OUTCOME REA

HÔPITAUX UNIVERSITAIRES PARIS NORD VAL DE SEINE
Bichat - Claude Bernard

MI² Medical Infectious diseases Intensive care unit

CAPA épidemiologie-diagnostic-traitement

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Infection • Antimicrobiens • Modélisation • Evolution

Université de Paris

Inserm

Liens d’intérêt

- Lecture: Merck, Pfizer, Gilead, Shionogi, Biomerieux
- Ad board: Merck, Pfizer, Shionogi, Beckton, Medimune
- Subvention de recherche: Merck, Pfizer, Thermofischer.

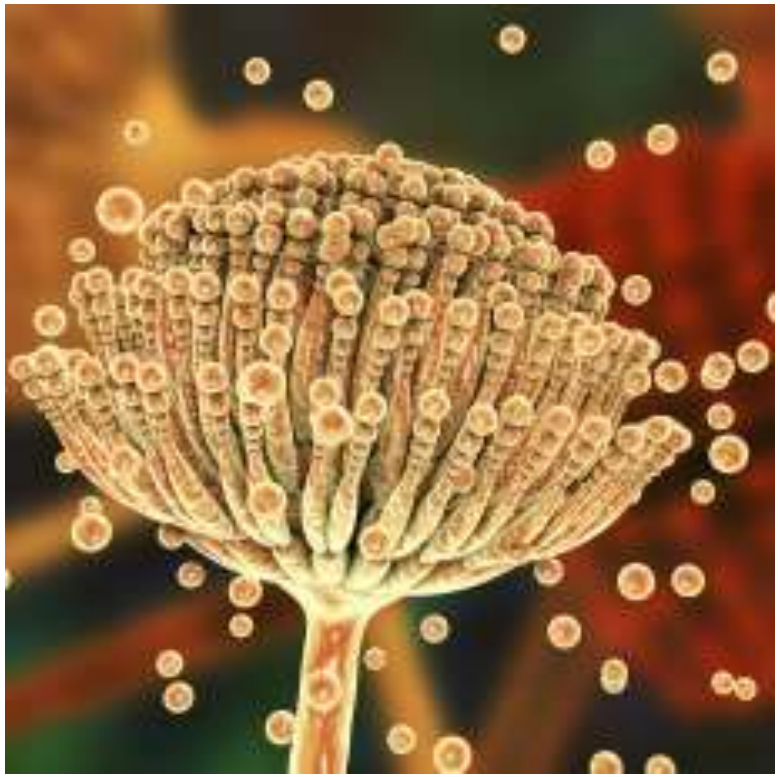
Infections fongiques en réanimation

- Patients immunodéprimés
- Patients en sepsis sévère
- Patients en SDRA
- Sars Cov2?

→ Candida/immunoparalysie

→ Aspergillus/colonisation/altération immunité locale

→ Orage cytokinique
Altération immunitaire locale
Immunosuppresseurs/corticoides
Perturbation des mesures d'hygienes
Contamination environementale
Durée très longue de ventilation

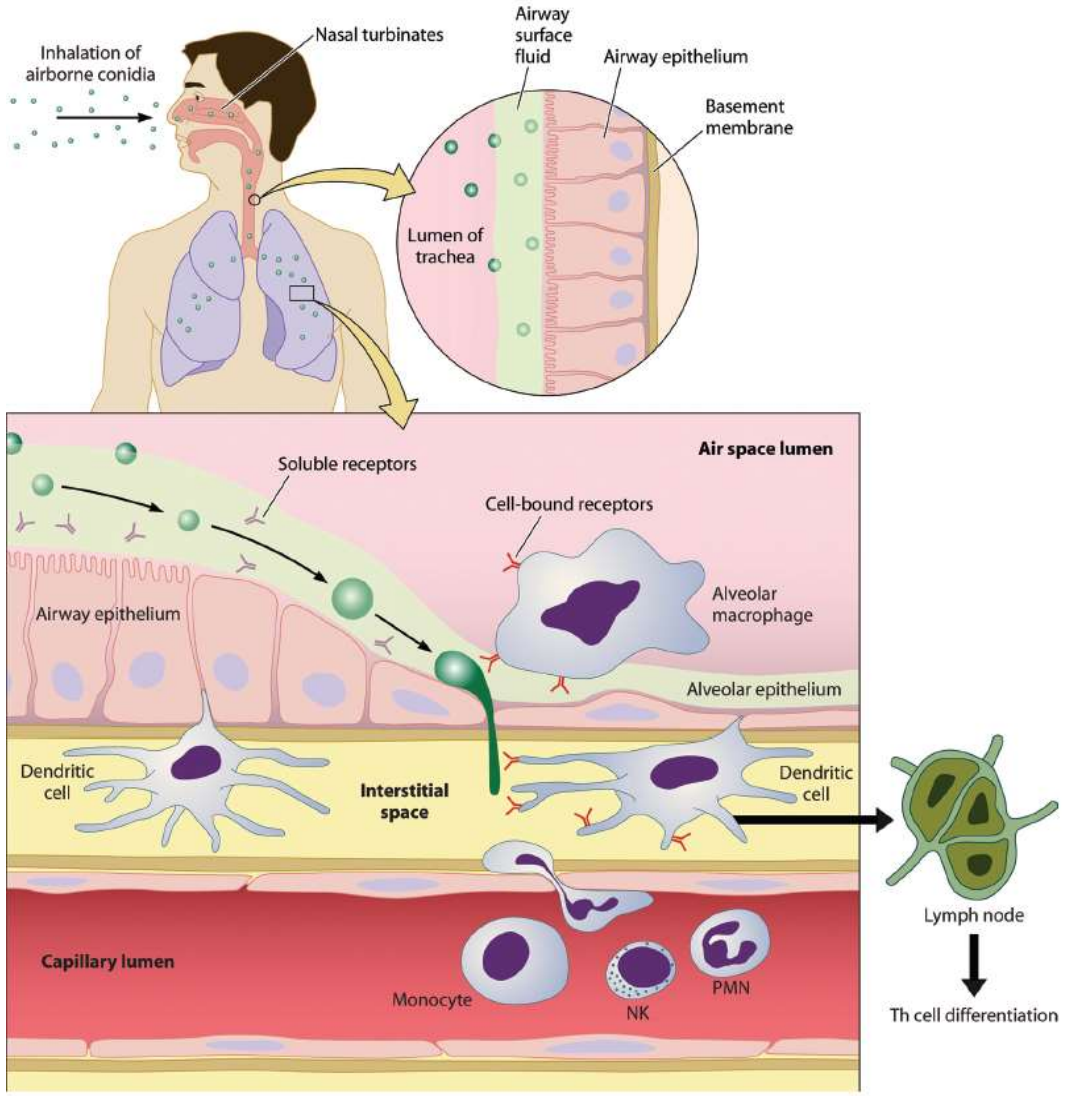


ASPERGILLUS SP.

Immune defenses against Aspergillus

- Physical:
  - Nasal turbinates
  - Ciliary action
  - → A few nasal *Aspergillus conidia* (2 to 5 µm diameter) escape

- Activation of resident innate immunity
  - lung leukocytes dendritic cells and alveolar macrophages
  - → Clearance of residual conidiae

