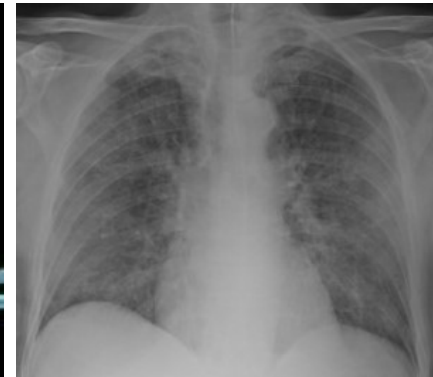
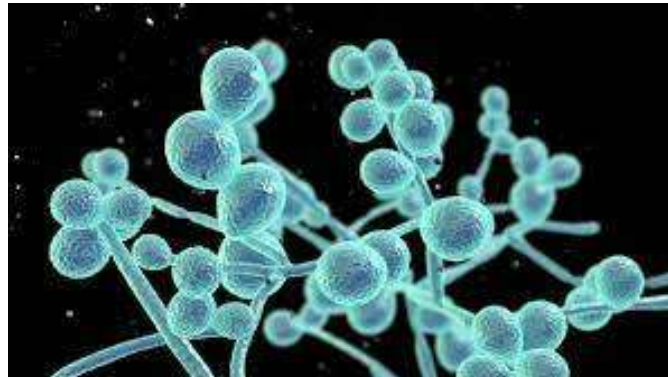
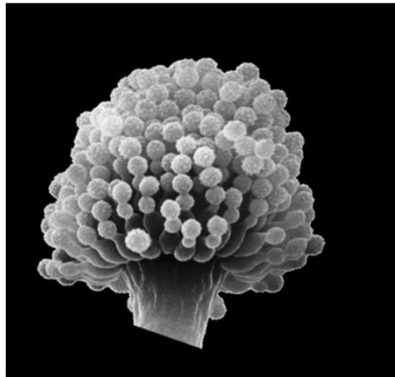


