

*Session Bon usage des anti-infectieux, Prévention et contrôle des infections : les leçons de la pandémie COVID*

# Aspergilloses pulmonaires des patients présentant une COVID : quelles leçons ?

**Dr. Fanny Vuotto**





Service de Maladies infectieuses  
Centre Hospitalier universitaire de Lille



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

**Intervenant :** Fanny Vuotto

**Titre :** Aspergilloses pulmonaires des patients présentant une COVID

- |  |   |   |
|--|---|---|
|  Consultant ou membre d'un conseil scientifique  | <input type="checkbox"/> OUI            | <input checked="" 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 type="checkbox"/> OUI            | <input checked="" type="checkbox"/> NON |

# Ce que ce topo ne sera pas...



## Fungal infections in mechanically ventilated patients with COVID-19 during the first wave: the French multicentre MYCOVID study

Jean-Pierre Gangneux\*, Eric Dannaoui\*, Arnaud Fekkar, Charles-Edouard Luyt, Françoise Botterel, Nicolas De Prost, Jean-Marc Tadié,

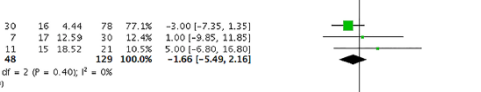
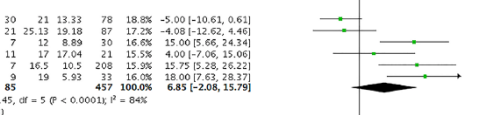


Figure 1: Multivariate analysis of factors associated with pr/pb CAPA. All significant variables in univariate analysis were included in the multivariate model, but only significant variables in the multivariate analysis are shown in the figure. CAPA=COVID-19-associated pulmonary aspergillosis. pr/pb=proven or probable.



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

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

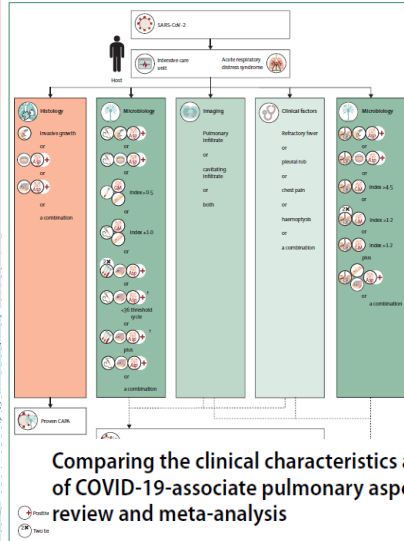


	odds ratio	p value
Ureae	2.0 (1.54-76)	0.49
Hypertension	2.18 (50%)	0.0034
Chronic obstructive pulmonary disease	2.6 (6%)	0.28
Asthma	5 (7%)	0.34
Lymphopenia	56 (74%)	0.48
Solid organ transplantation	8 (11%)	0.79
Haematological malignancy	0	0.69
Any immunosuppression	11 (14%)	0.15
Treatments received for COVID-19		
Inhaled corticosteroids	1.47 (1.04-1.80)	0.036
Systemic corticosteroids	3.32 (1.08-10.19)	0.064
Antifungals	1.68 (0.97-2.90)	0.110
Antibiotics	1.77 (0.77-4.06)	
Other	1.50 (0.73-3.05)	

	Prone position	64 (84%)	330 (76%)	1.65 (0.86-3.17)
<b>Clinical course data</b>				
Duration of mechanical ventilation, days (n=508)†	76: 31.8 (25.8)	432: 26.3 (18.4)	1.01 (1.00-1.02)	
Simplified Acute Physiology II at admission (n=485)†	74: 47.3 (17.4)	411: 43.5 (15.9)	1.01 (1.00-1.03)	
SOFA at admission (n=298)†	67: 7.8 (3.8)	331: 7.3 (4.0)	1.02 (0.96-1.10)	
SOFA at day 7 (n=366)†	61: 9.8 (3.8)	305: 8.5 (4.3)	1.07 (1.01-1.15)	
SOFA at day 15 (n=261)†	51: 9.8 (3.9)	210: 8.1 (4.7)	1.08 (1.01-1.16)	
SOFA at discharge (n=285)†	53: 9.2 (6.4)	232: 5.4 (5.7)	1.10 (1.05-1.16)	

Data are n (%), mean (SD), or n (mean (SD)), pr/pb=proven or probable. CAPA= COVID-19-associated pulmonary aspergillosis. IL=interleukin. SOFA=Sequential Organ Failure Assessment. \*CAPA status according to Kc (Samples too small to calculate effect estimate and 95% CIs. †Number of patients with available data.

Table 3: Demographic and baseline characteristics, immunosuppressive and antimicrobial clinical course data between patients with and without pr/pb CAPA



## Comparing the clinical characteristics and outcomes of COVID-19-associated pulmonary aspergillosis (CAPA): a systematic review and meta-analysis

Woon Hean Chong<sup>1</sup>, Biplab K. Saha<sup>2</sup>, Kristoffer P. Neu<sup>3</sup>

Sample Type	Pros	Cons	Outcomes
Tracheal aspirate	Easy to obtain in patients who are intubated	Less representative of lower respiratory tract than is bronchoalveolar lavage; not validated for biomarker detection	Often positive in patients with COVID-19 who are critically ill but can represent upper airway colonisation
Sputum	Easy to obtain in most patients	Less representative of lower respiratory tract than is bronchoalveolar lavage; not validated for biomarker detection	Often positive in patients with COVID-19 who are critically ill but can represent upper airway colonisation
Serum	Highly indicative for IPA (galactomannan, lateral flow assay, and PCR); validated specimen for galactomannan, lateral flow assay, (1-3)-β-D-glucan, and PCR; easy to obtain	Variable performance in non-neutropenic patients; (1-3)-β-D-glucan not pathogen specific	Commonly negative in CAPA, including proven cases <sup>11</sup>

Table 2: Pros and cons of diagnostic procedures and their samples in patients with COVID-19

# Ce que ce topo ne sera pas...



## Fungal infections in mechanically ventilated patients with COVID-19 during the first wave: the French multicentre MYCOVID study

Jean-Pierre Gangneux\*, Eric Dannaoui\*, Arnaud Fekkar, Charles-Edouard...



**Figure 1: Multivariate analysis of factors associated with pr/pb CAPA**  
All significant variables in univariate analysis were included in the multivariate model, but only significant in the multivariate analysis are shown in the figure. CAPA=COVID-19-associated pulmonary aspergillosis. pr/pb=proven or probable.

**1.1.2 BMI (kg/m<sup>2</sup>)**

Bartolotti et al.	28	3.7	30	29	3.7	78	34.6%	-1.00 [-2.56, 0.56]
Deilliere et al.	28	2.96	21	28				
Gangneux et al.	25	2.37	7	27				
Van Biesen et al.	30	5.93	9	27				
<b>Subtotal (95% CI)</b>								
<b>Heterogeneity:</b> Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 5.61, df = 3 (P = 0.13); I <sup>2</sup> = 0.0%								
<b>Test for overall effect:</b> Z = 0.61 (P = 0.54)								

## Defining and managing COVID-19-associated pulmonary aspergillosis: the 2020 ECMM research and clinical guidance

**1.1.3 SOFA Score**

Deilliere et al.	7.1	4.5	21	5:8
Gangneux et al.	9	7.41	7	7
Lahmer et al.	12	2	11	9
<b>Subtotal (95% CI)</b>				
<b>Heterogeneity:</b> Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 1.61, df = 2 (P = 0.45); I <sup>2</sup> = 0.0%				
<b>Test for overall effect:</b> Z = 4.52 (P < 0.00001)				

**1.1.4 Illness Onset to ICU Admission (D)**

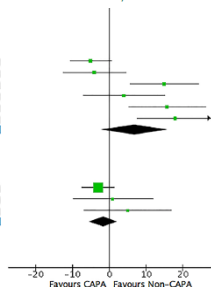
Bartolotti et al.	8	5.65	30	9
Lahmer et al.	3	1	11	4
<b>Subtotal (95% CI)</b>				
<b>Heterogeneity:</b> Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.00, df = 1 (P = 1.00); I <sup>2</sup> = 0%				
<b>Test for overall effect:</b> Z = 2.97 (P = 0.003)				

