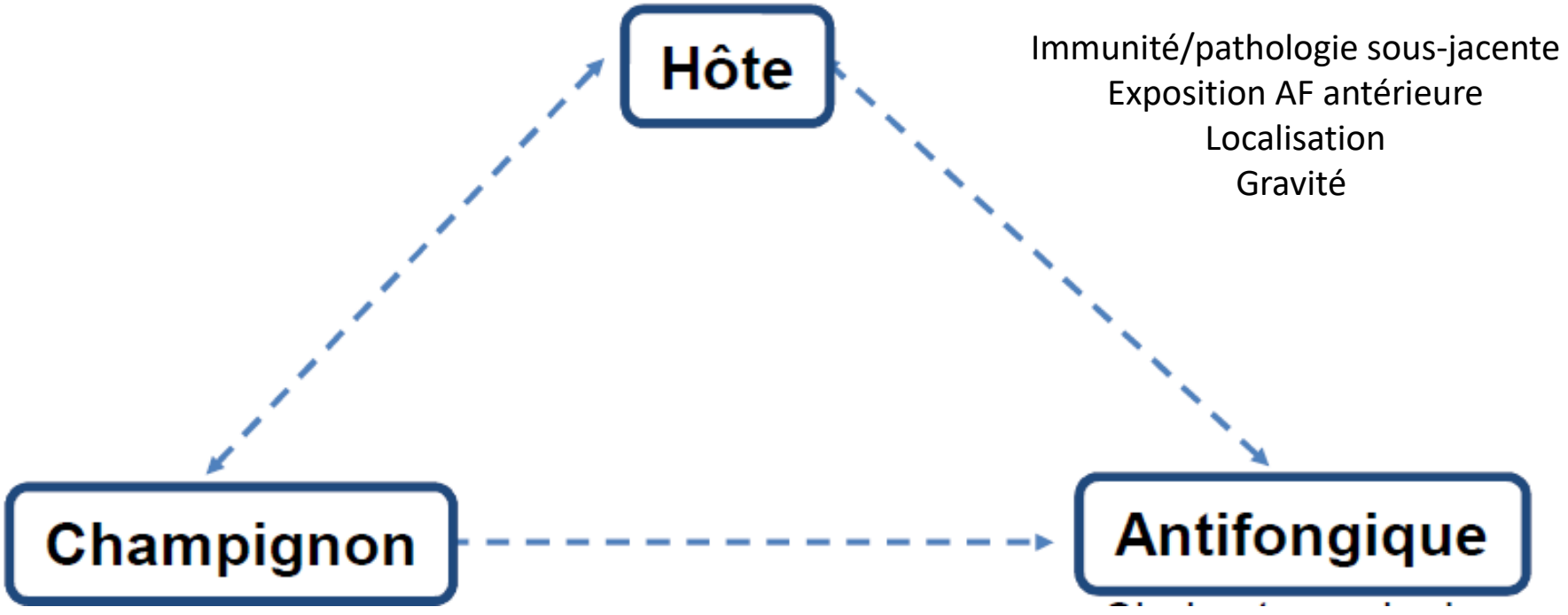
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 2002, p. 2564–2568
0066-4804/02/$04.00+0 DOI: 10.1128/AAC.46.8.2564–2568.2002

Vol. 46, No. 8

Efficacy of Caspofungin Alone and in Combination with Voriconazole in a Guinea Pig Model of Invasive Aspergillosis

William R. Kirkpatrick,[1]* Sofia Perea,[1] Brent J. Coco,[1] and Thomas F. Patterson[1,2]

Rationnel


Hôte
Immunité/pathologie sous-jacente
Exposition AF antérieure
Localisation
Gravité
Champignon
Espèce
Résistance primaire/secondaire
Antifongique
Choix
Posologie
PK/PD
Dosage
Interactions
Précocité ttt