10/10/2023

29^{ème} JRPI Lille Session : Mon année en 3 papiers



Infections fongiques







Dr. Fanny Vuotto

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



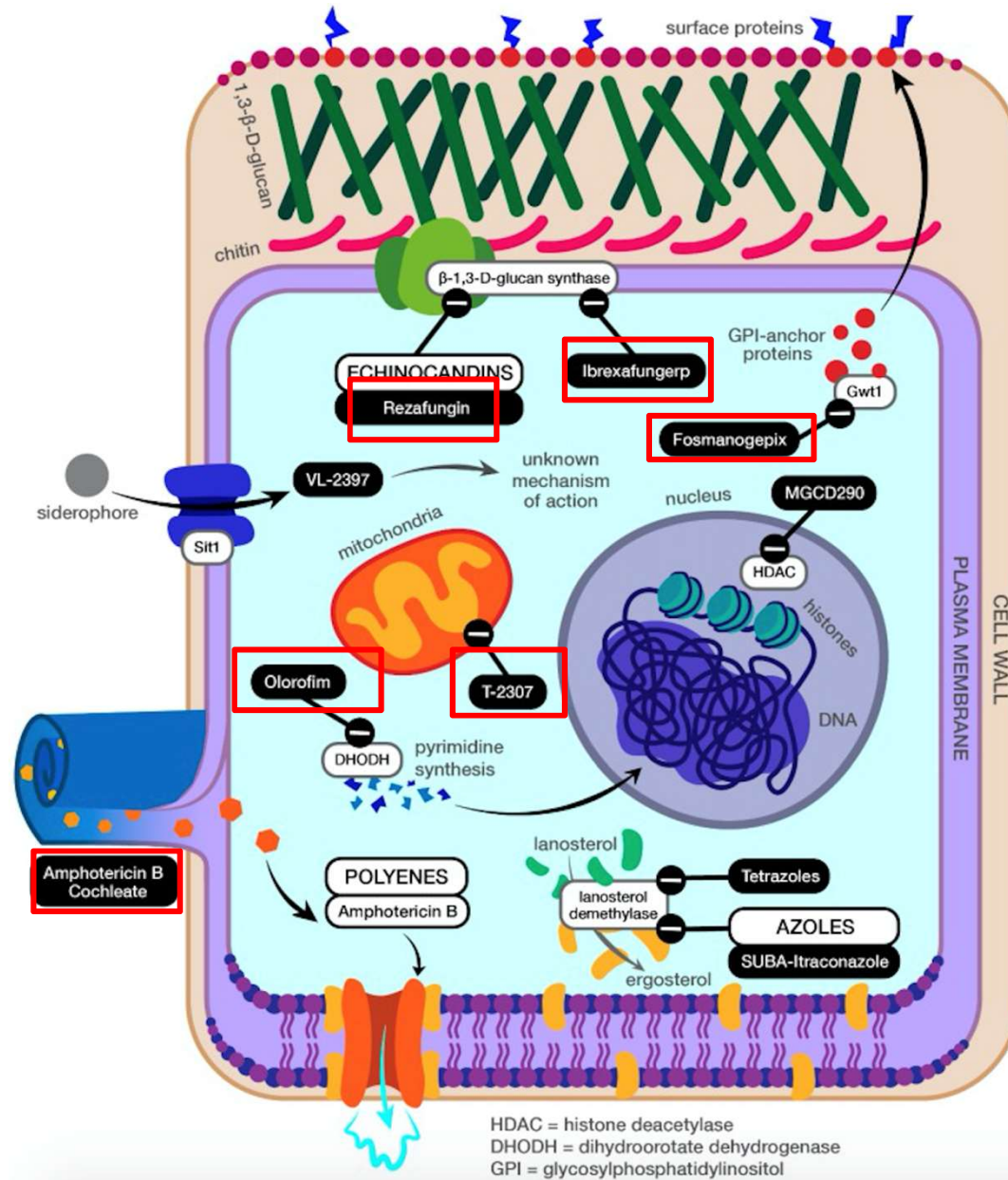
Déclaration de liens d'intérêt avec les industries de santé en rapport avec le thème de la présentation (loi du 04/03/2002) :

Titre : Mon année en 3 papiers – Infections fongiques

- | | | |
|--|---|---|
|  Consultant ou membre d'un conseil scientifique | <input checked="" type="checkbox"/> OUI | <input type="checkbox"/> NON |
|  Conférencier ou auteur/rédacteur rémunéré d'articles ou documents | <input type="checkbox"/> OUI | <input checked="" type="checkbox"/> NON |
|  Prise en charge de frais de voyage, d'hébergement ou d'inscription à des congrès ou autres manifestations | <input checked="" type="checkbox"/> OUI | <input type="checkbox"/> NON |
|  Investigateur principal d'une recherche ou d'une étude clinique | <input checked="" type="checkbox"/> OUI | <input type="checkbox"/> NON |



Back to...JRPI 2021



Rezafungin versus caspofungin for treatment of candidaemia and invasive candidiasis (ReSTORE): a multicentre, double-blind, double-dummy, randomised phase 3 trial

Lancet 2023; 401: 49–59

George R Thompson III, Alex Soriano, Oliver A Cornely, Bart Jan Kullberg, Marin Kollef, Jose Vazquez, Patrick M Honore, Matteo Bassetti, John Pullman, Methee Chayakulkeeree, Ivan Poromanski, Cecilia Dignani, Anita F Das, Taylor Sandison, Peter G Pappas, on behalf of the ReSTORE trial investigators