**1.1.5 ICU LOS (D)**

Bartolotti et al.	16	13.33	30	21	13.33	78	18.8%	-5.00 [-10.61, 0.61]
Deilliere et al.	21.05	17.6	21	25.13	19.18	87	17.2%	-4.08 [-12.62, 4.46]
Gangneux et al.	27	11.85	7	12	8.89	30	16.6%	15.00 [5.66, 24.34]
Lahmer et al.	21	14.97	11	17	17.04	21	15.5%	4.00 [-7.06, 15.06]
Segrelles-Cahvo et al.	32.25	14	7	16.5	10.5	208	15.3%	15.75 [5.28, 26.22]
Van Biesen et al.	37	15.56	9	19	5.93	33	16.0%	18.00 [7.63, 28.37]
<b>Subtotal (95% CI)</b>								
<b>Heterogeneity:</b> Tau <sup>2</sup> = 102.19; Chi <sup>2</sup> = 30.45, df = 5 (P < 0.0001); I <sup>2</sup> = 84%								
<b>Test for overall effect:</b> Z = 1.50 (P = 0.13)								

**1.1.6 IMV Duration (D)**

Bartolotti et al.	13	11.85	30	16	4.44	78	77.1%	-3.00 [-7.35, 1.35]
Gangneux et al.	18	13.33	7	17	12.59	30	12.4%	1.00 [-9.85, 11.85]
Lahmer et al.	20	14.81	11	15	18.52	21	10.5%	5.00 [-6.80, 16.80]
<b>Subtotal (95% CI)</b>								
<b>Heterogeneity:</b> Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 1.82, df = 2 (P = 0.40); I <sup>2</sup> = 0%								
<b>Test for overall effect:</b> Z = 0.85 (P = 0.39)								



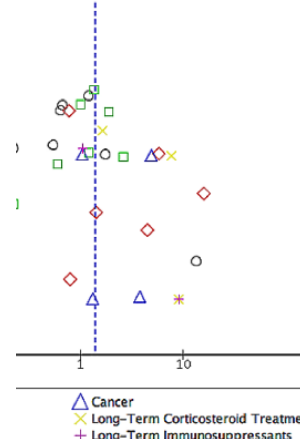
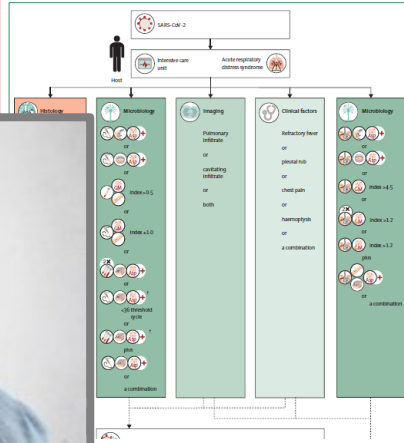
Philippp Koehler, Matteo Bassetti, Arunaloke Chakrabarti, Sharon CA Chen, Arnaldo Lopes Colombo, Martin Hoenigl, Nikolay Klimko,

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Data are n (%), mean (SD), or n; mean (SD), pr/pb=proven or probable. CAPA= COVID-19-associated pulmonary aspergillosis. IL=interleukin. SOFA=Sequential Organ Failure Assessment. \*CAPA status according to Kikuchi et al. †Samples too small to calculate effect estimate and 95% CIs. ‡Number of patients with available data.

**Table 3: Demographic and baseline characteristics, immunosuppressive and antimicrobial clinical course data between patients with and without pr/pb CAPA**

odds ratio	p value
2.32	0.49



## Comparing the clinical characteristics and outcomes of COVID-19-associated pulmonary aspergillosis (CAPA): a systematic review and meta-analysis

Woon Hean Chong<sup>1</sup>, Biplab K. Saha<sup>2</sup>, Kristoffer P. Neu<sup>3</sup>

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Serum	Highly indicative for IPA (galactomannan, lateral flow assay, and PCR); validated specimen for galactomannan, lateral flow assay, (1-3)-β-D-glucan, and PCR; easy to obtain	Variable performance in non-neutropenic patients; (1-3)-β-D-glucan not pathogen specific	Commonly negative in CAPA, including proven cases <sup>11</sup>

CAPA=COVID-19-associated invasive pulmonary aspergillosis. IAPA=influenza-associated pulmonary aspergillosis. IPA=invasive pulmonary aspergillosis.

**Table 2: Pros and cons of diagnostic procedures and their samples in patients with COVID-19**

# Plutôt...



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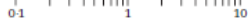


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Deilliere et al.	25.2	2.37	7	27.5				
Van Biesen et al.	30	5.93	9	27				
Subtotal (95% CI)	67							

Heterogeneity: Tau<sup>2</sup> = 1.01; Chi<sup>2</sup> = 5.61, df = 3 (P = 0.13); I<sup>2</sup> = 78.0%  
Test for overall effect: Z = 0.61 (P = 0.54)

### 1.1.3 SOFA Score

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Lahmar et al.	12	2	11	9				
Subtotal (95% CI)	39							

Heterogeneity: Tau<sup>2</sup> = 0.00; Chi<sup>2</sup> = 1.61, df = 2 (P = 0.45); I<sup>2</sup> = 44.7%  
Test for overall effect: Z = 4.52 (P < 0.00001)

### 1.1.4 Illness Onset to ICU Admission (D)

Bartolotti et al.	8	5.65	30	9				
Lahmar et al.	3	1	11	4				
Subtotal (95% CI)	41							

Heterogeneity: Tau<sup>2</sup> = 0.00; Chi<sup>2</sup> = 0.00, df = 1 (P = 1.00); I<sup>2</sup> = 0%  
Test for overall effect: Z = 2.97 (P = 0.003)

### 1.1.5 ICU LOS (D)

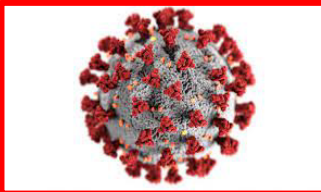
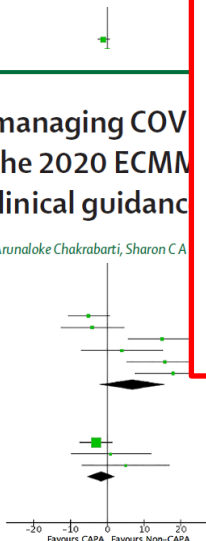
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Van Biesen et al.	37	15.56	9	19	5.93	33	16.0%	18.00 [7.63, 28.37]
Subtotal (95% CI)	85							6.85 [-2.08, 15.79]

Heterogeneity: Tau<sup>2</sup> = 102.19; Chi<sup>2</sup> = 30.45, df = 5 (P < 0.0001); I<sup>2</sup> = 84%  
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Lahmer et al.	20	14.81	11	15	18.52	21	10.5%	5.00 [-6.80, 16.80]
Subtotal (95% CI)	48							1.29 [-1.66, 4.08]

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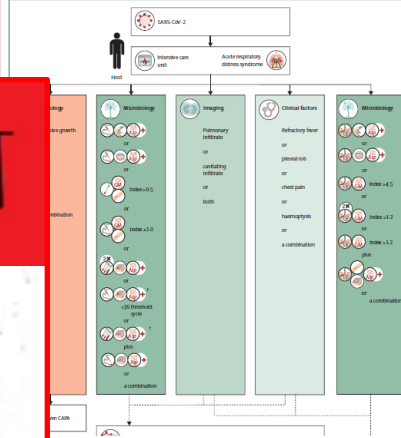
# THINK DIFFERENT



	SOFA at admission (n=239)†	61.9 (3.9)	334.7 (34.9)	1.93 (0.30-2.10)
SOFA at day 7 (n=366)‡	61.9 (3.8)	305.8 (4.3)	1.07 (1.01-1.15)	
SOFA at day 15 (n=261)‡	51.9 (3.9)	210.8 (4.7)	1.08 (1.01-1.16)	
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odds ratio  
p value



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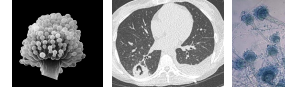
# Le pré COVID



~ 3000 lits sur 14 hôpitaux  
dont ~ 1100 lits de médecine aigue  
~ 250 lits de réanimation



Aspergilloses pulmonaires invasives (API)  
≈ 40/an



Où ?

- Hématologie
- Maladies Infectieuses (TOS)
- Pneumologie
- Réanimation

Par qui ?