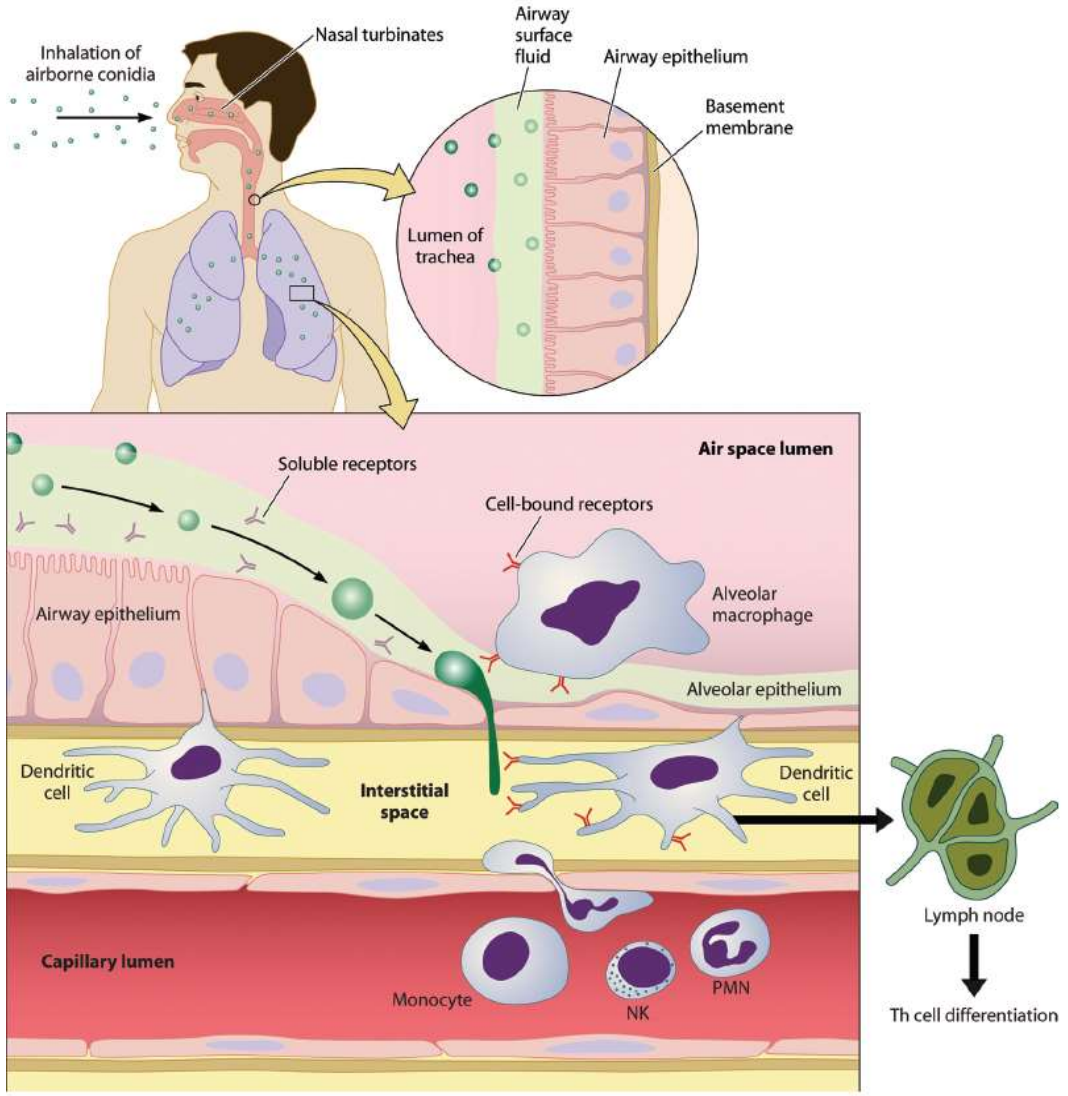


Park SJ et al- CLINICAL MICROBIOLOGY REVIEWS, Oct. 2009, p. 535–551

Immune defenses against Aspergillus

- If not: Germination → Hyphae (15hours)
- INVASION:
  - Pneumonia (tissue diffusion)
  - Hematogeneous dissemination (lung, brain…)
- Ag presentation and Aspergillus specific T-cell clones

→ specific immune response

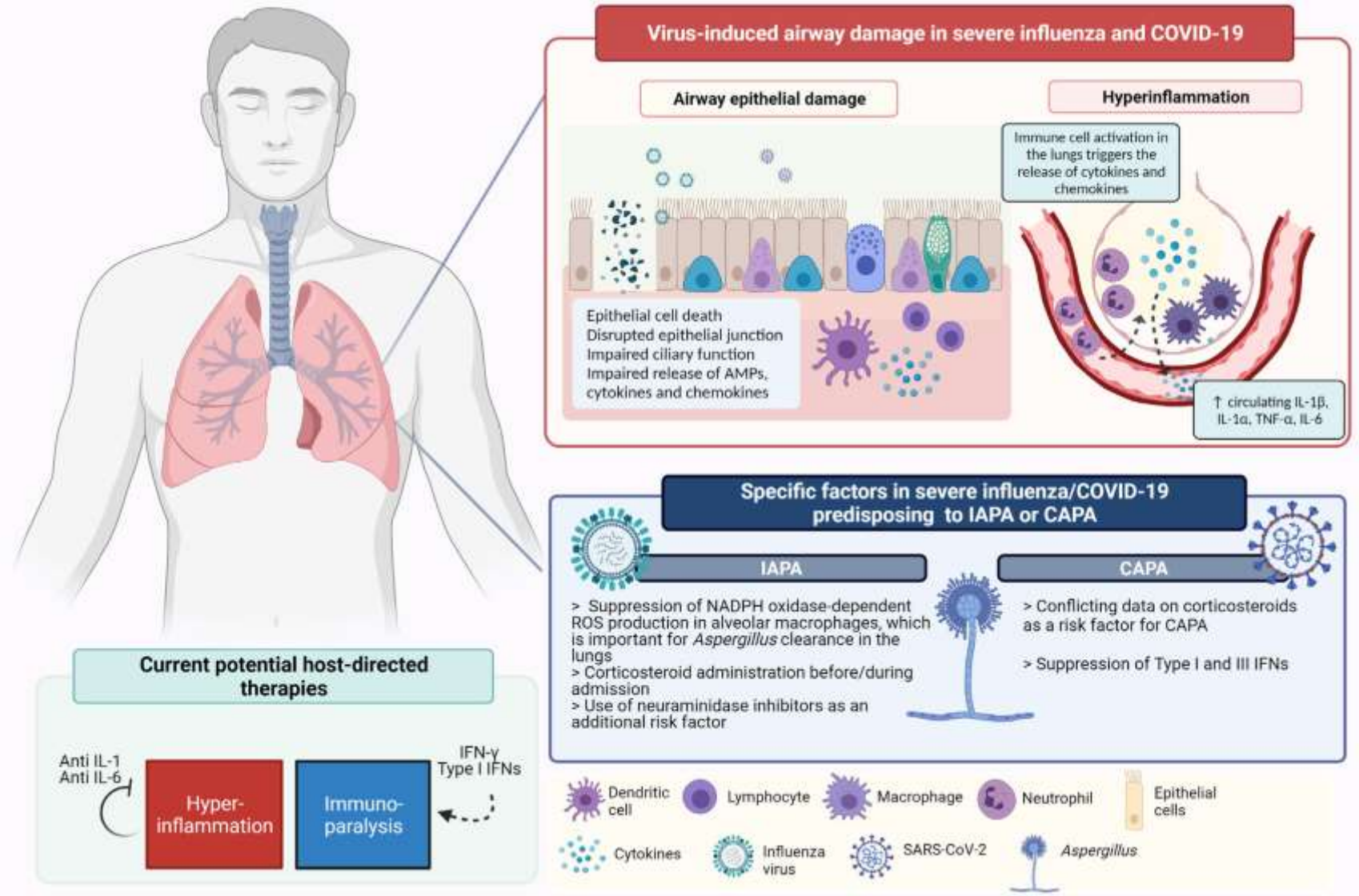


Park SJ et al- CLINICAL MICROBIOLOGY REVIEWS, Oct. 2009, p. 535–551

The host susceptibility will determine the morphological form, Ag structure and physical location of the fungus

- Normal subject:
  - few conidiae rapid local clearance
- COPD, bronchectasis, cavitations:
  - Germination in the airway → Hyphae
  - Solid inflammatory reaction centered in the airway
- Invasion in the lung parenchyma
  - Neutrophils impairement
  - ++role of non-neutrophilic immune system

Pneumonies virales et Aspergilloses



Dewi *et al,* Current Opinion in Microbiology 2021, 62:21–27

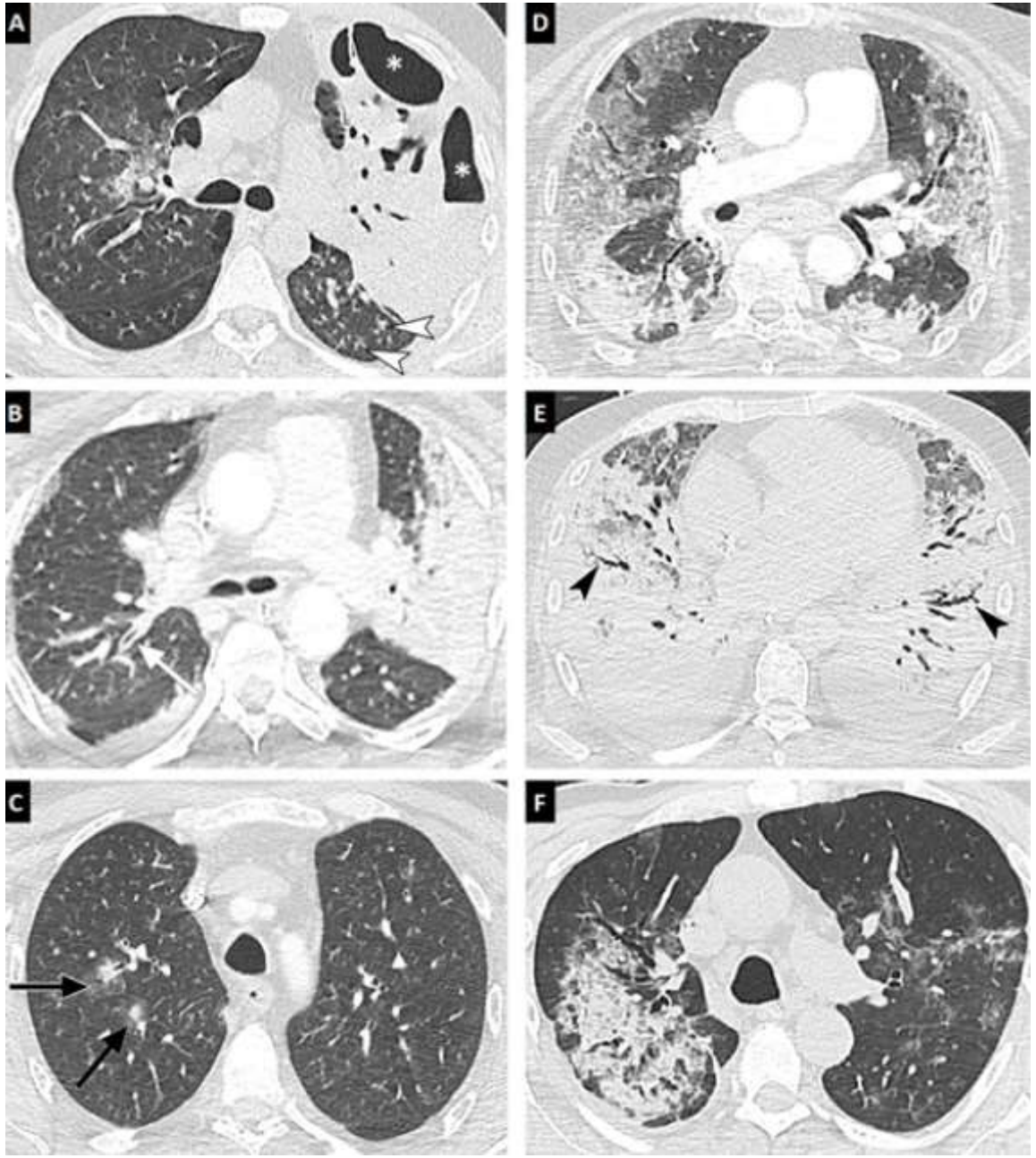
IAPA versus CAPA

	IAPA	CAPA
Prévalence	19%-25%	44%-74%
Angio invasion	+	-
Délai	Précoce (3 jours)	Tardif (8 jours)
FDR EORTC	30-78%	25%
autres	Inhibiteurs neuraminidase Corticoides Lymphopénie	Corticoides Lymphopénie Anti-IL6
Mortalité	51%	44%-74%