Candidémie : REZAFUNGINE versus caspofungine

Échinocandine à longue demi-vie (133 heures), dérivée de l’anidulafungine

- Administration hebdomadaire, voie IV
- > 98% de sensibilité des *Candida*

| Species | Anidulafungin BPs | | Proposed Rezafungin Preliminary BPs (Susceptible) | Rezafungin Preliminary ECVs (97.5% or 99%) |
|------------------------|-------------------|-----------|---|--|
| | Susceptible | Resistant | | |
| <i>C. albicans</i> | ≤ 0.25 | ≥ 1 | ≤ 0.25 | 0.06 |
| <i>C. glabrata</i> | ≤ 0.12 | ≥ 0.5 | ≤ 0.5 | 0.12 |
| <i>C. tropicalis</i> | ≤ 0.25 | ≥ 1 | ≤ 0.25 | 0.12 |
| <i>C. krusei</i> | ≤ 0.25 | ≥ 1 | ≤ 0.25 | 0.12 |
| <i>C. parapsilosis</i> | ≤ 2 | ≥ 8 | ≤ 2 | 4 |
| <i>C. auris</i> | NA | ≥ 4 | ≤ 0.5 | 0.5 |
| <i>C. dubliniensis</i> | | | ≤ 0.12 | 0.12 |

Evaluation of Rezafungin Provisional CLSI Clinical Breakpoints and Epidemiological Cutoff Values Tested against a Worldwide Collection of Contemporaneous Invasive Fungal Isolates (2019 to 2020)



Cecilia G. Carvalhaes,* Abby L. Klauer,* Paul R. Rhomberg,* Michael A. Pfaller,* Mariana Castanheira*

Rezafungin Versus Caspofungin in a Phase 2, Randomized, Double-blind Study for the Treatment of Candidemia and Invasive Candidiasis: The STRIVE Trial

George R. Thompson III,¹ Alex Soriano,² Athanasios Skoutelis,³ Jose A. Vazquez,⁴ Patrick M. Honore,⁵ Juan P. Horcajada,⁶ Herbert Spapen,⁷ Matteo Bassetti,⁸ Luis Ostrosky-Zeichner,⁹ Anita F. Das,¹⁰ Rolando M. Viani,¹¹ Taylor Sandison,¹¹ and Peter G. Pappas¹²; The STRIVE Trial Investigators

Clinical Infectious Diseases
MAJOR ARTICLE

CID 2021;73 (1 December)

Efficacité clinique J14 comparable à la capso

Rezafungin versus caspofungin for treatment of candidaemia and invasive candidiasis (ReSTORE): a multicentre, double-blind, double-dummy, randomised phase 3 trial

George R Thompson III, Alex Soriano, Oliver A Cornely, Bart Jan Kullberg, Marin Kollef, Jose Vazquez, Patrick M Honore, Matteo Bassetti, John Pullman, Methee Chayakulkeeree, Ivan Poromanski, Cecilia Dignani, Anita F Das, Taylor Sandison, Peter G Pappas, on behalf of the ReSTORE trial investigators

Lancet 2023; 401: 49-59

Candidémie : REZAFUNGINE versus caspofungine

- Phase 3, randomisée en DA, multicentrique, 2018-2021
199 patients adultes, candidémie ou candidose invasive
- Exclusion : IOA, EI, urinaire, neuro-méningée, oculaire, hépatopathie, cathéter non retirable
- **Rezafungine 400 mg S1 puis 200 mg/sem versus caspo ± FCZ (relais FCZ 36% dans le bras caspo)**
- Prédominance de *C. albicans* et *C. glabrata*
- Outcomes :
Mortalité J30, réponse J14, délai négativation des HC

| | Rezafungin group (n=100) | Caspofungin group (n=99) |
|---|--------------------------|--------------------------|
| Age | 59.5 (15.8) | 62.0 (14.6) |
| <65 years | 60 (60%) | 58 (59%) |
| ≥65 years | 40 (40%) | 41 (41%) |
| Sex | | |
| Male | 67 (67%) | 56 (57%)* |
| Female | 33 (33%) | 43 (43%) |
| Race | | |
| Asian | 27 (27%) | 31 (31%) |
| Black or African American | 5 (5%) | 4 (4%) |
| White | 61 (61%) | 60 (61%) |
| Other or not reported | 7 (7%) | 4 (4%) |
| Diagnosis | | |
| Candidaemia only | 70 (70%) | 68 (69%) |
| Invasive candidiasis* | 30 (30%) | 31 (31%) |
| Mean modified APACHE II score† | 12.5 (8.0) | 13.1 (7.1) |
| ≥20 | 15 (15%) | 18 (18%) |
| <20 | 84 (84%) | 81 (83%) |
| Body-mass index mean, kg/m ² | 25.4 (7.0) | 24.5 (6.5) |
| Absolute neutrophil count, <500 cells per μL† | 9 (9%) | 6 (6%) |