« Team fongique »



- Infectiologues
- Référents/spécialité : hémato, réa, radio
- Mycologues, toxicologue
- Pharmacien AF



Comment ?



**A Clinical Algorithm to Diagnose Invasive Pulmonary Aspergillosis in Critically Ill Patients**

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

Stijn I. Blot<sup>1</sup>, Fabio Silv  
Nele Brusselaers<sup>1</sup>, Geon  
Koenaard Vandewoude<sup>1</sup>

Thomas J. Patterson,<sup>1</sup> George H. Thompson III,<sup>2</sup> David W. Fleming,<sup>3</sup> Jay A. Fishman,<sup>4</sup> Susan Bradley,<sup>5</sup> Hazel Herberich,<sup>6</sup> Deborah R. ...

Karen A. Marr,<sup>7</sup> Craig A. ...

Richard G. ...

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

Frederic Tissot,<sup>1</sup> Samir Agrawal,<sup>2</sup> Livio Pagano,<sup>3</sup> Georgios Petrikos,<sup>4</sup>  
Andreas H. Groll,<sup>5</sup> Anna Skiada,<sup>6</sup> Cornelia Lass-Floir,<sup>7</sup> Thierry Calandra,<sup>8</sup>  
Claudio Viscoli<sup>9</sup> and Raoul Herbrecht<sup>10</sup>



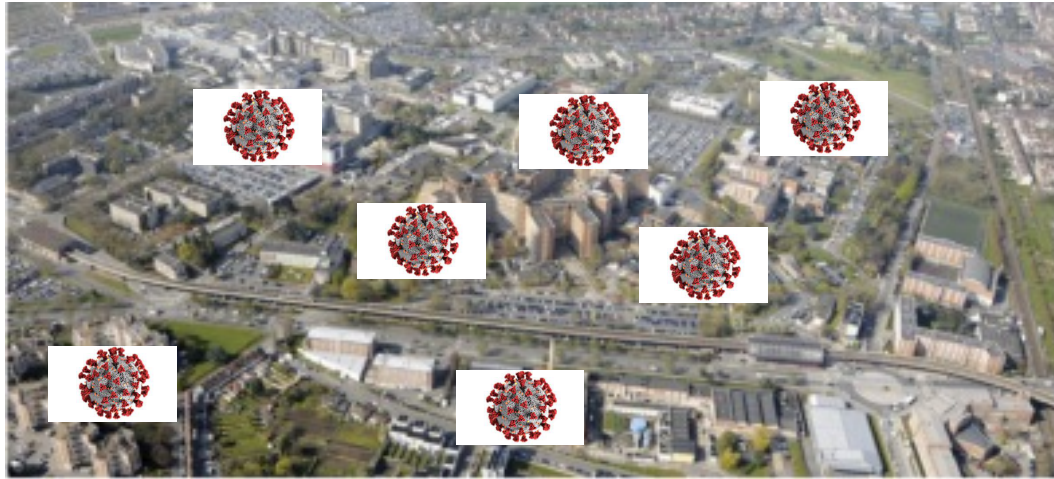
Diagnosis and management of Aspergillus diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline



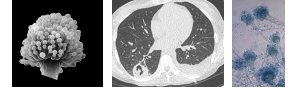
# Quelles conséquences ?



~ 3000 lits sur 14 hôpitaux  
 dont ~ 1100 lits de médecine aigue  
 ~ 250 lits de réanimation



Aspergilloses pulmonaires invasives (API)  
 ≈ 40/an



Où ?

- Hématologie
- Maladies Infectieuses (TOS)
- Pneumologie
- Réanimation

Par qui ?

« Team fongique »

- Infectiologues
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- Mycologues, toxicologue
- Pharmacien AF



Comment ?



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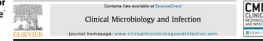
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Frederic Tisset<sup>1</sup>, Samir Agrawal<sup>2</sup>, Livio Pagano<sup>3</sup>, Georgios Petrikos<sup>4</sup>, Andreas H. Groll<sup>5</sup>, Anna Skliada<sup>6</sup>, Cornelia Lass-Floir<sup>7</sup>, Thierry Calandra<sup>8</sup>, Claudio Viscoli<sup>9</sup> and Raoul Herbrecht<sup>10</sup>



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

# Le patient ?

**API ≠ ≠ ≠ IAPA ≠ CAPA**

## API

**≠ ≠ ≠**

## CAPA

### Host factors

Recent history of neutropenia ( $<0.5 \times 10^9$  neutrophils/L [ $<500$  neutrophils/ $\text{mm}^3$ ] for  $>10$  days) temporally related to the onset of invasive fungal disease

### Hematologic malignancy<sup>a</sup>

Receipt of an allogeneic stem cell transplant

Receipt of a solid organ transplant

Prolonged use of corticosteroids (excluding among patients with allergic bronchopulmonary aspergillosis) at a therapeutic dose of  $\geq 0.3$  mg/kg corticosteroids for  $\geq 3$  weeks in the past 60 days

Treatment with other recognized T-cell immunosuppressants, such as calcineurin inhibitors, tumor necrosis factor- $\alpha$  blockers, lymphocyte-specific monoclonal antibodies, immunosuppressive nucleoside analogues during the past 90 days

Treatment with recognized B-cell immunosuppressants, such as Bruton's tyrosine kinase inhibitors, eg, ibrutinib

Inherited severe immunodeficiency (such as chronic granulomatous disease, STAT 3 deficiency, or severe combined immunodeficiency)

Acute graft-versus-host disease grade III or IV involving the gut, lungs, or liver that is refractory to first-line treatment with steroids

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

### Proposed case definition for CAPA

#### Host factors

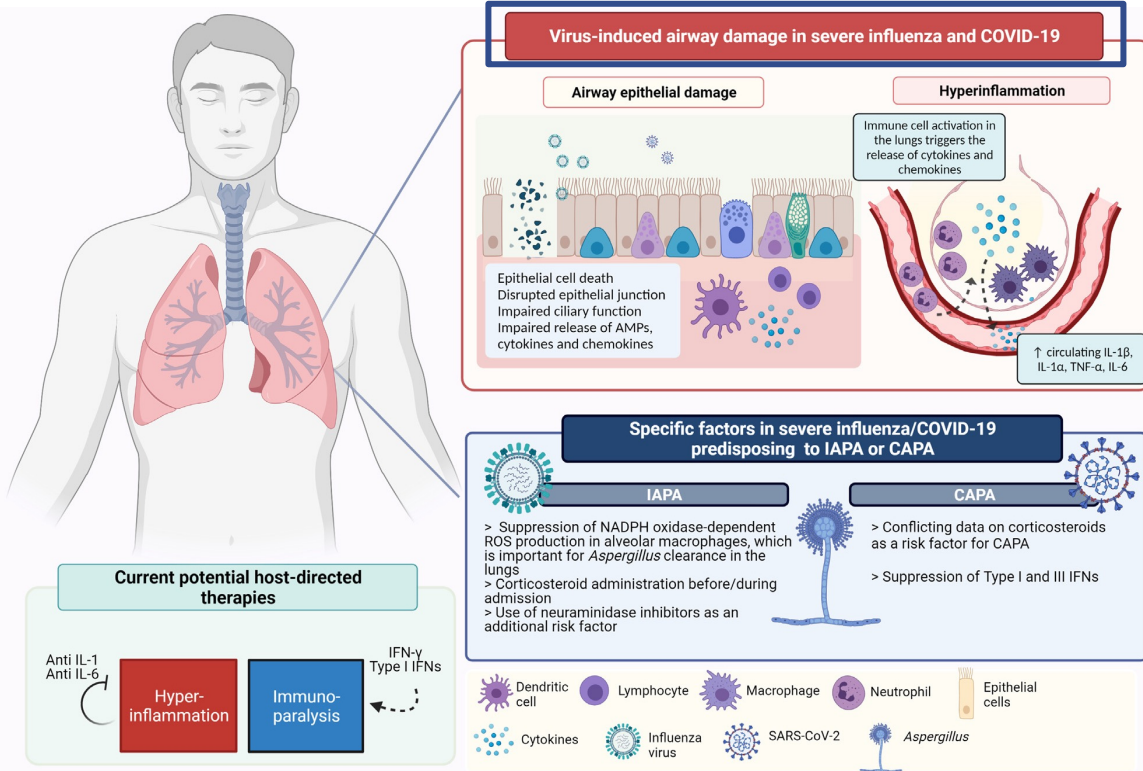
Patient with COVID-19 needing intensive care and a temporal relationship (entry criterion)