Données cliniques

- **Des données cliniques hétérogènes, limitées et pas toujours significatives**

Marr CID 2004	Vorico + caspo vs vorico	47 Hémopathies	Rétrospectif	Meilleure survie S12
Singh Transpl 2006	Vorico + caspo vs AmphoB	40 SOT	Prospectif, ttt initial	Meilleure survie car moins d'IR…
Kontoyiannis TID 2009	Mica vs mica + SOC	98 HSCT	Rétrospectif, 83/98 sauvetage	NS
Raad JAA 2015	Vorico + caspo vs vorico	181 Hémopathies	Sauvetage	NS

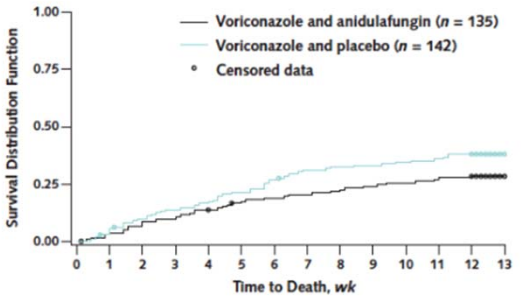
- **Combination Antifungal Therapy for Invasive Aspergillosis : A randomised Trial**

Marr An int Med 2015

Etude randomisée en double aveugle multicentrique
Vorico versus Vorico + anidulafungine
454 patients avec hémopathies avec AI probable/prouvée

Mortalité S6 :
19,3% combinaison vs 27,5% monothérapie (p=0,087)

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



Log-rank, $P = 0.086$.

Bithérapie d'emblée?

Clinical Infectious Diseases

IDSA GUIDELINE

Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America

Thomas F. Patterson,[1,a] George R. Thompson III,[2] David W. Denning,[3] Jay A. Fishman,[4] Susan Hadley,[5,b] Raoul Herbrecht,[6] Dimitrios P. Kontoyiannis,[7] Kieren A. Marr,[8] Vicki A. Morrison,[9] M. Hong Nguyen,[10] Brahm H. Segal,[11] William J. Steinbach,[12] David A. Stevens,[13] Thomas J. Walsh,[14] John R. Wingard,[15] Jo-Anne H. Young,[16] and John E. Bennett[17,a]

28. Combination antifungal therapy with voriconazole and an echinocandin may be considered in select patients with documented IPA (*weak recommendation; moderate-quality evidence*).

ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients

Frederic Tissot,[1] Samir Agrawal,[2] Livio Pagano,[3] Georgios Petrikkos,[4] Andreas H. Groll,[5] Anna Skiada,[6] Cornelia Lass-Flörl,[7] Thierry Calandra,[1] Claudio Viscoli[8] and Raoul Herbrecht[9]

Haematologica 2017
Volume 102(3):433-444

Table 7. ECIL-6 recommendations 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

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Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Diagnosis and management of *Aspergillus* diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline

Targeted therapy of pulmonary disease—first line

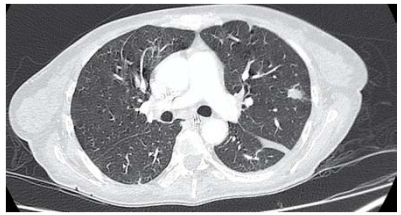
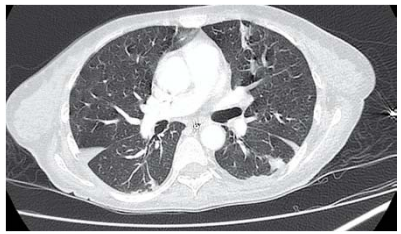
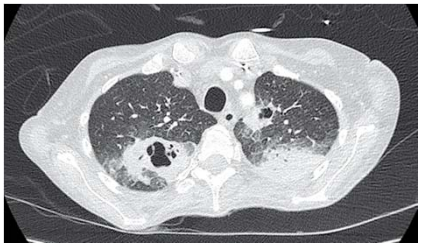
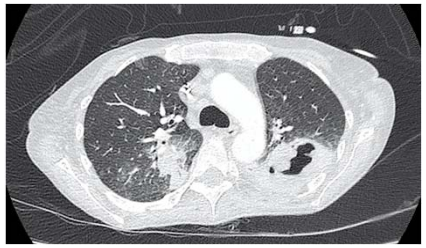
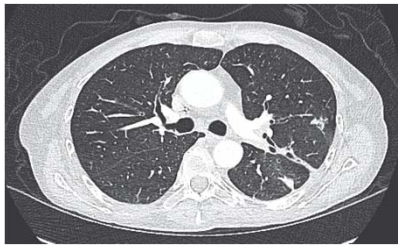
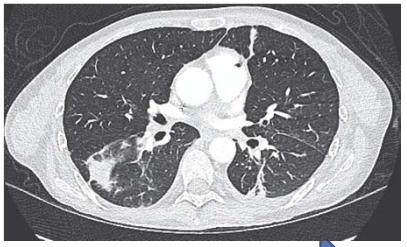
Population	Intention	Intervention	SoR	QoE[1]	QoE[2]	QoE[3]	Comment
1] Neutropenia (non-allo HSCT recipients) 2] Allo-HSCT (during neutropenia) 3] Allo-HSCT (w/o neutropenia) or other non-neutropenic patients	To increase response and survival rate	Isavuconazole 200 mg IV tid day 1–2, then 200 mg qd oral	A	I	II_t	II_t	D III, if mould active azole prophylaxis fewer adverse effects than voriconazole
		Voriconazole 2× 6 mg/kg IV (oral 400 mg bid) on day 1, then 2–4 mg/kg IV (oral 200–300 mg bid)	A	I	II_t	II_t	C III for start with oral; D III, if prior mould active azole prophylaxis; TDM
		L-AmB 3 mg/kg	B	II	II_t	II_t	
		Combination of voriconazole 6/4 mg/kg bid (after 1 week oral possible (300 mg bid)) + anidulafungin 200/100 mg	C	I	II_t	II_t	No significant difference compared to voriconazole, in GM-positive (subgroup) better survival; TDM
		Caspofungin 70 mg qd day 1, followed by 50 mg qd (if body weight <80 kg)	C	II	II	II	
		Itraconazole 200 mg q12 h IV on day 1, then 200 mg/qd	C	III	$II_{t,a}$	$II_{t,a}$	D III for start with oral, TDM D III, if mould active azole prophylaxis
		AmB lipid complex (ABLC) 5 mg/kg	C	III	III	III	
		Micafungin 100 mg	C	III	III	III	
		AmB colloidal dispersion (ABCD) 4–6 mg/kg	D	I	II_t	II_t	
		Conventional AmB 1–1.5 mg/kg	D	I	II_t	II_t	
		Other combinations	D	III	III	III	Efficacy unproven
Life-threatening haemoptysis	Bridging until neutrophil recovery	Arterial embolization, emergency surgical intervention	B	III	III	III	

En pratique

Mme A. 41 ans

Diagnostic LES mai 2018: atteinte cutanée, IRA, SAM, pancréatite, myocardite

Cyclophosphamide + bolus Cs

Juillet 2018 → **Septembre 2018** → **M3**

AI

J1 Vorico 7/7

J1 AmphoBL 9/7

1. ***Aspergillus fumigatus***
   Etest (Biomérieux)

	Résultat	CMI mg/l
Azolés		
Voriconazole	**Résistant**	6
Posaconazole	**Résistant**	2
Itraconazole	**Résistant**	>32
Isavuconazole	**Résistant**	2
Echinocandines		
Caspofongine	Sensible	0.032
Polyènes		
Amphotéricine B	Sensible	0.5