2 groupes comparables sauf âge

Rezafungin versus caspofungin for treatment of candidaemia and invasive candidiasis (ReSTORE): a multicentre, double-blind, double-dummy, randomised phase 3 trial

Lancet 2023; 401: 49-59

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Candidémie : REZAFUNGINE versus caspofungine

Table 2: All-cause mortality at day 30 and global response at day 14 in the modified intention-to-treat population

| | Rezafungin group (n=93) | Caspofungin group (n=94) | Treatment difference (95% CI) |
|---|----------------------------|-----------------------------|----------------------------------|
| All-cause mortality at day 30 (US FDA primary outcome) | | | |
| Died | 22 (24%) | 20 (21%) | 2.4 (-9.7 to 14.4)* |
| Known to have died | 19 (20%) | 17 (18%) | .. |
| Unknown survival | 3 (3%) | 3 (3%) | .. |
| All-cause mortality at day 30 by diagnosis | | | |
| Candidaemia only | 18/64 (28%) | 17/67 (25%) | 2.8 (-12.5 to 18.0)* |
| Invasive candidiasis | 4/29 (14%) | 3/27 (11%) | 2.7 (-16.7 to 21.7)* |
| Global response at day 14 as assessed by DRC (EMA primary outcome) | | | |
| Cure | 55 (59%) | 57 (61%) | -1.1 (-14.9 to 12.7)† |
| Failure | 28 (30%) | 29 (31%) | .. |
| Indeterminate | 10 (11%) | 8 (9%) | .. |
| Global response at day 14 as assessed by DRC by diagnosis | | | |
| Candidaemia only | | | |
| Cure | 39/64 (61%) | 43/67 (64%) | -3.2 (-19.6 to 13.3)* |
| Failure | 21/64 (33%) | 19/67 (28%) | .. |
| Indeterminate | 4/64 (6%) | 5/67 (7%) | .. |
| Invasive candidiasis | | | |
| Cure | 16/29 (55%) | 14/27 (52%) | 3.3 (-22.4 to 28.6)* |
| Failure | 7/29 (24%) | 10/27 (37%) | .. |
| Indeterminate | 6/29 (21%) | 3/27 (11%) | .. |

- Non-infériorité démontrée dans toutes les analyses
- Tolérance globalement similaire

Mais :

- Score APACHE \geq 20 17%
- Réponse à J14 : Différence ajustée 1,1%
- Sous-exposition ? Pas d'adaptation de doses
- Transposabilité limitée des résultats
- Pas de données sur long terme

Rezafungin versus caspofungin for treatment of candidaemia and invasive candidiasis (ReSTORE): a multicentre, double-blind, double-dummy, randomised phase 3 trial

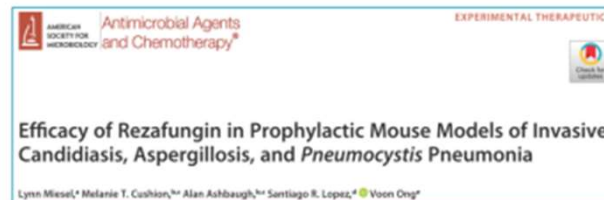
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REZAFUNGINE

- **AMM fin 2023**, demande d'accès précoce refusée début mai - REZZAYO®
Positionnement : difficultés d'abord veineux ?

- **Prophylaxie** : essai en cours ReSPECT



- **Traitement pneumocystose PVVIH**: essai en cours
- **Possible en compassionnel**
20 accès autorisés en juin 2023 dont 5 en France (Aspergillose, *Cladophilophora*...)