CT findings

IAPA

Typical CT findings in LAPA are unilateral or bilateral **areas of consolidation** with **air bronchogram** (**A,B), cavity formation (asterisks), tree in bud (white arrowheads),** bronchial wall thickening (white arrow), or occasionally **nodules with halo signs** (**C, black arrows).**



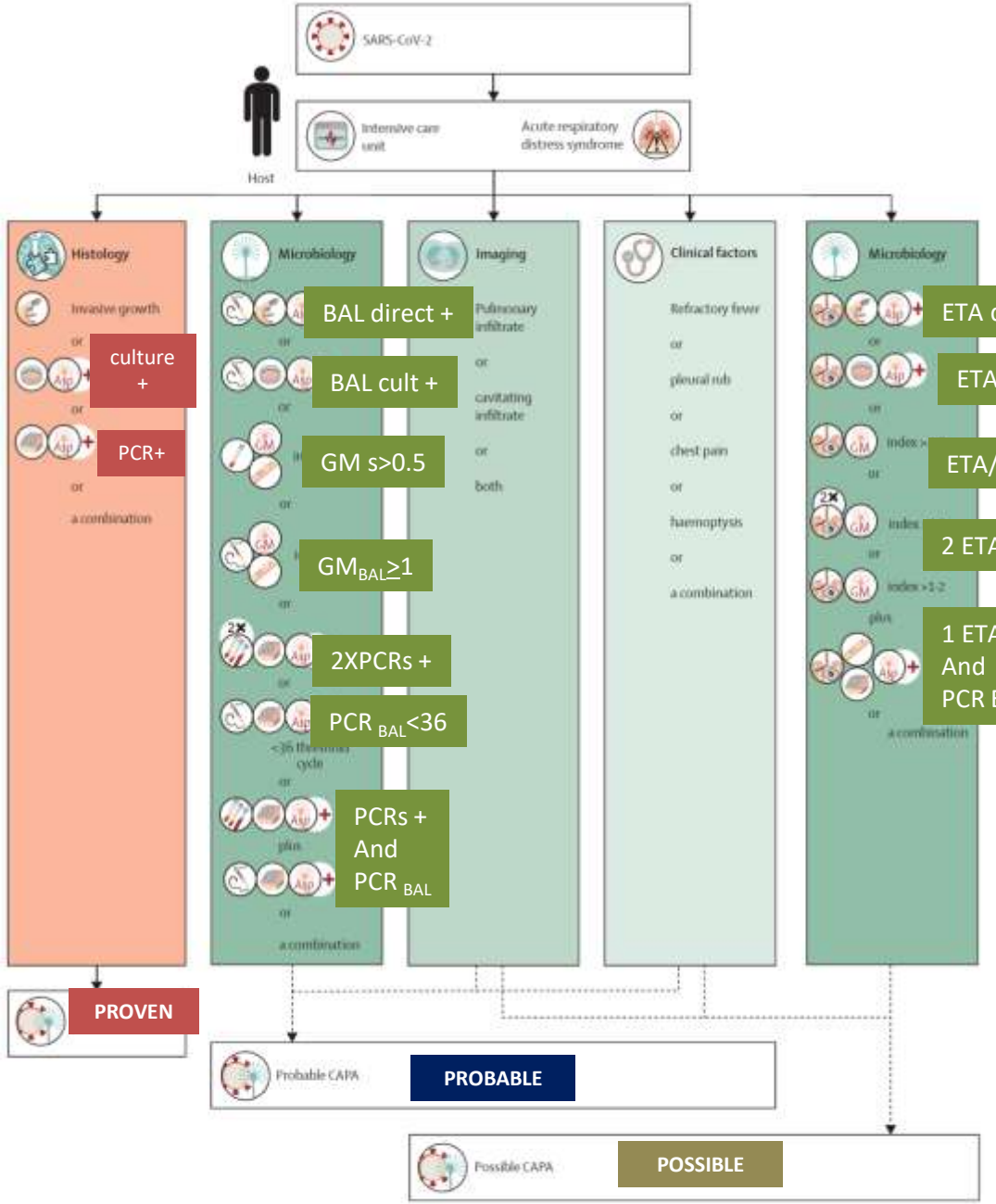
CAPA

Patients may exhibit **non-specific CT findings**, such as bilateral areas of ground-glass opacity and/or crazy paving (**D), extensive consolidations** areas associated with **peripheral traction bronchiectasis** (E, black arrowheads), or, more rarely, unilateral consolidation areas (**F**).

Despite not being very specific for a SARS COV2 infection, findings observed in (D,E) pictures can be seen frequently in severe COVID-19 patients..

Reizine et al – J. Fungi ***2021, 7, 388.***

Definitions CAPA



Koehler et al - ***Lancet Infect Dis 2020;*** https://doi.org/10.1016/ S1473-3099(20)30847-1

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Prévalence/incidence variables

TABLE 2 Overview of CAPA patients in published case series

Country	Diagnostic criterium CAPA	Patients CAPA/ total cohort (%)	Serum GM positive/ tested (%)	Serum BDG positive/ tested (%)	Mortality (%)
Belgium[5]	Verweij et al.	7/34 (20.6)	0/3 (0)	N/A	4/7 (57.1)
China[11]	EORTC/MSGERC	4/50 (8)	N/A	N/A	N/A
Denmark[10]	AspICU algorithm	2/27 (7.4)	0/2 (0)	N/A	2/2 (100)
France[8]	AspICU algorithm	19/106 (17.9)	1/12 (8.3)	N/A	7/19 (36.8)
France[9]	N/A[a]	9/27 (33.3)	1/9 (11.1)	4/8 (50)	4/9 (44.4)
Germany[6]	AspICU algorithm	5/19 (26.3)	2/5 (40)	N/A	3/5 (60)
Italy[7]	Verweij et al.	30/108 (27.8)	1/16 (6.3)	N/A	13/30 (43.3)
Mexico[12]	AspICU algorithm	14/144 (9.7)	6/14 (42.9)	N/A	8/14 (57.1)
Switzerland[13]	Verweij et al.	3/80 (3.8)	1/3 (33)	1/2[b] (50)	1/3 (33.3)
The Netherlands[3]	Verweij et al.	6/31 (19.4)	0/3 (0)	N/A	4/6 (66.7)
The Netherlands[4]	N/A[a]	9/42 (21.4)	N/A	N/A	2/9 (22.2)
The Netherlands - this case series	ECMM/ISHAM consensus criteria	13/66 (19.7)	0/6 (0)	1/1 (100)	6/13 (46.2)
United Kingdom[1]	Verweij et al.[a]	15/ 122(12.3)	2/3 (66.7)	7/7 (100)	8/15 (53.3)
United Kingdom[2]	AspICU algorithm	15/61 (24.6)	5/15 (33.3)	12/15 (80)	N/A
Total		151/917 (16.5)	19/91 (20.9)	25/33 (75.8)	62/132 (47.0)

Meijer *et al,* Mycoses 2021

Impact of CAPA definitions on incidence

Incidence of CAPA (COVID-19-associated pulmonary aspergillosis) among non-immunocompromised patients in published cohorts according to definition criteria

Consideration of publications in the paper by Koehler et al.	References	Date of online availability	Incidence of COVID-19-associated aspergillosis reported by the authors[a]	Incidence of proven/probable cases according to Koehler et al.	Incidence of possible cases according to Koehler et al.
Publications referenced in the paper by Koehler et al.	Koehler et al. [3]	15th May 2020	26.3% (5/19)	21.1% (4/19)	0% (0/19)
	Alanio et al. [2]	29th May 2020	30.8% (8/26)	19.2% (5/26)	3.8% (1/26)
	Rutsaert et al. [16]	1st June 2020	31.6% (6/19)	26.3% (5/19)	5.3% (1/19)
	Van Arkel et al. [4]	1st July 2020	19.4% (6/31)	9.7% (3/31)	6.5% (2/31)
	Heard et al. [13] [b]	3rd July 2020	0% (0/57)	0% (0/57)	1.8% (1/57)
	Gangneux et al. [6]	10th July 2020	20.0% (9/45)	Not calculable	Not calculable
	Nasir et al. [5]	18th July 2020	21.7% (5/23)	0% (0/23)	21.7% (5/23)
	Bartoletti et al. [7]	28th July 2020	28.2% (29/103)	28.2% (29/103)	0% (0/103)
	White et al. [8]	29th August 2020	14.1% (19/135)	2.2% (3/135)	8.1% (11/135)
	Subtotal		**19.0% (87/458)**	**11.9% (49/413)**	**5.1% (21/413)**
Publications not referenced in the paper by Koehler et al.	Wang et al. [14]	5th June 2020	7.7% (8/104)	3.8% (4/104)[c]	3.8% (4/104)
	Lamoth et al. [11]	10th July 2020	3.8% (3/80)	1.3% (1/80)	2.5% (2/80)
	Brown et al. [12]	6th August 2020	0% (0/60)	0% (0/60)	6.7% (4/60)
	Subtotal		**4.5% (11/244)**	**2.0% (5/244)**	**4.1% (10/244)**
Publications not available at the time the paper by Koehler et al. was written	Dupont et al. [19]	10th September 2020	17.9% (19/106)	8.5% (9/106)	7.5% (8/106)
	Chauvet et al. [18]	11th November 2020	9.8% (4/41)	4.9% (2/41)	0% (0/41)
	Roman-Montes et al. [21]	20th November 2020	9.7% (14/144)	3.5% (5/144)	6.3% (9/144)
	Fekkar et al. [20]	2nd December 2020	2.4% (3/125)	1.6% (2/125)[d]	0.8% (1/125)
	Segrelles-Calvo et al. [22]	3rd December 2020	3.3% (7/215)	2.8% (6/215)[c]	0.5% (1/215)
	Subtotal		**7.4% (47/631)**	**3.8% (24/631)**	**3.0% (19/631)**
All publications	**Total**		**10.9% (145/1333)**	**6.1% (78/1288)**	**3.9% (50/1288)**
			10.9%	6.1%	3.9%