# Le patient ?

# API ≠ ≠ ≠ IAPA ≠ CAPA

## IAPA - CAPA

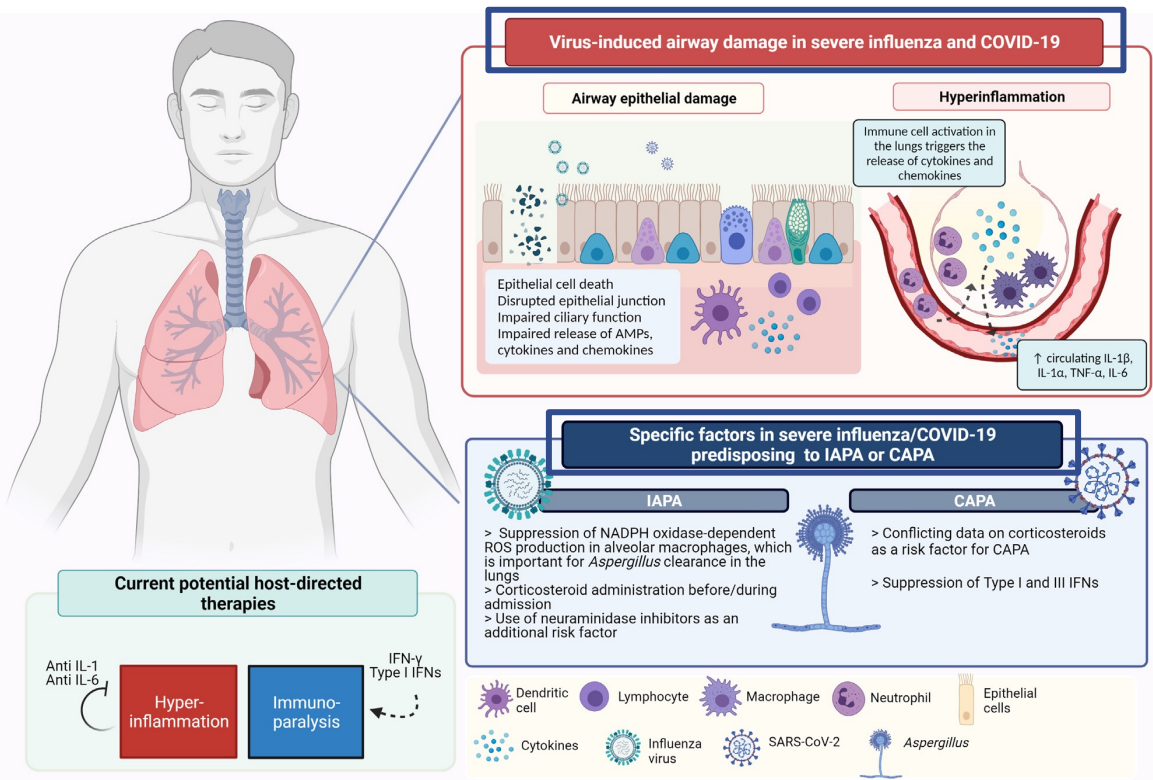


**Surinfection - « Super infection »**  
→ Lésions épithélium respiratoire  
→ Hyper-inflammation

# Le patient ?

# API ≠ ≠ IAPA ≠ CAPA

## IAPA - CAPA



### Surinfection - « Super infection »

- Lésions épithélium respiratoire
- Hyper-inflammation

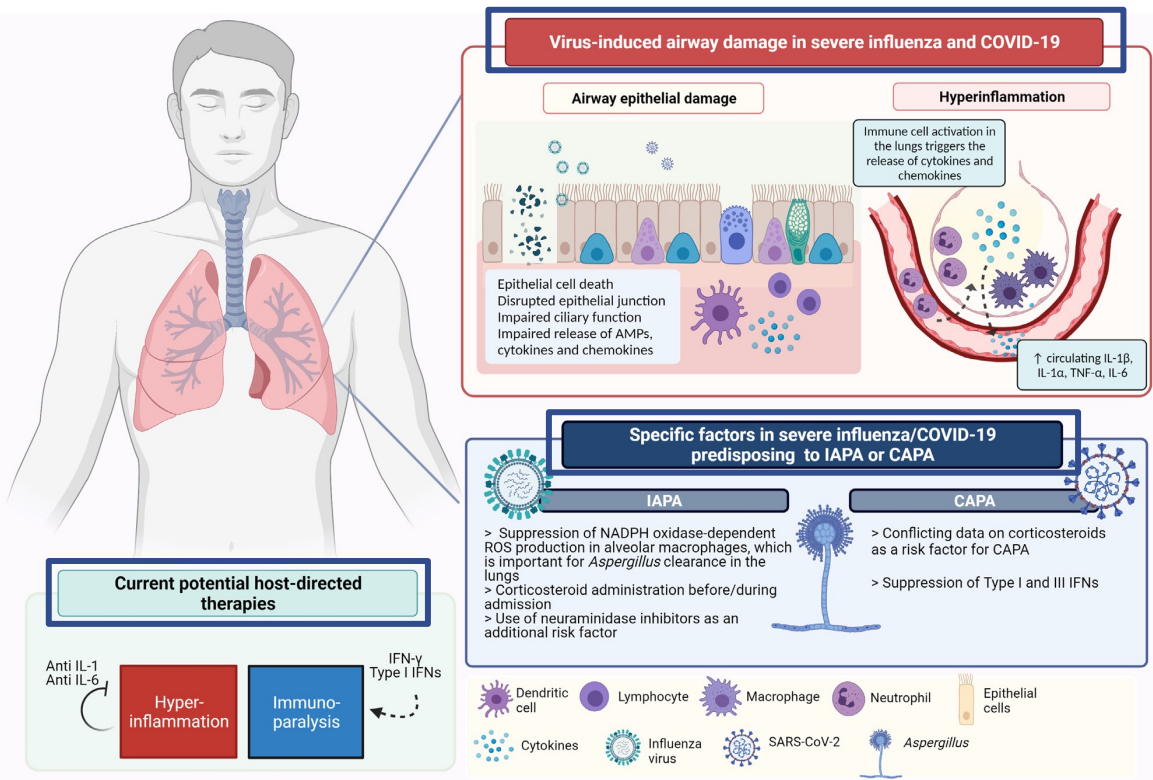
### Virus

- Déficit IFN I et III : auto Ac ≈ 10%
- Immunoparalysie réa

# Le patient ?

# API ≠ ≠ ≠ IAPA ≠ CAPA

## IAPA - CAPA



### Surinfection - « Super infection »

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### Virus

- Déficit IFN I et III : auto Ac  $\approx$  10%
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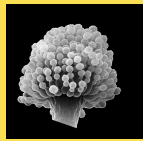
### Thérapeutiques

- Anti IL-6, anti IL-1, anti JAK
- Corticoïdes ?

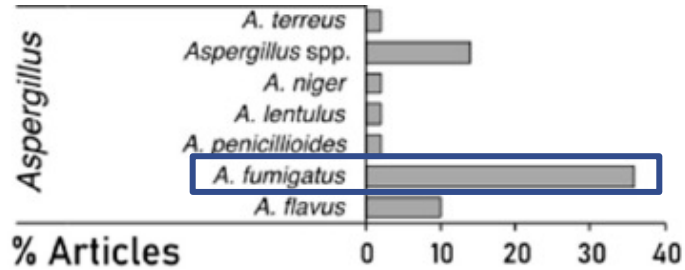
### En bonus

- Terrain : IS, pathologies respiratoires
- Antibiothérapie large spectre
- Exposition environnementale

# Le champignon ?



- Epidémiologie habituelle



- Clinique

- moins d'angioinvasion
- trachéobronchite aspergillaire
- atteinte parenchymateuse