Oral Lipid Nanocrystal Amphotericin B for Cryptococcal Meningitis: A Randomized Clinical Trial

David R. Boulware,^{1,a,*} Mucunguzi Atukunda,^{2,a} Enoch Kagimu,² Abdu K. Musubire,² Andrew Akampurira,² Lillian Tugume,² Kenneth Ssebambulidde,^{2,3} John Kasibante,² Laura Nsangi,² Timothy Mugabi,² Jane Gakuru,² Sarah Kimuda,² Derrick Kasozi,² Suzan Namombwe,² Isaac Turyasingura,² Morris K. Rutakingirwa,² Edward Mpoza,² Enos Kigozi,⁴ Conrad Muzoora,⁴ Jayne Ellis,² Caleb P. Skipper,¹ Theresa Matkovits,⁵ Peter R. Williamson,³ Darlisha A. Williams,¹ Ann Fieberg,⁶ Kathy H. Hullsiek,⁶ Mahsa Abbasi,¹ Biyue Dai,⁶ and David B. Meya^{1,2}

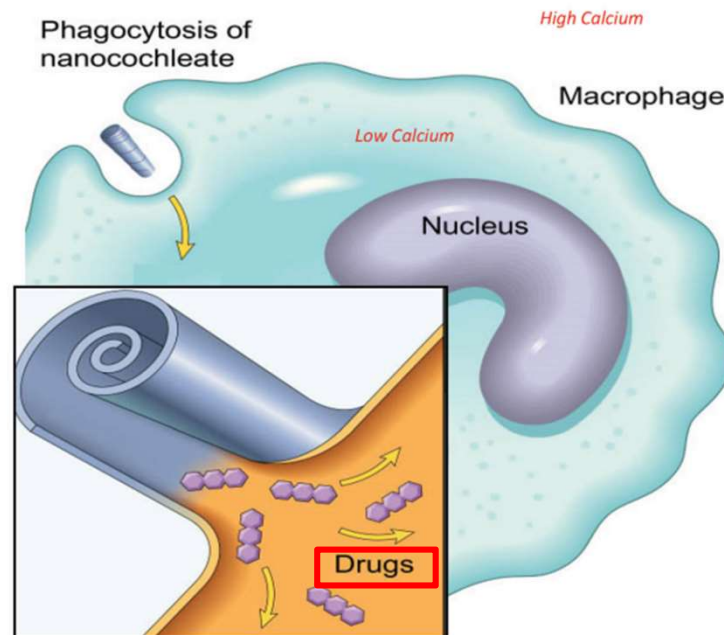
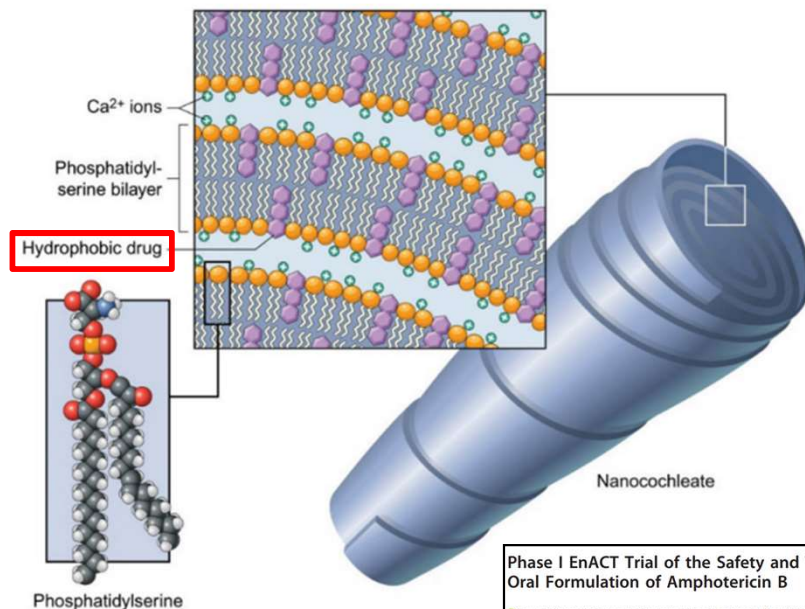
Clinical Infectious Diseases®
August 2023



Nanocristaux lipidiques d'Amphotéricine B

Microparticule : AmphoB intégrée dans la bicouche de phosphatidylsérine + ions Ca
→ absorption orale