Fekkar et al - Clinical Microbiology and Infection 27 (2021) 1376e1378

Invasive mould: autopsies of 443 sars-Cov2

2 %

	Invasive mould disease (n=10 [2%])	No invasive mould disease (n=433 [98%])
Median age, years (IQR)	60 (40–75·5)	70 (57–79)*
Male	9/9 (100%)	260/393 (66%)
Pre-existing lung disease	1/9 (11%)	94/392 (24%)
Immunocompromised	1/9 (11%)	26/407 (6%)
Median duration from symptom onset to death, days (IQR)	9 (6·8–22·5)†	14 (9–26)†
Median hospital length of stay, days (IQR)	14·0 (5·5–26·0)‡	10·0 (5·0–22·5)§
Ventilated	6/10 (60%)	172/339 (51%)
Median ventilation time, days (IQR)	7·0 (6·5–15·5)¶	9·0 (5·0–20·0)‖
Host-directed therapies for COVID-19	1/9 (11%)	59 (14%)

Data missing for *60 decedents, †3 decedents, ‡5 decedents, §112 decedents, ¶1 decedent, and ‖37 decedents.

Table 3: **Individual-level data for decedents with and without autopsy-proven invasive mould disease**

Aspergillus (8), Mucor (1) not identified (2)

Kula BE et al - Lancet Microbe 2021; 2: e405–14

Quels prélèvements?

	Pros	Cons	Comments related to CAPA
Lung biopsy	Provides proof of IPA	Risk of sampling error; scarcely used due to high risk of complications	CT-guided biopsies post mortem have been used as alternative to autopsy[29]
Bronchoscopy with bronchoalveolar lavage	Allows visualisation of lesions (eg, plaques); bronchoalveolar lavage well validated for the diagnosis of IPA and IAPA; validated specimen for aspergillus antigen test (eg, enzyme immunoassay and lateral flow assay) and PCR; targeted sampling possible	Aerosol generation and contamination of surfaces	In some centres, use is decreased because of risk of nosocomial transmission and SARS-CoV-2 infection of health-care workers;[22,30] SARS-CoV-2 infectiousness correlates with PCR-signal strength, which can be used as guidance on when it's safe to perform bronchoscopy[31–33]
Non-bronchoscopic lavage	Obtains material from lower respiratory tract; technique validated for diagnosis of ventilator-associated pneumonia; closed-system sampling	Not fully validated for IPA diagnosis; not fully validated for aspergillus antigen and PCR detection; non-targeted sampling	Suggested as alternative to bronchoalveolar lavage to diagnose CAPA; small number of validation studies[12,34]
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[11]

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

Table 1: Pros and cons of diagnostic procedures and their samples in patients with COVID-19

Koehler et al - ***Lancet Infect Dis*** December 14, 2020 https://doi.org/10.1016/S1473-

Risk factors of CAPA (systematic review)

Traditionally recognized risk factors for IPA

- Haematological diseases
- Organ transplant receipients
- HCST
- Long-term CS therapy
- Immunosuppressive agents

- COPD
- Liver cirrhosis
- Chronic kidney diseases

- infection and Intensive Care Unit (ICU) admission.

Reported for CAPA

- Host factors
  - Respiratory diseases
  - Cardiovascular diseases (Hypertension, coronary diseases, cardiomyopathy)
  - Hepatic diseases (chronic hepatitis B)
  - Type 2 Diabetes
  - Renal failure
- ICU management factors
  - Median time from ICU adm 8 days
  - Mechanical ventilation
- Covid-19 immunomodulating therapies
  - Corticosteroids
  - Tocilizumab
- Intercurrent infections
  - Previous bacterial infections?
  - Previous broad-spectrum antibacterial therapy
- Environmental and logistic factors
  - Negative atmospheric pressure?
  - isolation conditions, ventilation systems,
  - Building renovation works,
  - Overcrowding? (temporal spread with respect to pandemic waves)

Montrucchio *et al. Ann. Intensive Care (2021) 11:136*

Impact of negative air pressure in ICU rooms on the risk of pulmonary aspergillosis in COVID-19 patients

ICU Covid-19 + patients

Date (DD/MM)	< 22/03	22/03	09/04	15/04	24/04	27/04	4/05	15/07
Air Room pressure Mean (Pa)	Positive +15 ± 5	Negative -11.1 ± 3.9		Slightly Negative -5		Slightly Positive 1.2 ± 1.5		
Patients (n=26)		Proven or probable pulmonary Aspergillosis (AF) ; n=6 Colonisation by AF; n=2			0 new case of pulmonary aspergillosis 0 new case of *Aspergillus* colonisation			
Room air cultures (n=15)		AF (+) : 3 of the 4 rooms tested		AF (-) : 11 rooms AF (+) : 4 rooms (2, 124, 108, 78 CFU/m³)		AF (-) : 8 rooms AF (+) : 7 rooms (4, 2, 6, 4, 4, 4, 2 CFU/m³)	AF (-) : 14 rooms AF (+) : 1 room : 2 CFU/m³	Absence of AF: 15 rooms

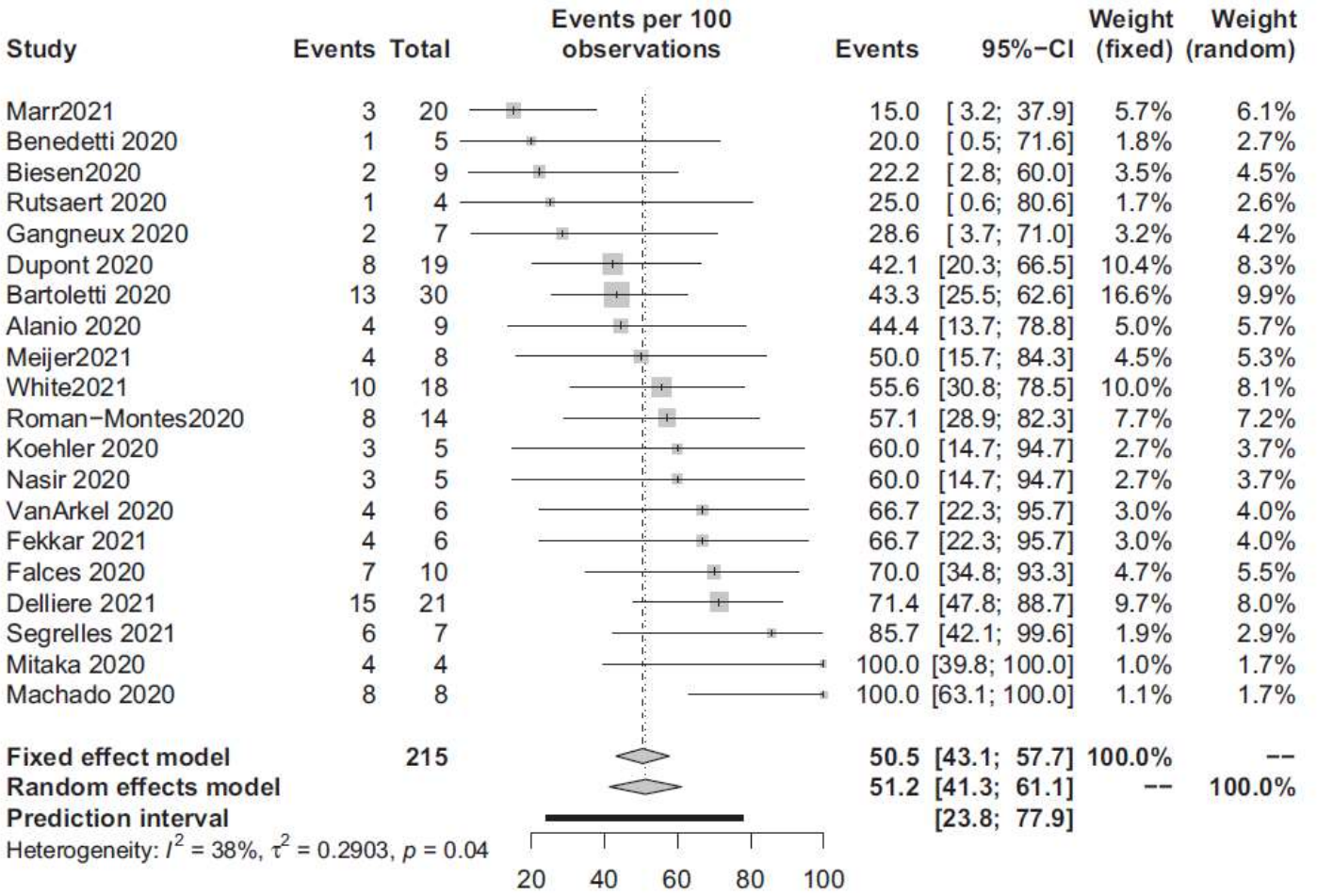
Prophylactic antifungal therapy

*AF, *Asp. fumigatus*, AF (+); presence of *Asp. fumigatus*, AF (-); absence of *Asp. fumigatus*

Role of negative pressure
Poor ventilation
Overcrowding?