Case Report

## Azole-Resistant COVID-19-Associated Pulmonary Aspergillosis in an Immunocompetent Host: A Case Report



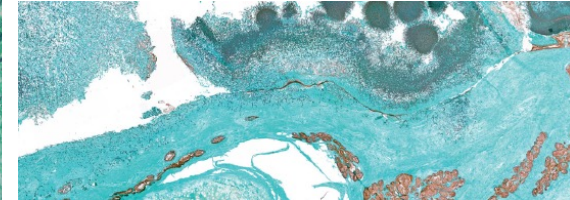
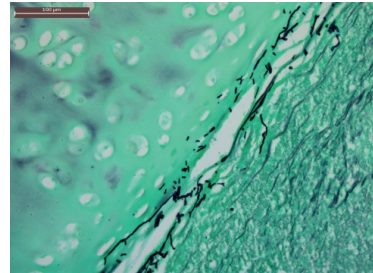
Eelco F. J. Meijer <sup>1,2,3</sup>, Anton S. M. Dofferhoff <sup>3,4</sup>, Oscar Hoiting <sup>5</sup>, Jochem B. Buil <sup>1,2</sup> and Jacques F. Meis <sup>1,2,3,6,\*</sup>

Ezeokoli J Fungi 2021

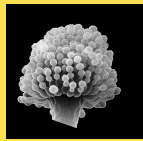
CAPA



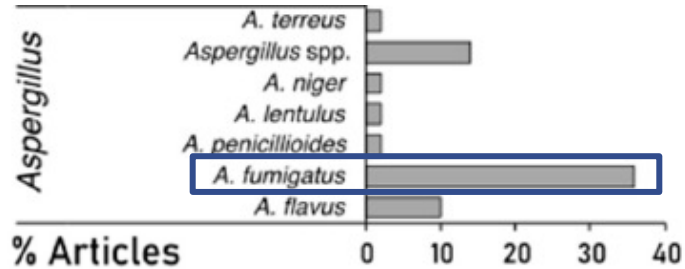
≠ IAPA



# Le champignon ?



- Epidémiologie habituelle



- Clinique

- moins d'angioinvasion
- trachéobronchite aspergillaire
- atteinte parenchymateuse

Case Report

## Azole-Resistant COVID-19-Associated Pulmonary Aspergillosis in an Immunocompetent Host: A Case Report

Eelco F. J. Meijer<sup>1,2,3</sup>, Anton S. M. Dofferhoff<sup>3,4</sup>, Oscar Hoiting<sup>5</sup>, Jochem B. Buil<sup>1,2</sup> and Jacques F. Meis<sup>1,2,3,6,\*</sup>



Ezeokoli J Fungi 2021

### 2 key timepoints

- 1. Co-infection à l'admission en réa
- 2. Surinfection précoce  
5-7 jours d'admission en réa

# Les outils du diagnostic

## Outils mycologiques

### Proposed case definition for CAPA

Microbiology

or
   
  
 or
   
  
 index > 0.5
   
 or
   
  
 index ≥ 1.0
   
 or
   
  
 or
   
  
 < 36 threshold cycle
   
 or
   
  
 plus
   
  
 or
   
 a combination

	Sensibilité	Spécificité
<b>Sang</b> (< 50 % de sensibilité)		
GM > 1	19 %	100 %
13BDG > 80	42 - 60 %	85 %
<b>LBA</b> (sous réserve d'accessibilité)		
GM > 1	74 %	99 %
Culture +	53 - 60 %	100 %
PCR +	42 %	100 %
Lateral flow +	52 - 75 %	79 - 98 %

??? Distinguer

- Colonisation
- Trachéobronchite
- Atteinte parenchymateuse

### Proposed case definition for CAPA

Microbiology

or
   
  
 or
   
  
 or
   
  
 or
   
  
 or
   
  
 or
   
  
 plus
   
  
 or
   
 a combination

	Sensibilité	Spécificité
<b>Sang</b> ( <i>&lt; 50 % de sensibilité</i> )		
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- ??? Distinguer
- Colonisation
  - Trachéobronchite
  - Atteinte parenchymateuse



Clinical Infectious Diseases

MAJOR ARTICLE



Revision and Update of the Consensus Definitions of Invasive Fungal Disease From the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium

J. Peter Donnelly<sup>1</sup>, Sharon C. Chen<sup>2</sup>, Carol A. Kauffman<sup>3</sup>, William J. Steinbach<sup>4</sup>, John W. Biddley<sup>5</sup>, Paul E. Verweij<sup>6</sup>, Cornelius J. Clancy<sup>7</sup>, John R. Wingard<sup>8</sup>

The presence of 1 of the following 4 patterns on CT:

- Dense, well-circumscribed lesions(s) with or without a halo sign
- Air crescent sign
- Cavity
- Wedge-shaped and segmental or lobar consolidation

Other pulmonary mold diseases

As for pulmonary aspergillosis but also including a reverse halo sign

Tracheobronchitis

Tracheobronchial ulceration, nodule, pseudomembrane, plaque, or eschar seen on bronchoscopic analysis



## Proposed case definition for CAPA



Imaging

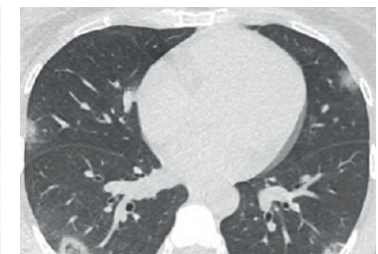
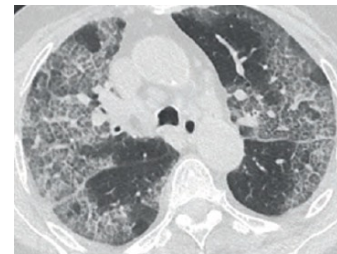
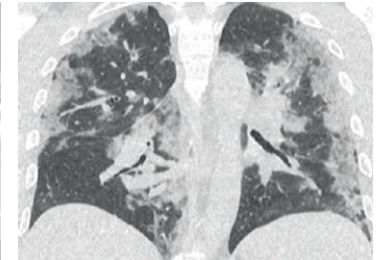
Pulmonary infiltrate

or

cavitating infiltrate

or

both

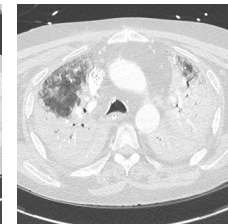


Invasive aspergillosis in solid organ transplantation: Diagnostic challenges and differences in outcome in a Spanish national cohort (Diaspersot study)

Francesca Gioia<sup>1</sup> | Eta Filigheddu<sup>1</sup> | Laura Corbella<sup>2,3</sup> | Mario Fernández-Ruiz<sup>2,3</sup>

### Radiological features in CT

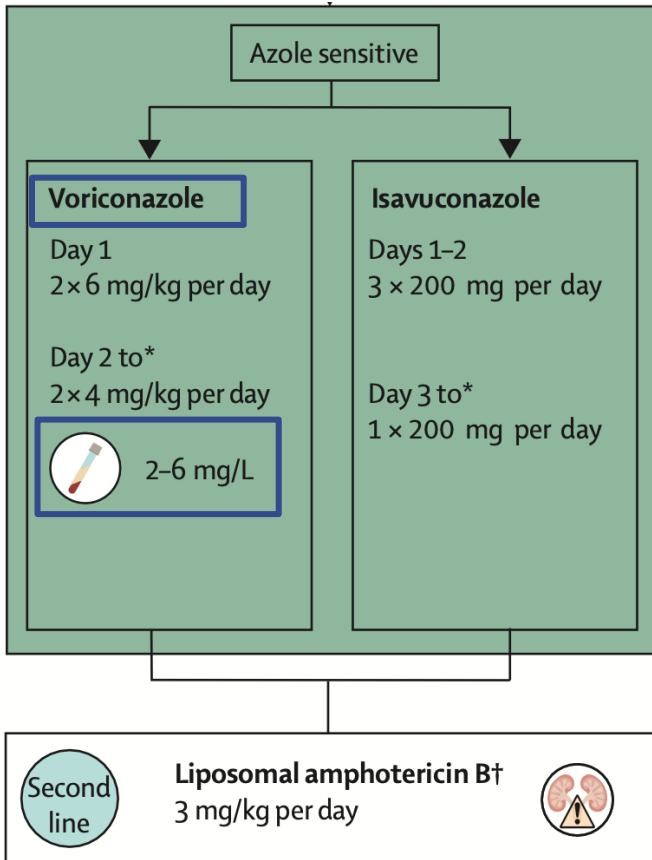
Halo sign	8 (6.3)
Air crescent	0
Nodule	61 (48.4)
Cavitation	25 (19.8)
Tree-in-bud	26 (20.6)
Ground-glass	45 (35.7)





# Les traitements

## Recommended treatment for CAPA



### Difficultés d'équilibration +++

- Interactions via CYP450 : CYP2C19, CYP2C9, CYP3A4
  - Hyper-inflammation
  - Dexaméthasone