Phagocytose
Gradient calcique → ouverture de la particule
→ administration intracell AmphoB



Phase I EnACT Trial of the Safety and Tolerability of a Novel Oral Formulation of Amphotericin B

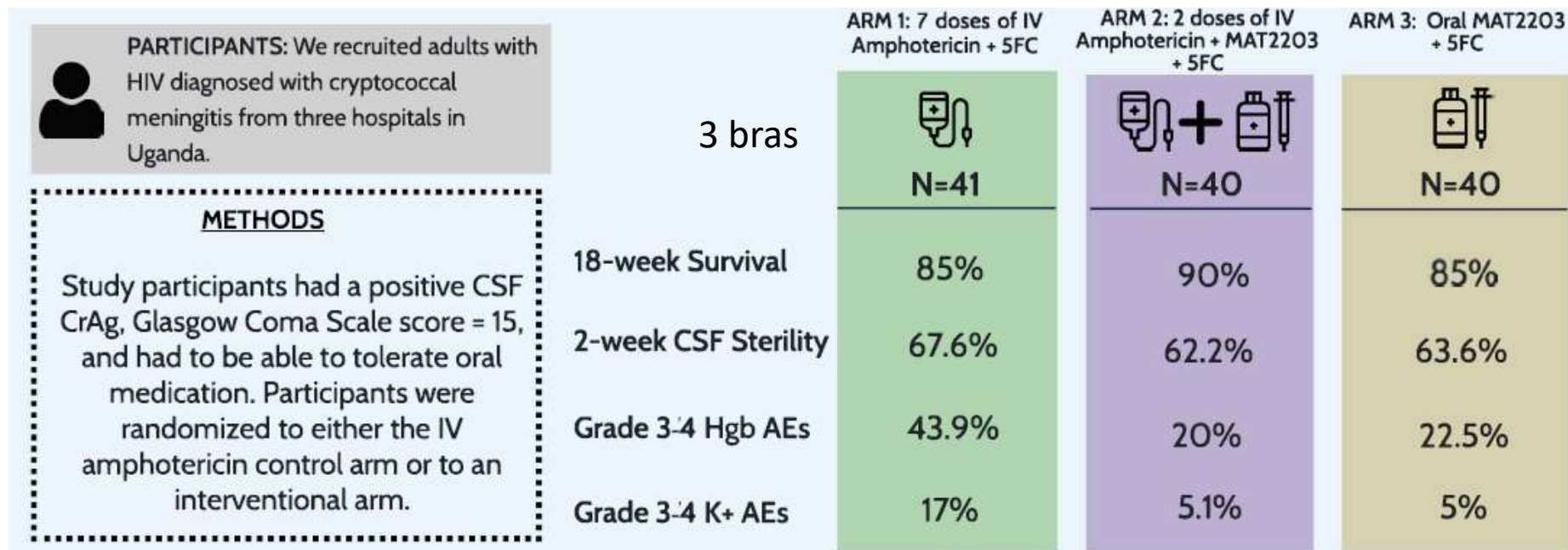
© Caleb P. Skipper,^{1,*} Mucunguzi Atukunda,^{2,*} Anna Stadelman,^{1,2} Nicole W. Engen,¹ Ananta S. Bangdiwala,¹ Katherine H. Hullsiek,⁶ Mahsa Abbasi,¹ Joshua Rhein,⁶ Melanie R. Nicol,⁶ Eva Laker,⁶ Darlisha A. Williams,⁶ Raphael Mannino,¹ Theresa Matkovits,⁵ David B. Meya,^{1,2,*} © David R. Boulware¹

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Nanocristaux lipidiques d'Amphotéricine B

- Etude ouverte randomisée de phase II sur 3 centres en Ouganda
Méningites à *Cryptococcus neoformans* chez adultes VIH+



- Survie à S18 et stérilisation du LCS comparables à J15
- Meilleure tolérance +++

La phase III !!!