Aggravation

J1 AmphoBL+caspo 1/9

Recommandations en sauvetage

Clinical Infectious Diseases
IDSA GUIDELINE

Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America

Thomas F. Patterson,[1,a] George R. Thompson III,[2] David W. Denning,[3] Jay A. Fishman,[4] Susan Hadley,[5,b] Raoul Herbrecht,[6] Dimitrios P. Kontoyiannis,[7] Kieren A. Marr,[8] Vicki A. Morrison,[9] M. Hong Nguyen,[10] Brahm H. Segal,[11] William J. Steinbach,[12] David A. Stevens,[13] Thomas J. Walsh,[14] John R. Wingard,[15] Jo-Anne H. Young,[16] and John E. Bennett[17,a]

40. In the context of salvage therapy, an additional antifungal agent may be added to current therapy, or combination antifungal drugs from different classes other than those in the initial regimen may be used *(weak recommendation; moderate-quality evidence)*.

ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients

Frederic Tissot,[1] Samir Agrawal,[2] Livio Pagano,[3] Georgios Petrikkos,[4] Andreas H. Groll,[5] Anna Skiada,[6] Cornelia Lass-Flörl,[7] Thierry Calandra,[1] Claudio Viscoli[8] and Raoul Herbrecht[9]

Haematologica 2017
Volume 102(3):433-444

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

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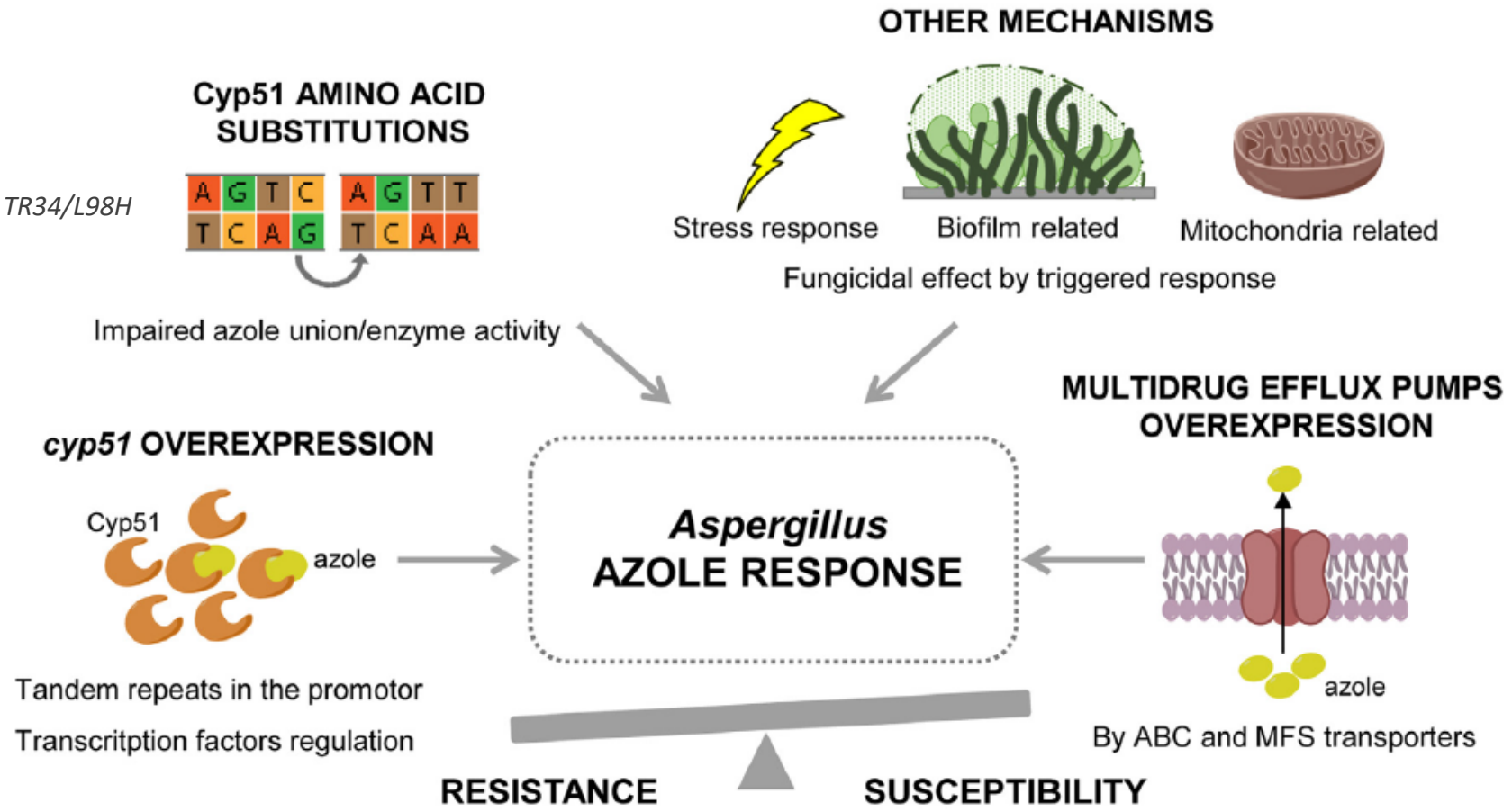
Antifungal drugs in refractory disease