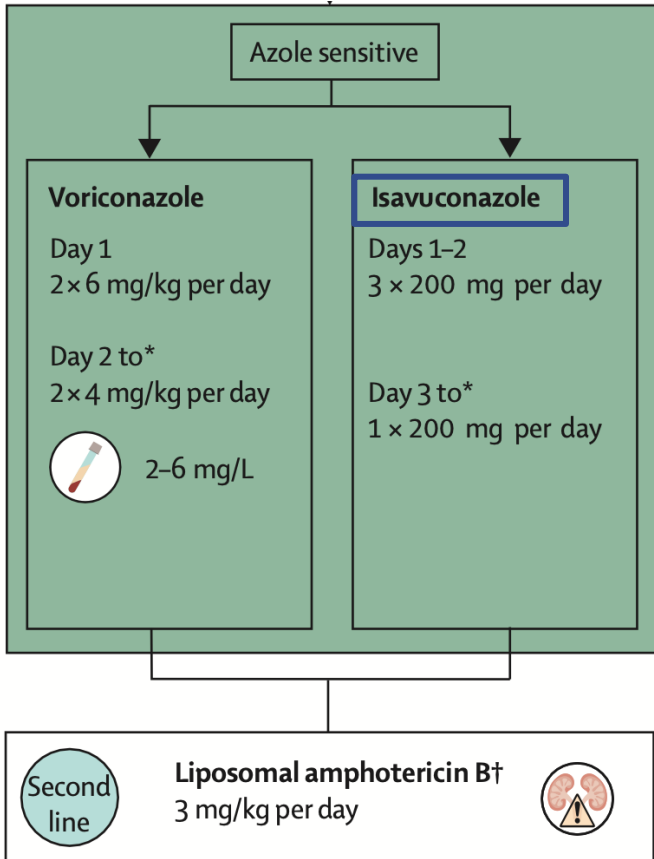
### Interactive Effects of Glucocorticoids and Cytochrome P450 Polymorphisms on the Plasma Trough Concentrations of Voriconazole

*Su-jie Jia<sup>1,2</sup>, Ke-qin Gao<sup>3</sup>, Pan-hao Huang<sup>1,2</sup>, Ren Guo<sup>1,2</sup>, Xiao-cong Zuo<sup>1,2</sup>, Qing Xia<sup>4</sup>, Shuang-yao Hu<sup>4</sup>, Zhen Yu<sup>5</sup> and Yue-liang Xie<sup>1,2\*</sup>*

- ECMO
  - Variabilité ≈ 30 %
- Toxicité hépatique, neurologique

# Les traitements

## Recommended treatment for CAPA



### Difficultés d'équilibration +++

- Nécessité d'un suivi thérapeutique 
- Doses insuffisantes chez les patients de réanimation ?

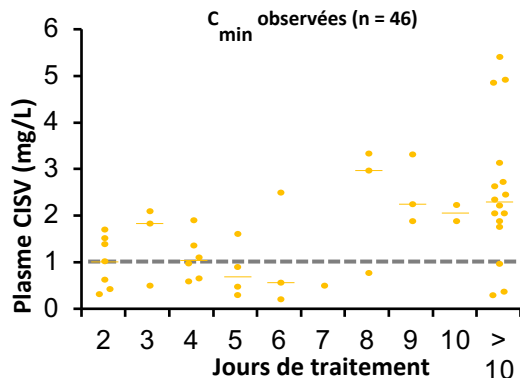
# Concentrations plasmatiques de l'isavuconazole chez les patients de réanimation

ECCMID 2023

D'après Rabault C, abstr. O0213

• 22 patients

*C résiduelle très variable*  
*C > 1 mg/L : 34 %*



• Simulation de Monte-Carlo :

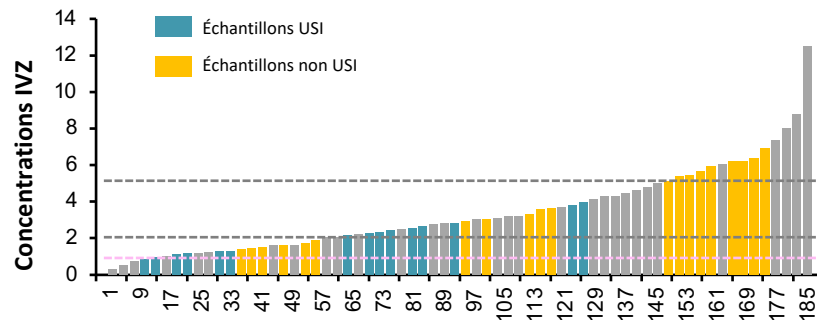
↗ dose de charge : atteinte de la cible chez presque tous les patients mais transitoire

↗ dose de charge et ↗ dose d'entretien : risque d'atteinte de concentrations toxiques

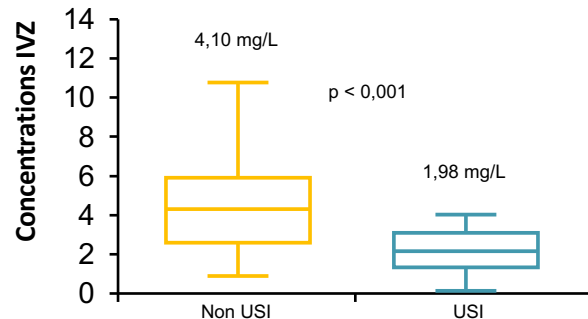
ECCMID 2023

D'après Melchio M, abstr. O0217

• 72 patients

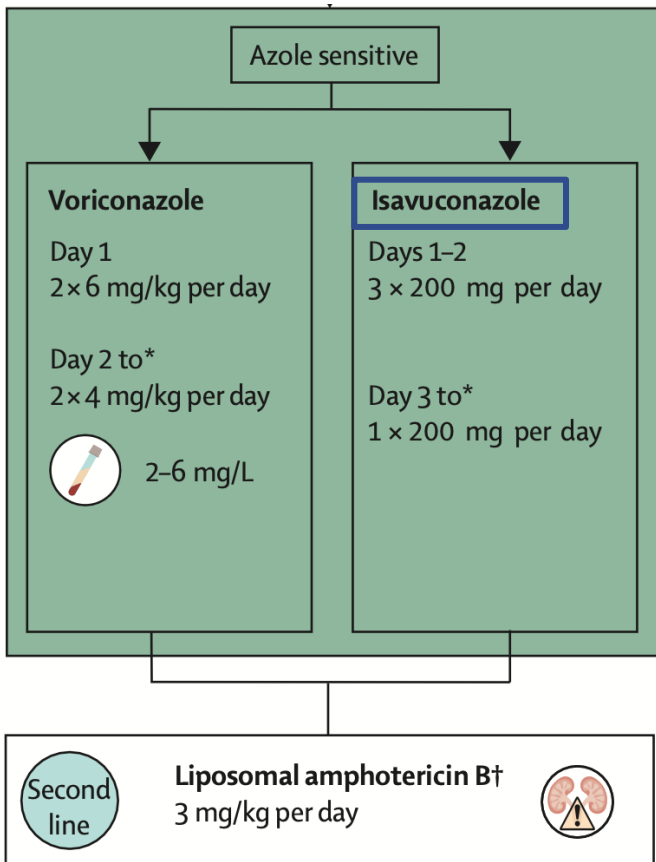


*C résiduelle plus basses*  
*chez les patients de*  
*réanimation*  
*C infrathérapeutique :*  
*33 %*



# Les traitements

## Recommended treatment for CAPA



### Difficultés d'équilibration +++

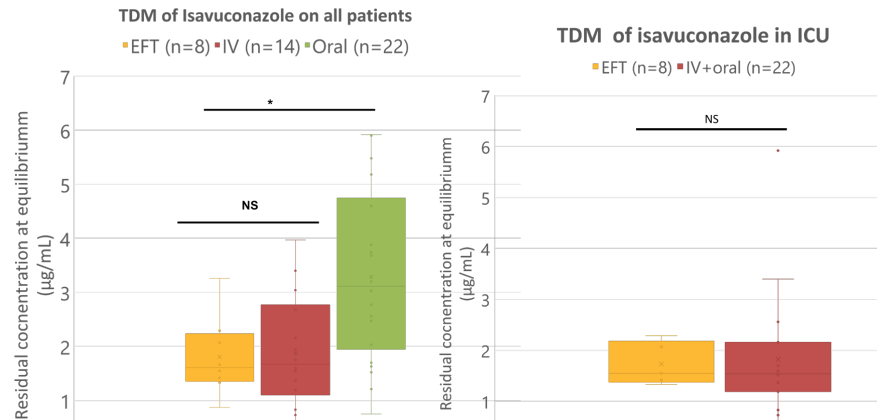
- Nécessité d'un suivi thérapeutique
- Doses insuffisantes chez les patients de réanimation ?
- Tensions d'approvisionnement