Article

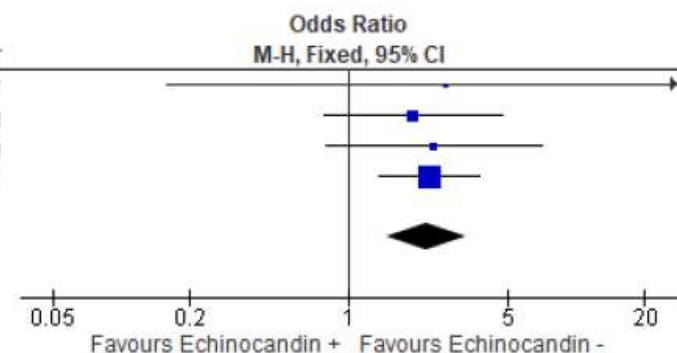
Efficacy of Trimethoprim–Sulfamethoxazole in Combination with an Echinocandin as a First-Line Treatment Option for Pneumocystis Pneumonia: A Systematic Review and Meta-Analysis

Hideo Kato ^{1,2,3}, Mao Hagihara ^{1,4}, Nobuhiro Asai ¹, Takumi Umemura ¹, Yuichi Shibata ¹, Jun Hirai ¹, Yuka Yamagishi ¹, Takuya Iwamoto ^{2,3} and Hiroshige Mikamo ^{1,*}

Bithérapie TMP/SMX + CASPOFUNGINE dans la pneumocystose modérée à grave

- Méta-analyse de 4 études rétrospectives
Asie, 2 chez VIH+, 2 chez VIH- dont 1 chez TOS,
301 patients monothérapie TMP/SMX, 235 association à candine
- Mortalité : 35,2% monothérapie versus 20,9% association (OR = 2,2)

| Study or Subgroup | Echinocandin - | | Echinocandin + | | Weight | Odds Ratio M-H, Fixed, 95% CI | Year |
|--|----------------|------------|----------------|------------|---------------|----------------------------------|------|
| | Events | Total | Events | Total | | | |
| Lu Y | 2 | 5 | 1 | 5 | 1.9% | 2.67 [0.16, 45.14] | 2017 |
| Jin F | 33 | 91 | 8 | 35 | 22.9% | 1.92 [0.78, 4.71] | 2019 |
| Wang M | 14 | 70 | 5 | 52 | 14.3% | 2.35 [0.79, 7.01] | 2019 |
| Tian Q | 57 | 135 | 35 | 143 | 61.0% | 2.25 [1.35, 3.76] | 2021 |
| Total (95% CI) | | 301 | | 235 | 100.0% | 2.20 [1.46, 3.31] | |
| Total events | 106 | | 49 | | | | |
| Heterogeneity: Chi ² = 0.13, df = 3 (P = 0.99); I ² = 0% | | | | | | | |
| Test for overall effect: Z = 3.79 (P = 0.0002) | | | | | | | |



- Bénéfice +++ chez les patients VIH+ et forme grave chez les patients VIH-

Article

Efficacy of Trimethoprim–Sulfamethoxazole in Combination with an Echinocandin as a First-Line Treatment Option for Pneumocystis Pneumonia: A Systematic Review and Meta-Analysis

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Bithérapie TMP/SMX + CASPOFUNGINE dans la pneumocystose modérée à grave

→ Which trial do we need? Combination treatment of *Pneumocystis jirovecii* pneumonia in non-HIV infected patients

Philipp Koehler ^{1,2,a}, Juergen Prattes ^{1,2,a}, Michaela Simon ³, Luise Haensel ^{1,2}, Martin Hellmich ⁴, Oliver A. Cornely ^{1,2,5,6,*}



Clinical Microbiology and Infection 29 (2023) 1225–1228

→ Re: 'Which trial do we need? Combination treatment of *Pneumocystis jirovecii* pneumonia in non-HIV infected patients' by Cornely et al.