Ichai *et al,* Crit Care . 2020 Sep 1;24(1):53

Pooled mortality of CAPA

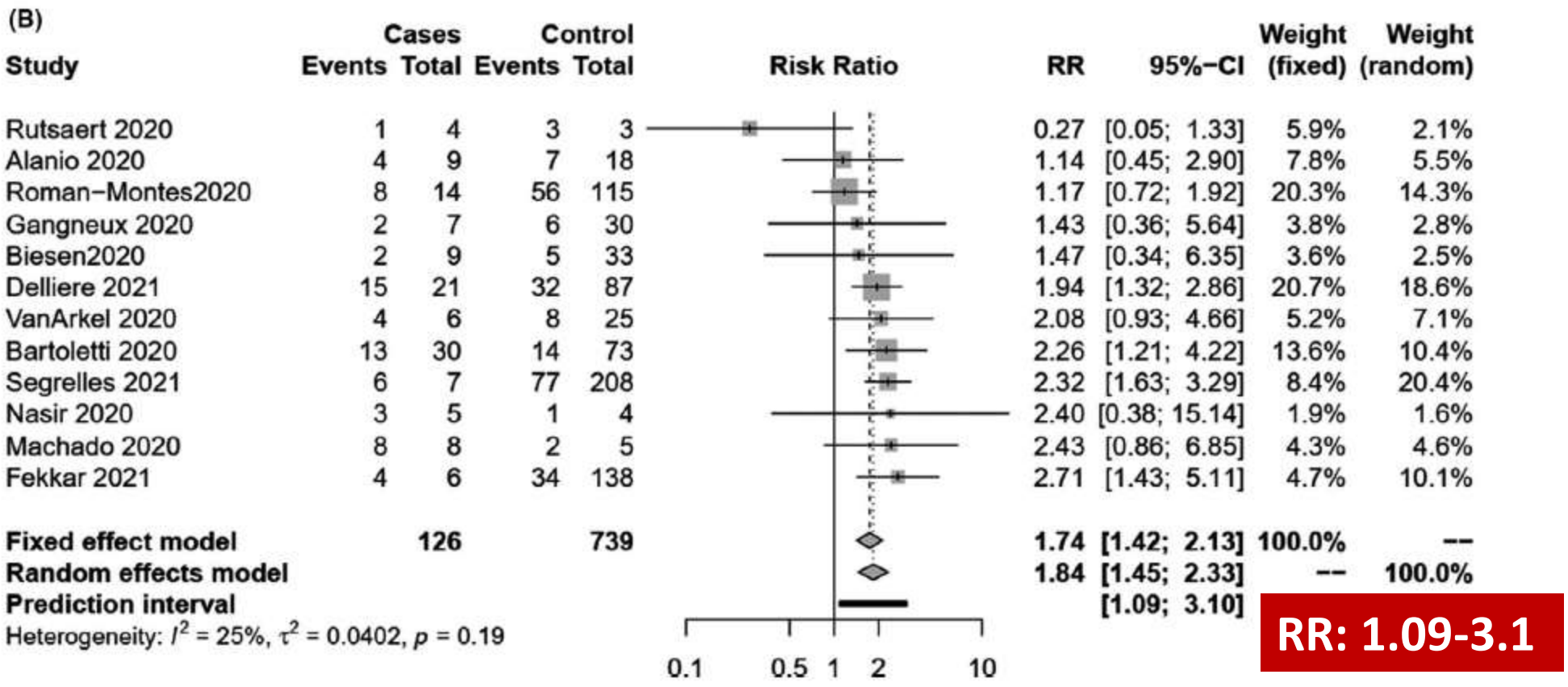


51.2%

Singh et al - Mycoses. 2021;64:1015–1027

Pooled mortality of CAPA

(B)



RR: 1.09-3.1

Singh et al - Mycoses. 2021;64:1015–1027

Serum positive test ←→ prognosis

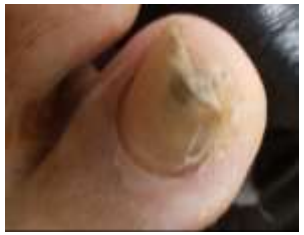
Case/control CAPA
ECMM ISHAM classification
219 critically ill
1 proven/38 probable/19 possible
21 colonized, 7 BDG = only, 133 nothing

	N death(%)/n survivors (%)	OR	P value
Age		**1.054 (1.021-1.089)**	**0.001**
Hematological malignancies	**6 (66.7) vs 47 (28.8)**	**4.936 (1.185-20.560)**	**0.028**
BAL culture	9 (52.9) vs 16 (30.8)	2.531 (0.826-7.756)	0.10
BAL GM>1.0	10 (45.5) vs 15 (36.6)	1.444 (0.504-4.139)	0.49
BAL PCR positive	4 (57.1) vs 11 (30.6)	3.030 (0.578-15.880)	0.19
Serum GM>0.5	**7 (87.5) vs 38 (27.7) 18.237**	**(2.171-153.217)**	**0.008**
Serum BDG>80 pg/ml	**9 (90.0) vs 29 (30.2)**	**20.793 (2.517-171.750)**	**0.005**
Serum Aspergillus PCR +	4 (80.0) vs 12 (38.7)	6.333 (0.630-63.639)	0.12
CAPA (Case/control)	21 (53.8) vs 32 (24.1)	3.682 (1.749-7.753)	0.001
Treatment/no treatment	25 (56.8) vs 28 (21.9)	4.699 (2.267-9.742)	<10-4

Ergun M - J Clin Microbiol 2021 doi:10.1128/JCM.0122

La routine n'est pas simple….

- M B 59 ans J45 VM/ ECMO sevrée
- VAP KP traitée depuis 12 jours/ prelevement de contrôle 10 ufc KP.
- 13/10 T° 39°C persistante, PF ratio 150 mmHg
- Bilan fungique:



- Abces persistant
- 27/10 Pneumomediastin
- 13/10 10 colonies de KP + FA+
- 9/11 Hemoptysie → embolisation
- 18/11 surinfection Citrobacter NDM+

Date	Prélèvement	Résultat
14/09/2021	Sérum	GM = 0,03, BDG=<8
20/09/2021	LBA	ED, culture, PCR A fum et A spp, GM = 0,03, négatifs
20/09/2021	Sérum	GM = 0,04, BDG=16
27/09/2021	LBA	ED, culture, PCR A fum et A spp, GM= 0,23, négatifs
27/09/2021	Sérum	GM = 0,02, BDG=18
01/10/2021	LBA	ED, culture, PCR A fum et A spp, GM = 0,15 négatifs
04/10/2021	LBA	ED, culture, PCR A fum et A spp, GM= 0,01 négatifs
04/10/2021	Sérum	GM = 0,07, BDG=51
11/10/2021	LBA	ED, culture, PCR A fum et A spp, GM= 0,29 négatifs
14/10/2021	**LBA**	**ED, culture, PCR A fum et A spp, négatifs, GM= 15,7 positif**
14/10/2021	**Sérum**	**GM = 0,11, BDG=<8**
17/10/2021	**LBA**	**ED, culture, PCR A fum et A spp négatifs, GM = 22,34 positif**
18/10/2021	**Ongles de pieds**	**ED positifs filaments septés, culture en cours neg**
18/10/2021	**Sang**	**PCR A fum et A spp negatif**
18/10/2021	**Sérum**	**Sérologie aspergillaire neg, BDG neg**
18/10/2021	**Sérum**	**GM: 1,75 et BDG <8**
19/10/2021	**LBA**	**GM 1,0**
27/10/2021	**LBA**	**GM LBA 2.21/**
27/10/2021	**serum**	**PCR + A fumigatus CT 36**
18/11/2021	**LBA**	**Negatif (pcr/GM/culture**
18/11/2021	**sérum**	**BDG/GM/PCR Negatif**