Population	Intention	Intervention	SoR	QoE	Comment
Haematological patients with refractory IA	Achieve complete or partial response, or stable disease, improve survival	Switch to another drug class	A	III	
		Any combination	C	III	No prospective study demonstrated superiority of combination therapy over monotherapy

Recommandations en cas de souche azolés R

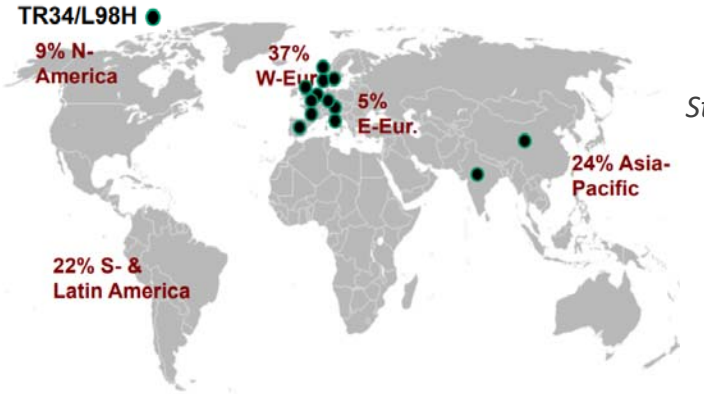
A. fumigatus azolésR



Pérez-Cantero Int J of Antimicrob Ag 2019

Recommandations en cas de souche azolés R

A. fumigatus azolésR



Stensvolf Fung of Reports 2012

Facteurs de risque

- Infections chroniques
- Aspergillome
- Exposition aux azolés
  - Thérapeutique
  - Environnementale

France = 1er utilisateur de pesticides (1/3 triazolés)

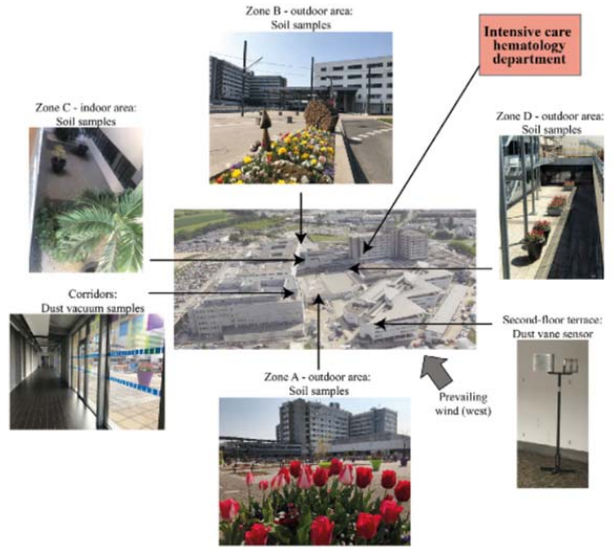
1 malade = plusieurs souches

Données de Rennes 2015-2019

4,1%

15,1% CF

Guegan Front Cell Infect Microbiol 2021



Godeau Am J of Infection 2019

Données évolutives Europe

Lestrade Emerging Inf Dis 2020

Recommandations en cas de souche azolés R

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journal homepage: www.clinicalmicrobiologyandinfection.com