ISV gélules dans la SNG (EFT)

44 patients

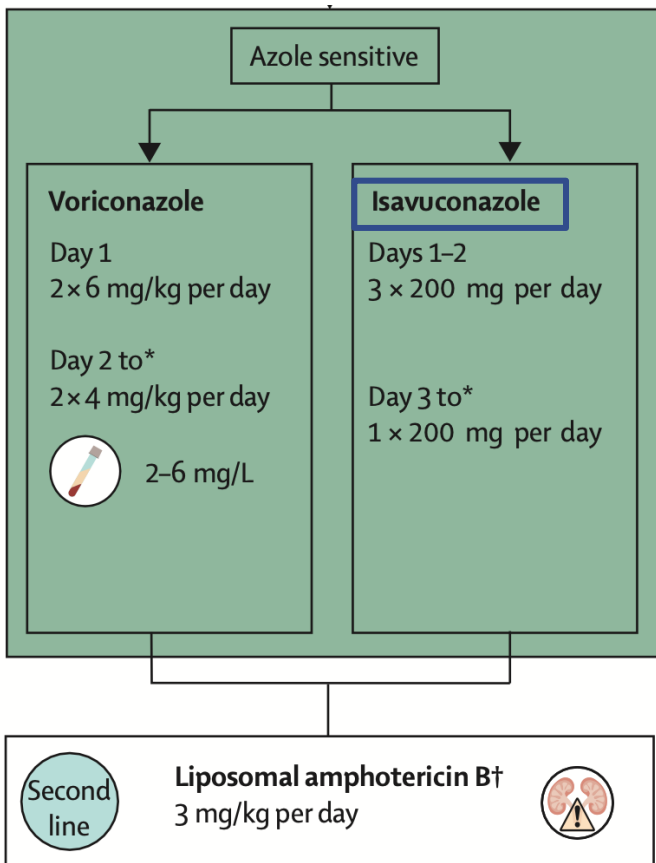
C résiduelles :

- Voie IV = voie SNG
- IV et SNG < PO
- Réa < Med



# Les traitements

## Recommended treatment for CAPA

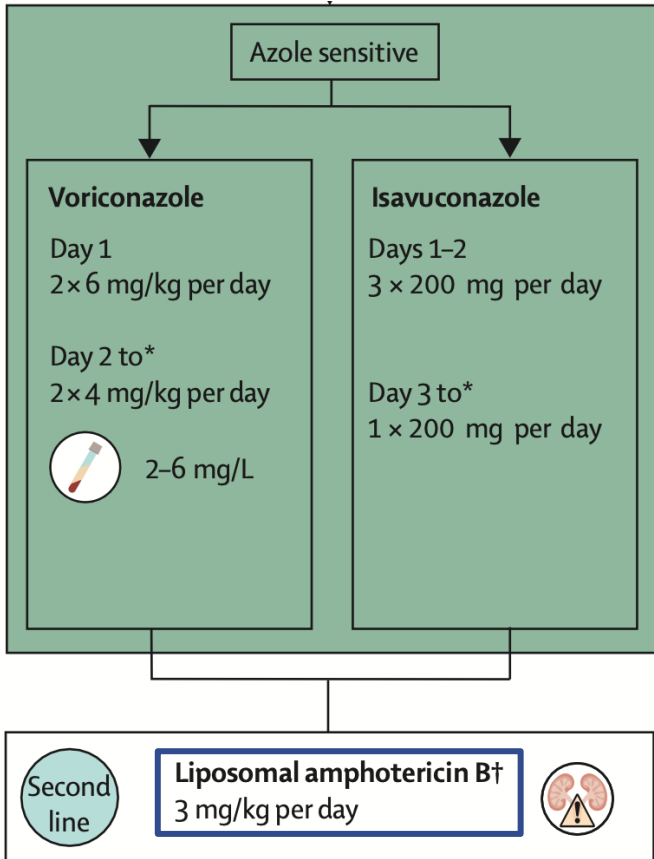


### Difficultés d'équilibration +++

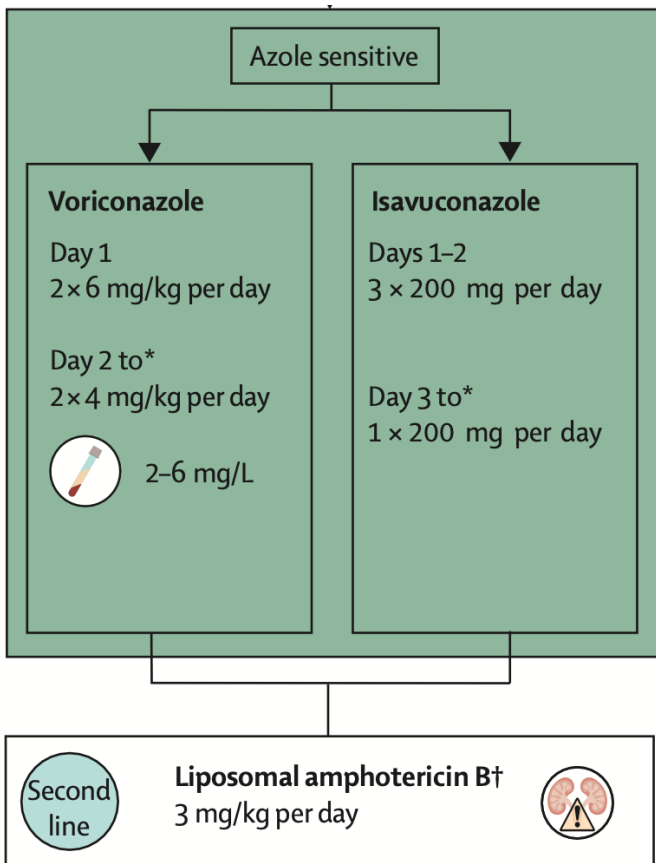
- Nécessité d'un suivi thérapeutique
- Doses insuffisantes chez les patients de réanimation ?
- Tensions d'approvisionnement
- ECMO

# Les traitements

## Recommended treatment for CAPA



- Toxicité rénale
- ECMO ?
- Pas de possibilité de dosage en routine



- **Voriconazole 1<sup>ère</sup> ligne** : OUI mais
  - plutôt 2 x 8 mg/kg J1 et 2 x 6 mg/kg
  - suivi thérapeutique
  - bithérapie jusqu'au dosage pour certains
- **Alternative en Ampho B L** en 1<sup>ère</sup> ou 2<sup>ème</sup> ligne
  - ECMO : à forte dose
- **Isavuconazole** :
  - plutôt en recours en cas de toxicité ou « prophylaxie » avec épargne de toxicité
  - suivi thérapeutique
  - via la SNG quand rupture d'IV

BRIEF REPORT

Open Access

## Impact of COVID-19 pandemic on antifungal consumption: a multicenter retrospective analysis



Anne-Lise Bienvenu<sup>1,2\*</sup>, Audrey Bestion<sup>3</sup>, Pierre Pradat<sup>4</sup>, Jean-Christophe Richard<sup>5</sup>, Laurent Argaud<sup>6</sup>, Céline Guichon<sup>7</sup>, Sandrine Roux<sup>8</sup>, Vincent Piriou<sup>9</sup>, Carole Paillet<sup>10</sup>, Gilles Leboucher<sup>1</sup> and the Antifungal study group

## ↗ des consommations ?

- Variabilité inter-centres
- Pas de corrélation avec cas  
Ttt prophylactiques/préemptifs  
Place des candines

**Table 1** Antifungal consumption including voriconazole, caspofungine and fluconazole, expressed in defined daily dose (DDD) per 1000 patient-days, in 2019 and 2020