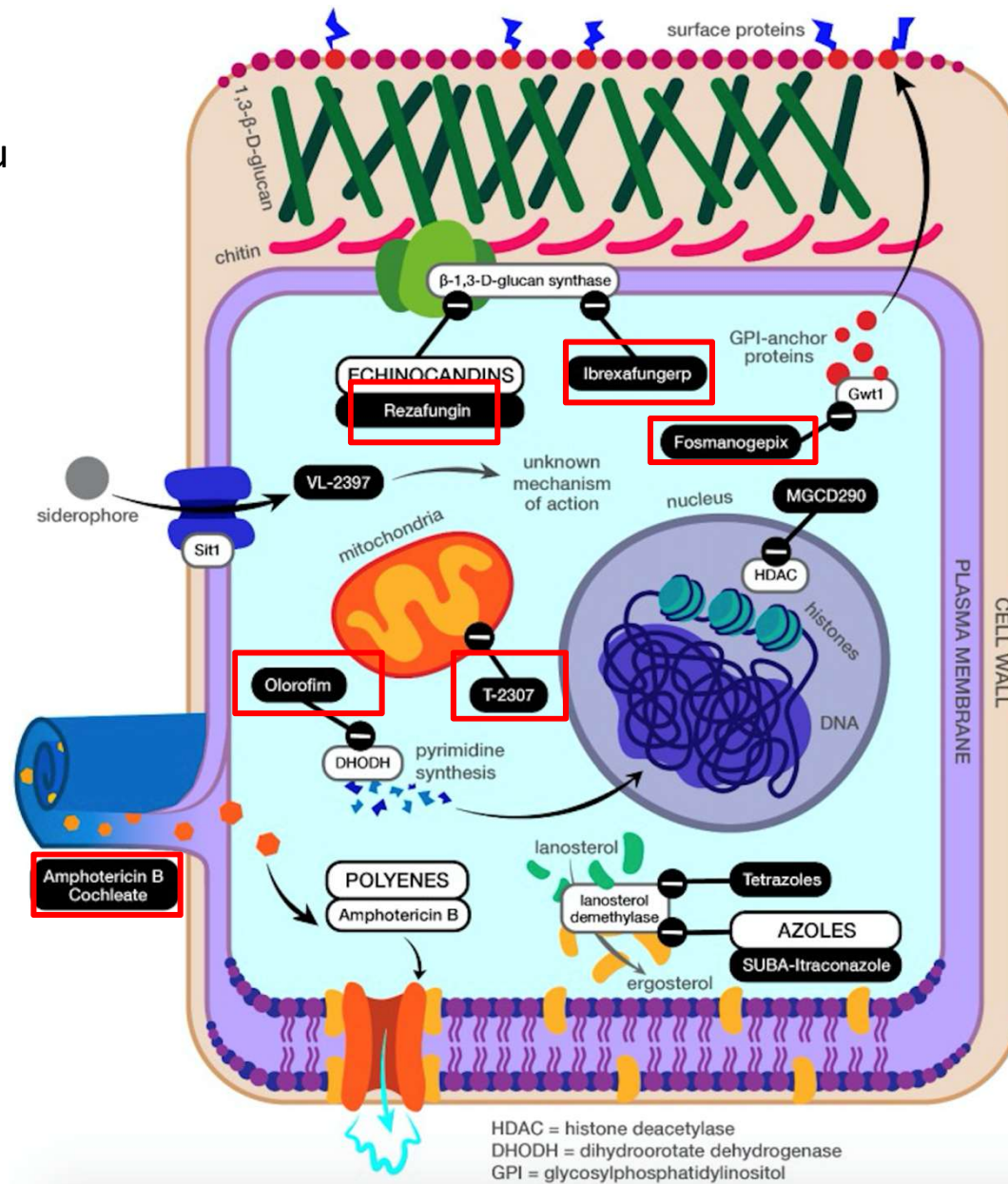
Guillaume Desoubeaux ^{1,2,*}, Adrien Lemaigen ³, Alexandre Alanio ^{4,5}, Stephan Ehrmann ^{2,6}

However, we believe that providing echinocandins directly into the lungs through an aerosolization process could be even more efficient. Indeed, high molecular weight (1093.31 g/mol) and

→ **CASPONEB : 27 centres français en 2024**

2023

- Nouvelles molécules
- Nouvelles associations ou mode d'administrations



2023

- Nouvelles molécules
- Nouvelles associations ou mode d'administrations



Merci pour votre attention