13/10

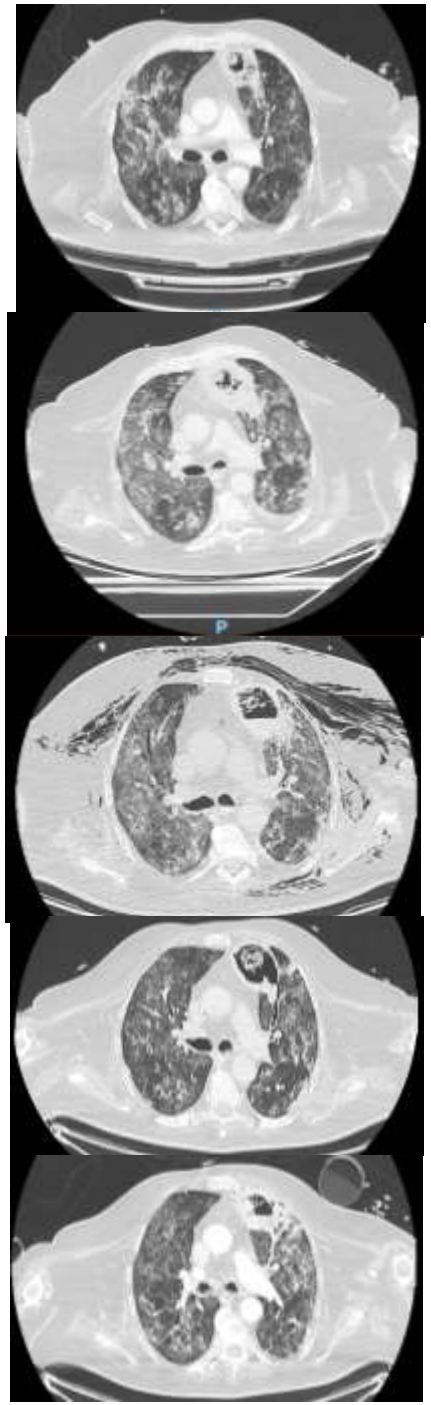
18/10

AmBL VRZ

27/10

9/11

18/11



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ICU management

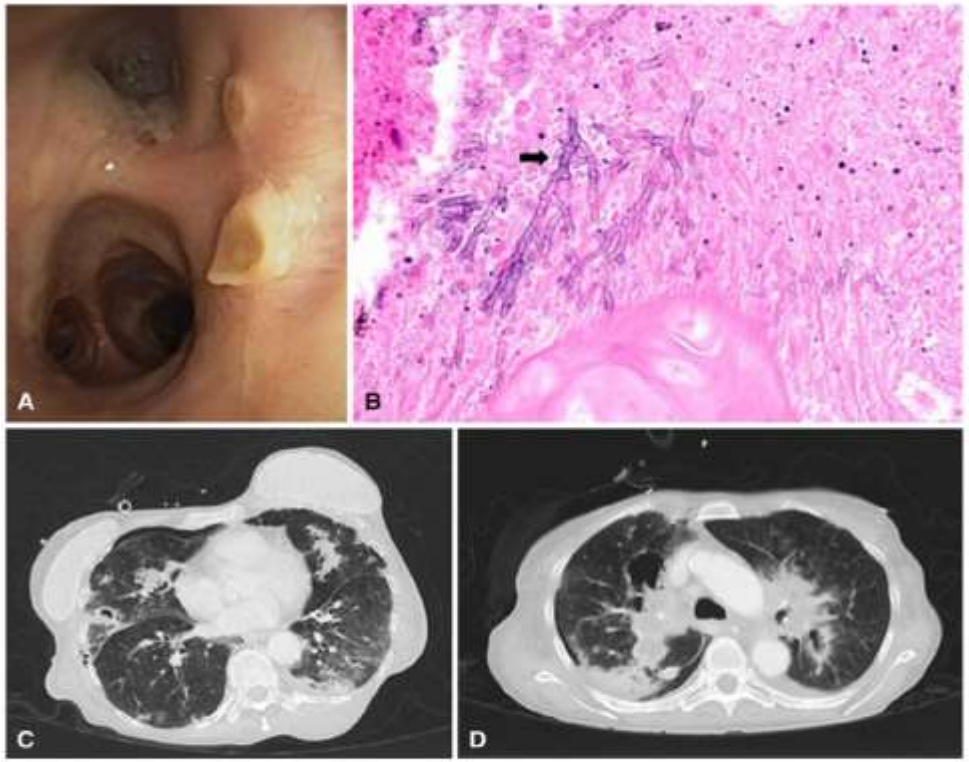
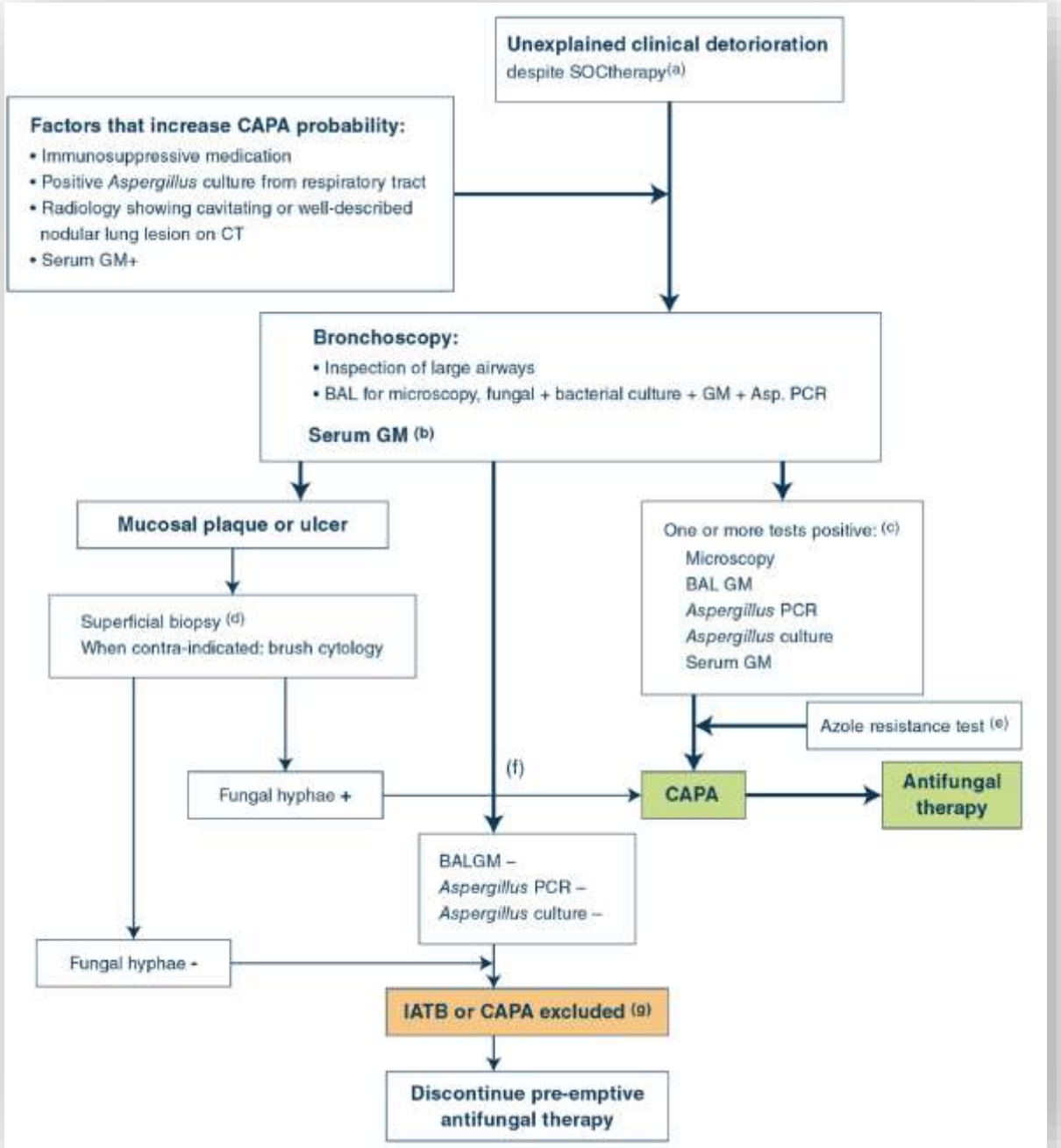


Fig. 1 **a** Multiple tracheal ulcerations on day 3. **b** Histology of lung parenchyma with invasive pulmonary aspergillosis (*arrow*). **c** CT scan of the lungs on day 4 showing bilateral alveolar and peribronchial lesions compatible with invasive aspergillosis. **d** CT scan of the lungs on day 11 showing progressive bilateral cavities

IATB: invasive aspergillus tracheobronchitis
CAPA: covid associated pulmonary aspergillosis



International task force - *Intensive Care Med (2021) 47:819–834*

When to consider CAPA?

1. **CAPA occurs predominantly in patients on mechanical ventilation >5 days**
2. Risk factors: High-dose or long administration of corticosteroids; EORTC/MSGERC host/risk factor; structural lung disease
3. Diagnostic work-up recommended in clinically deteriorating patients with no other explanation or with cavitary and/or nodular lesions on CT scan. Halo sign and hypodense consolidation lesions may be absent in CAPA. Bronchoscope inspection of airways warranted

How to diagnose CAPA?

1. Bronchoscopy with BAL
2. Microbiological investigations of BAL: microscopy, culture, GM, and/or Aspergillus PCR
3. **Mucosal biopsy when plaques are visible in trachea and/or bronchi**
4. Serum GM or BDG are not recommended for patient monitoring, but when positive indicative of advanced CAPA. Serum BDG not specific for *Aspergillus*
5. **Patients with cavitary lung lesions, exclude necrotising pneumonia due to bacterial pathogen (e.g. *S. pneumoniae, S. aureus*)**

How to treat CAPA?