Antifungal	2019 (DDD/1000 patient-days)	2020 (DDD/1000 patient-days)	Variation in DDD/1000 patient-days (%)
<i>Systemic antifungals</i>			
Whole hospital	40.1	49.0	+ 22.2
ICU	170.9	196.2	+ 14.8
<i>Voriconazole</i>			
Whole hospital	6.2	8.7	+ 40.3
ICU	29.8	48.8	+ 63.7



	2019	2020	2021
AmphoB	25 235	11 304	14 835
VCZ	11 922	14 506	11 720
ISA	3 108	3 013	3 321



# Le médecin



Jusque 420 lits COVID  
- géographie modifiée  
- activités modifiées  
- non protocolisé



## Ttt préemptifs +++

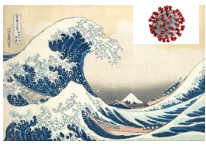
- patients graves
- thérapeutiques limitées
- 1 marqueur fongique +

## Suivi systématique

- sortie de réanimation : discussion sur diagnostic et durée de ttt
- centre ambulatoire de Maladies Infectieuses

## Collatéral

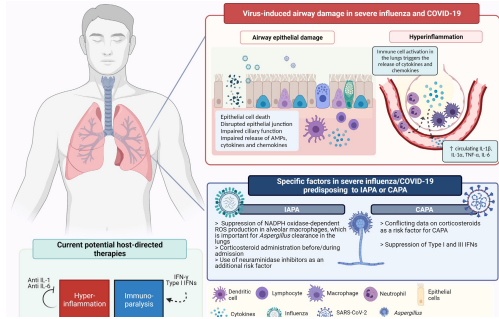
- ttt et prophylaxie API chez TOS
- prophylaxie AF TOS + CAPA



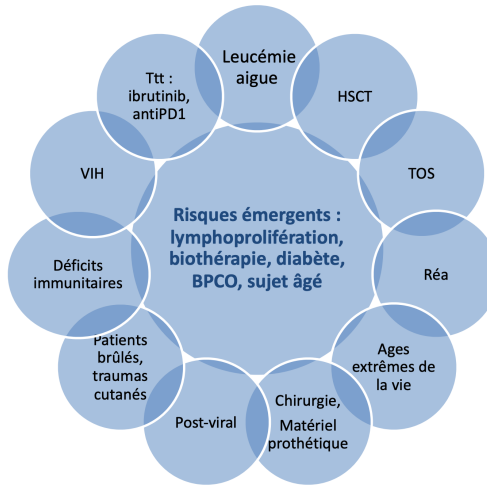
# Les leçons...et perspectives ?



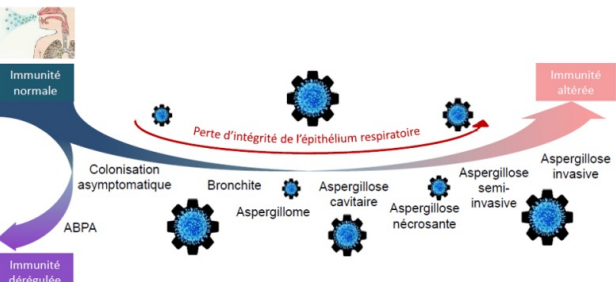
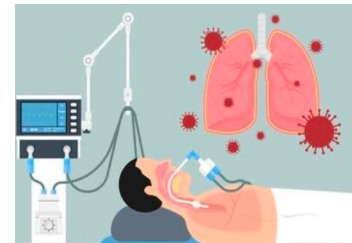
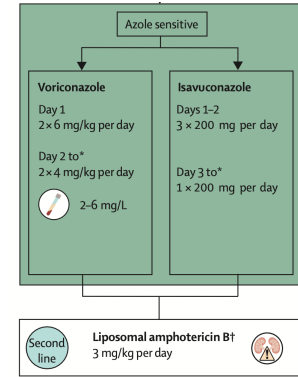
## CAPA : nouvelle maladie dans une famille connue



## Limites des critères diagnostiques



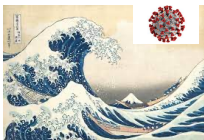
## Variabilité inter-individuelle



## Nouvelles populations à risque

## Nouveaux outils ?

Variant, vaccin : Même maladie ???



# Les leçons...et perspectives ?



## Faut-il débuter une prophylaxie anti-aspergillaire ?

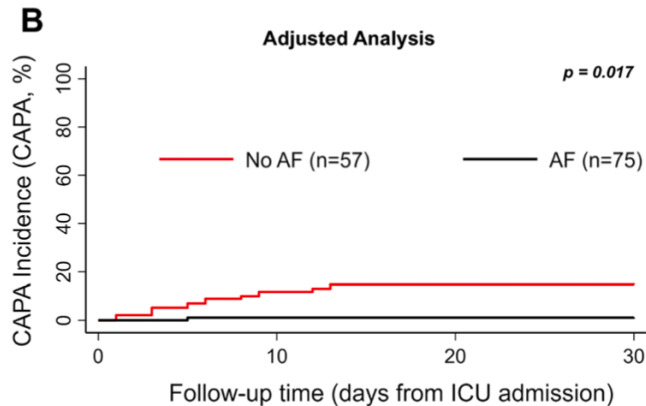
RESEARCH

Open Access

Antifungal prophylaxis for prevention of COVID-19-associated pulmonary aspergillosis in critically ill patients: an observational study



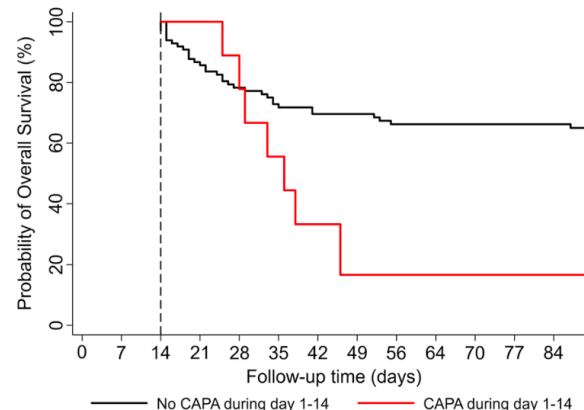
Hatzl *et al. Crit Care* (2021)

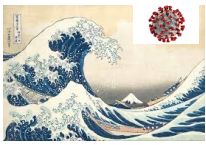


↘ risque de 92%  
17,5 versus 1,4 %

Mais pas d'impact sur  
mortalité

132 patients  
Prophylaxie par posaconazole





# Les leçons...et perspectives ?

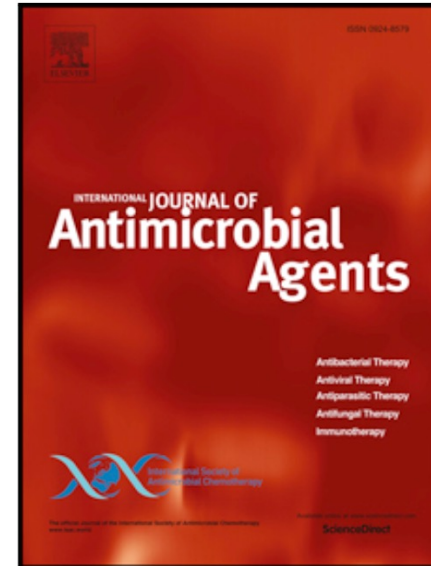


## Stewardship antifongique ?

### Journal Pre-proof

The battle against fungi- lessons in antifungal stewardship from COVID-19 times: a consensus statement on behalf of the International Society of Antimicrobial Chemotherapy, Alliance for the Prudent Use of Antibiotics, European Society of Clinical Microbiology and Infectious Diseases Study Group for Antimicrobial Stewardship, and European Society of Clinical Microbiology and Infectious Diseases Fungal Infection Study Group

Souha S. Kanj , Sara F. Haddad , Jacques F. Meis ,  
Paul E. Verweij , Andreas Voss , Riina Rautemaa-Richardson ,  
Gabriel Levy-Hara , Anuradha Chowdhary , Abdul Ghafur ,  
Roger Brüggemann , Abhijit M. Bal , Jeroen Schouten



# Merci pour votre attention



Merci à la « team fongique » du CHU de Lille

en particulier pour ce topo

- Dr Séverine Loridant en Mycologie
- Dr Angélique Leroy en Pharmacie
- Dr Anahita Rouze en Réanimation
- Dr Benjamin Hennart en Toxicologie



Merci à Socrate pour son aide dans la gestion de la crise COVID...