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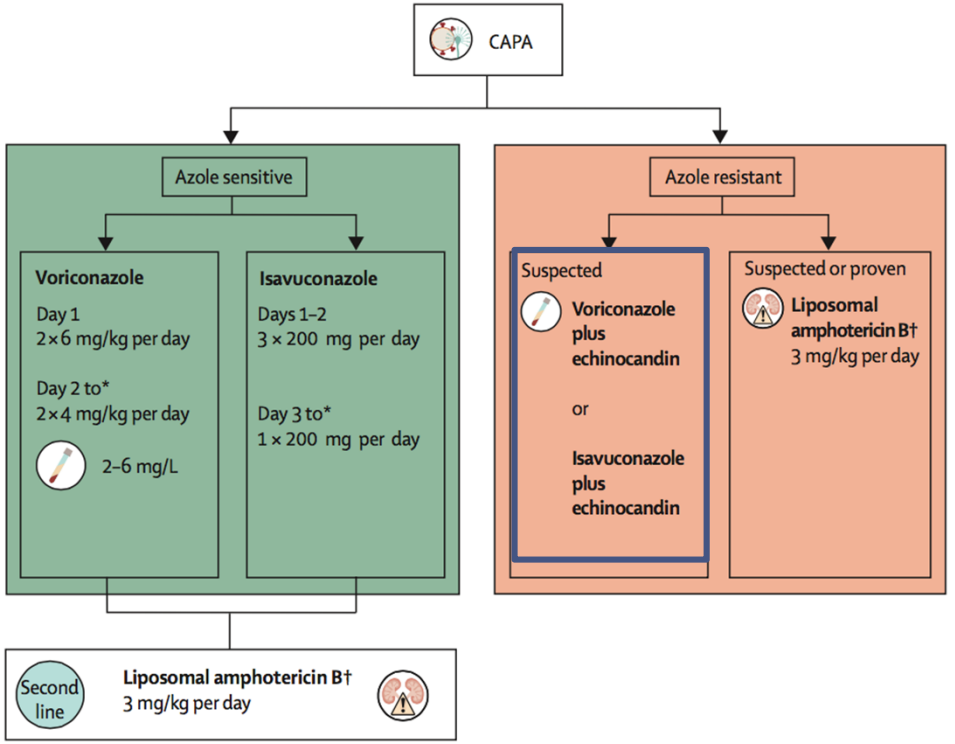
Optimal therapy in documented azole-resistance

Population	Intention	Intervention	SoR	QoE	Comment
Isolate with voriconazole MIC = 2 mg/mL	To cure IA	Voriconazole + echinocandin combination therapy or L-AmB monotherapy for IA (as well as for CPA)	A	III	The probability of voriconazole treatment failure may be higher than in voriconazole MIC <2
Isolate with voriconazole MIC >2 mg/mL	To cure IA	L-AmB	A	II_u	
		AmB lipid complex	C	III	
		Voriconazole & anidulafungin	B	III	
		Posaconazole & caspofungin	C	III	Posaconazole not licensed for primary treatment
		Caspofungin or micafungin	C	III	Patients with contra-indications to AmB and other azoles

Defining and managing COVID-19-associated pulmonary aspergillosis: the 2020 ECMM/ISHAM consensus criteria for research and clinical guidance

Philipp Koehler, Matteo Bassetti, Arunaloke Chakrabarti, Sharon C A Chen, Arnaldo Lopes Colombo, Martin Hoenigl, Nikolay Klimko,

***Lancet Infect Dis* 2021;**
21: e149–62



To be continued...

Données cliniques limitées
1/ Sauvetage
2/ Aspergillus résistant aux azolés

A venir
Recos ESCMID 2022