1. **Antifungal prophylaxis is not recommended in mechanically ventilated COVID-19 patients**
2. Empirical antifungal treatment for visible plaques in trachea and/or bronchi or in patients rapidly deteriorating
3. Antifungal therapy in IATB confirmed and Aspergillus+ BAL, GM or PCR tests
4. 1L voriconazole, as per (inter)national guidelines
5. TDM for patients receiving voriconazole
6. **Stop empirical antifungal if BAL GM and culture are negative**

International task force - *Intensive Care Med (2021) 47:819–83*

RECENT DATA

Risk factors and prognosis of CAPA

Multivariable Model	Variable	Multivariable hazard ratio	95% CI	p value
#1 ($n = 592$)	CAPA	1.77	1.31–2.37	<0.001
	Age	1.04	1.03–1.05	<0.001
#2 ($n = 592$)	CAPA	2.23	1.66–2.99	<0.001
	Study centre	0.96	0.94–0.98	<0.001
#3 ($n = 592$)	CAPA	1.97	1.46–2.67	<0.001
	Active malignancy	1.47	0.98–2.23	0.062
	Solid organ transplantation	1.38	0.74–2.58	0.304
	Cardiovascular disease	1.19	0.92–1.54	0.178
	Diabetes mellitus	1.31	1.00–1.72	0.047
	History of smoking	1.46	1.02–2.08	0.037
#4 ($n = 592$)	CAPA	1.68	1.23–2.28	0.001
	Age	1.04	1.03–1.06	<0.001
	Study centre	0.95	0.94–0.97	<0.001
	Active malignancy	1.30	0.86–1.97	0.207
	Solid organ transplantation	1.59	0.85–2.98	0.145
	Cardiovascular disease	0.84	0.64–1.09	0.204
	Diabetes mellitus	1.36	1.04–1.78	0.022
	History of smoking	1.50	1.04–2.15	0.028

In multivariate Cox models CAPA was associated with an increased risk of death

SAT initiated in 99 out of 109 patients with CAPA (90.7%). 50/99 were alive at ICU discharge vs 2/20 if not treated

Prattes J et al., CMI, https://doi.org/ 10.1016/j.cmi.2021.08.014

MYCOVID- Sars-Cov2 mechanically ventilated patients

509 MV patients/ 17 centres prospectif

Screening systématique X 2/ sem bronchique +- sérum

PCR Asperg/PJP/Mucor

Table 2. Prevalence of infections in 509 mechanically ventilated COVID-19 patients in the intensive care unit (ICU) and antifungal treatments.

	Prevalence of infections n (%, [95% CI])
CAPA status*	
- pr/pb invasive aspergillosis	76 (14·9% [11·9 – 18·3])
- pos invasive aspergillosis	24 (4·7% [3·0 - 6·9])
AspICU status#	
- pr/pu invasive aspergillosis	57 (11·2% [8·6 - 14·3])
- Aspergillus colonization	48 (9·4% [7·0 - 12·3])
Other invasive fungal infections (one or more)	38 (7·5% [5·3 - 10·1])
- Candidemia	32 (6·3% [4·3 - 8·8])
- Invasive mucormycosis	6 (1·2% [0·4 - 2·5])
- Invasive fusariosis	1 (0·2% [0·0 - 1·])
Bacterial VAP (509)	374 (73·5% [69·4 - 77·3])
CMV infection (491)	49 (10·0% [7·5 - 13·0])
HSV1 infection (491)	76 (15·5% [12·4 - 19·0])

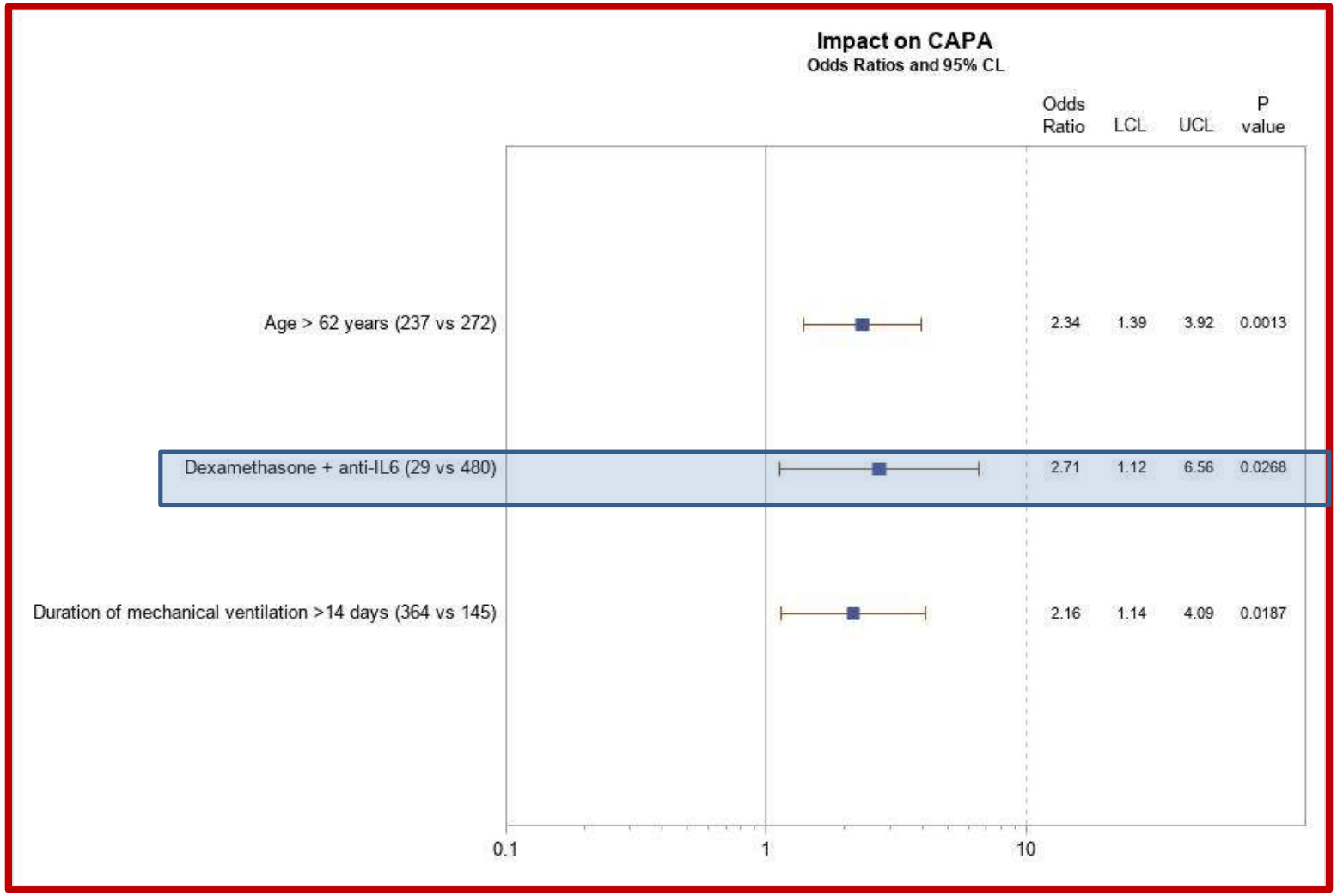
Gangneux et al – Lancet Respir Med. 2021 Nov 26:S2213-2600(21)00442-2.

MYCOVID- Risk of CAPA (Pr/Pr n=76/509)

509 MV patients/ 17 centres prospectif

Screening systématique X 2/ sem bronchique +- sérum

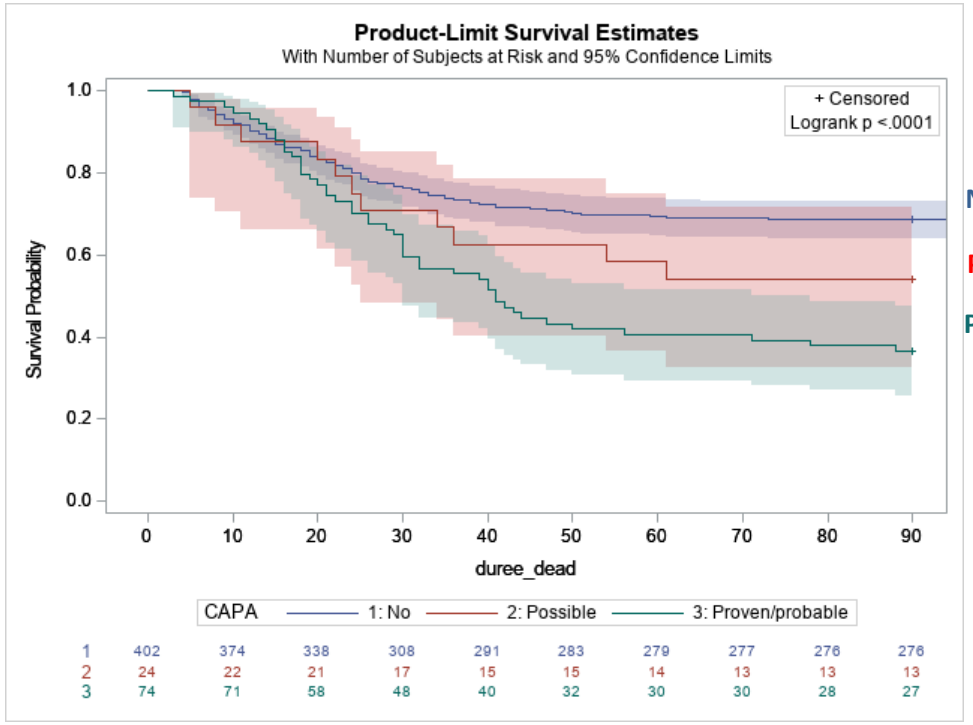
PCR Asperg/PJP/Mucor



Multivariate analysis

Gangneux et al – Lancet Respir Med. 2021 Nov 26:S2213-2600(21)00442-2.

MYCOVID- risk of mortality



No CAPA : 30.9%

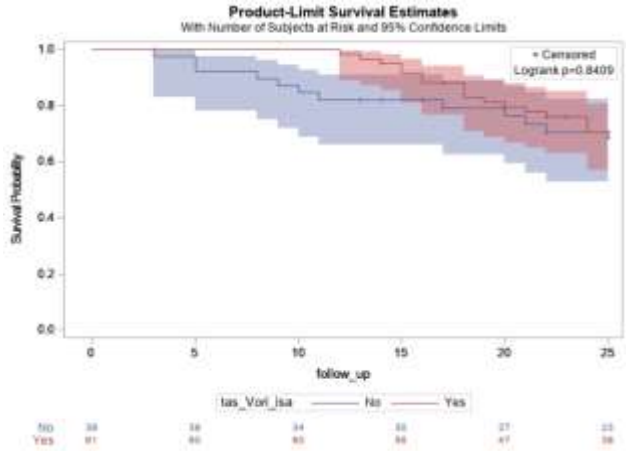
Possible CAPA : 45.8%

Proven/probable CAPA : 59.8%

Classification of CAPA according to Koehler et al. The Lancet Infectious Diseases, 14 Dec 2020

Multivariate Cox model of death	
Age > 62	HR=1.71, p=0.005
SOT (n=35)	HR=2.46, p=0.0015
Proven probable CAPA (n=76)	HR=1.45, p=0.032
Candidemia (n=26)	HR=1.11, p=0.71

Vori/isa treatment not associated with prognosis



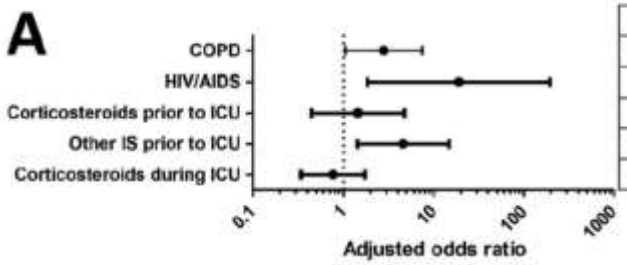
Gangneux et al – Lancet Respir Med. 2021 Nov 26:S2213-2600(21)00442-2.

Risk factors of CAPA (vs CAPA excluded)

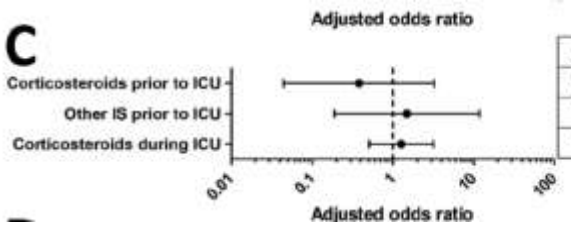
Cohort 1 n=519 (Belgium)

Cohort 2 n=304 (France)

Risk factors of CAPA

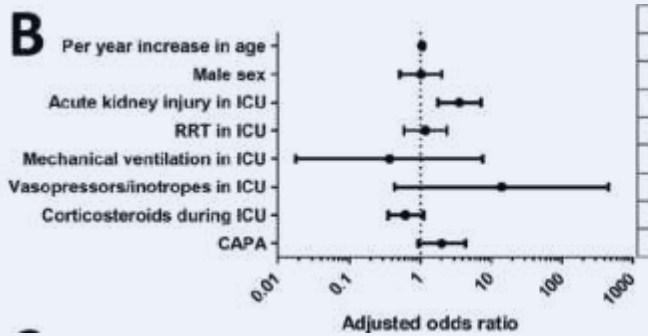


aOR (95% CI)	p value
2.80 (1.05–7.46)	0.039
18.96 (1.84–195.11)	0.013
1.45 (0.44–4.78)	0.54
4.59 (1.43–14.76)	0.011
0.77 (0.34–1.73)	0.52



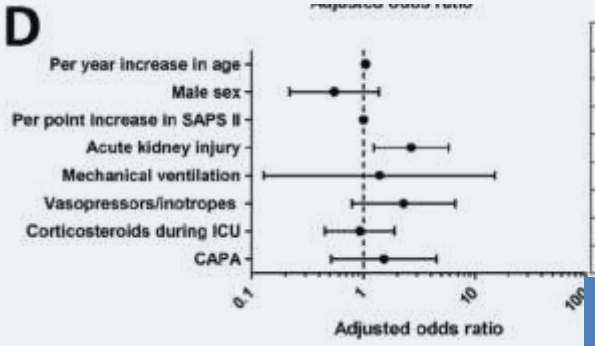
aOR (95% CI)	p value
0.38 (0.04–3.25)	0.38
1.49 (0.19–11.84)	0.71
1.27 (0.50–3.19)	0.62

Risk factors of death



aOR (95% CI)	p value
1.07 (1.03–1.10)	< 0.0001
1.02 (0.52–2.03)	0.95
3.59 (1.78–7.22)	0.0003
1.19 (0.59–2.39)	0.63
0.37 (0.02–7.60)	0.52
14.17 (0.44–458.28)	0.14
0.62 (0.35–1.11)	0.11
2.03 (0.94–4.37)	0.07

OR 2.03, p=0.07



aOR (95% CI)	p value
1.04 (1.01–1.08)	0.014
0.55 (0.22–1.38)	0.20
1.00 (0.98–1.02)	0.97
2.69 (1.24–5.82)	0.012
1.40 (0.13–15.23)	0.78
2.29 (0.78–6.67)	0.13
0.92 (0.45–1.91)	0.83
1.53 (0.51–4.55)	0.45

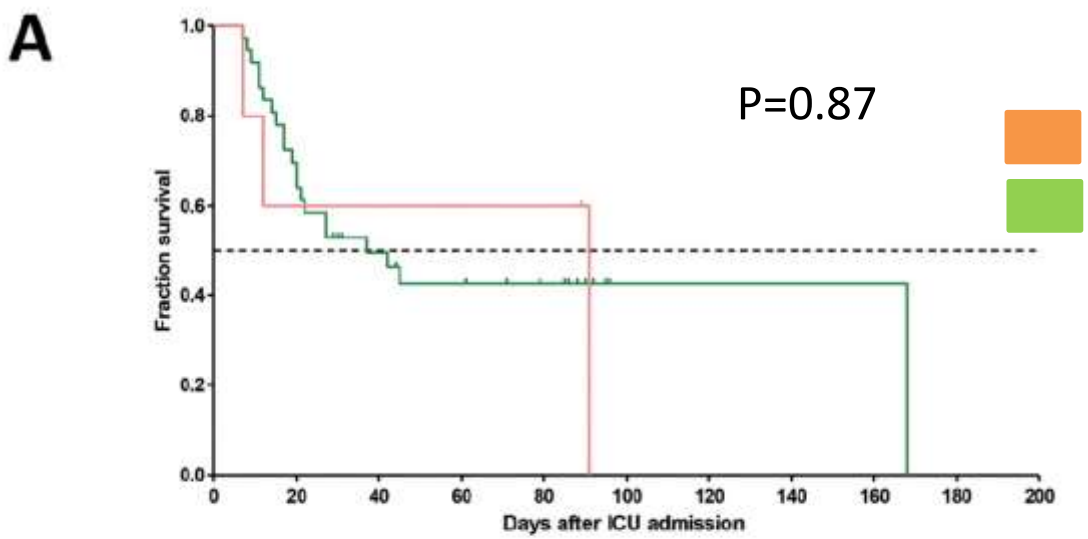
OR 1.53, p=0.45

Janssen et al - Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 27, No. 11, November 2021

Impact of antifungal therapy on mortality

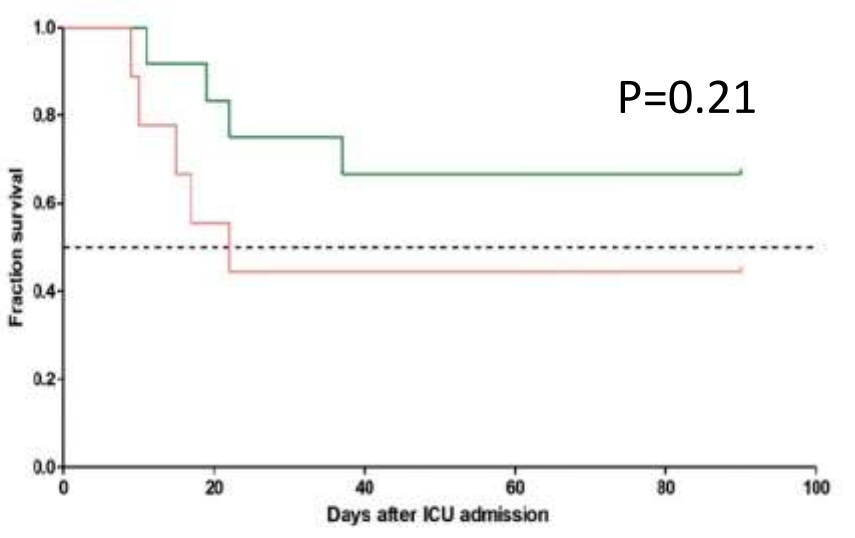
(proven or probable CAPA)

Cohort 1 n=519 (Belgium)



Number at risk									
CAPA, AF	37	25	16	13	10	2	2	2	2
CAPA, no AF	5	4	4	4	4	1	1	1	1

Cohort 2 n=304 (France)



Number at risk						
CAPA, AF	12	11	9	9	9	8
CAPA, no AF	9	6	5	5	5	4

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CAPA encore beaucoup d'incertitudes

- Définition non encore stabilisée.
  - Incertitude sur les techniques diagnostiques
  - Colonisation > invasion tissulaire > invasion vasculaire
- Aspect TDM atypique chez les immunocompétents
- Role des traitements immunosupresseurs
- Rôle de la contamination de l'environnement
- CAPA associée à un sur-risque de décès
  - Peu reversible en cas de traitement
    - Marqueur de gravité
    - traitement trop tardif
    - altération de la PK des antifongiques

Covid 19 et infections fongiques

- Immunoparalysie
- Immunosupresseurs
- Ventilation prolongée
- SDRA/ altérations immunitaires locales
- Rupture de la barrière digestive
- Contamination environnementale
- Surcharge de travail

CAPA

Candidémies

Merci

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