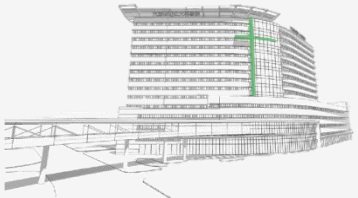
Mini review: 不能「黴」警覺: 新冠肺炎引起的黴菌感染診斷與治療 如何警覺與處置以減少死亡率

輔仁大學附設醫院

重症醫學科 劉偉倫醫師

Jul 31, 2021

輔大醫院
Fu Jen Catholic University Hospital

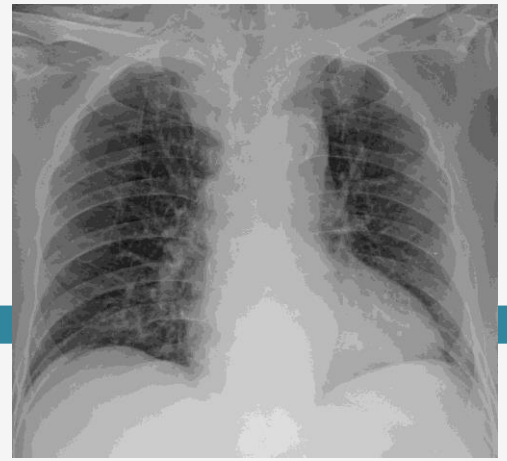


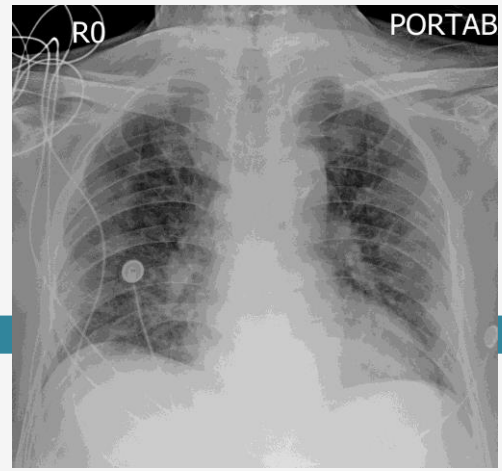
Patient Scenario

74 y/o man

- HTN, type 2 DM, hyperlipidemia

General weakness, nausea, fever



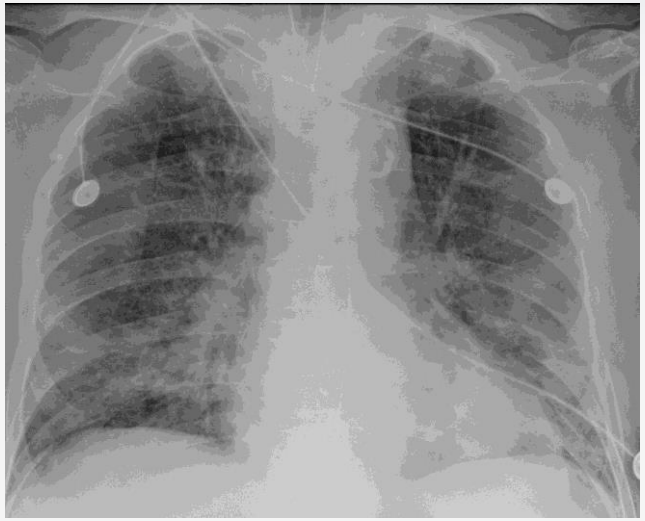


ER → **Ward** → **ICU**

- Vital signs stable without fever
- **COVID-19 PCR: Positive**
- CXR : bilateral lung markings and reticulations

- Elevated CRP (10.67mg/dl), impaired renal function (BUN: 30mg/dl, Cr: 1.7mg/dl)
- CXR bilateral lung infiltrates progress
- **SARS-CoV-2 infectious pneumonia with acute impending respiratory failure**

Patient Scenario



Fever 38.5, pattern shallow with desaturation, HFNC usage

ICU day 5

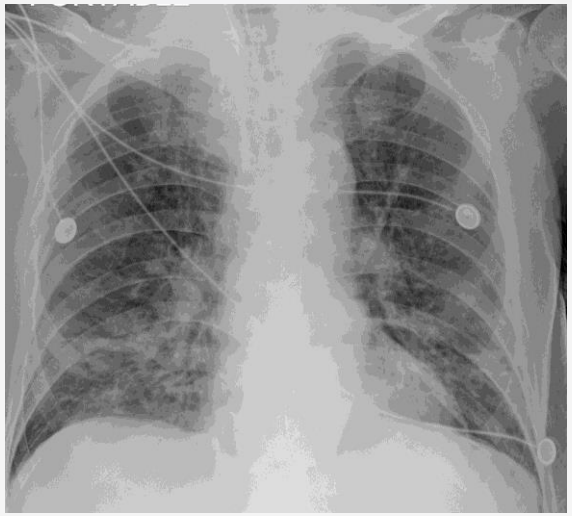
SICU

ICU day 4

Under HFNC respiratory type I failure, **ETT intubation**

Day 5 Endotracheal aspirate (ETA)
Aspergillus Ag (GM): 7.204 positive
Voriconazole added

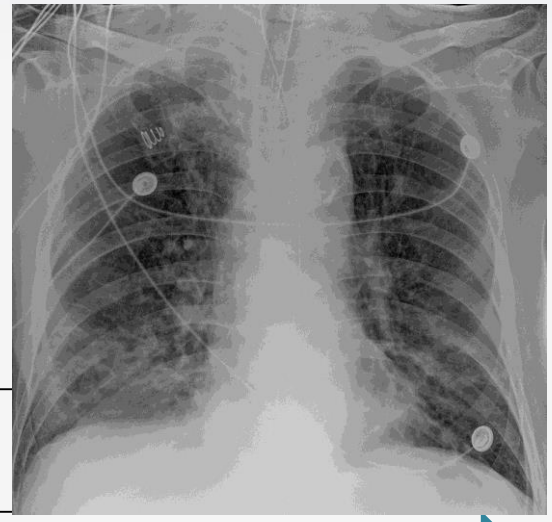
Patient Scenario



ICU day 6

ICU day 7-12

Day 12 ETA aspergillus Ag.: 7.204
Anidulafungin added



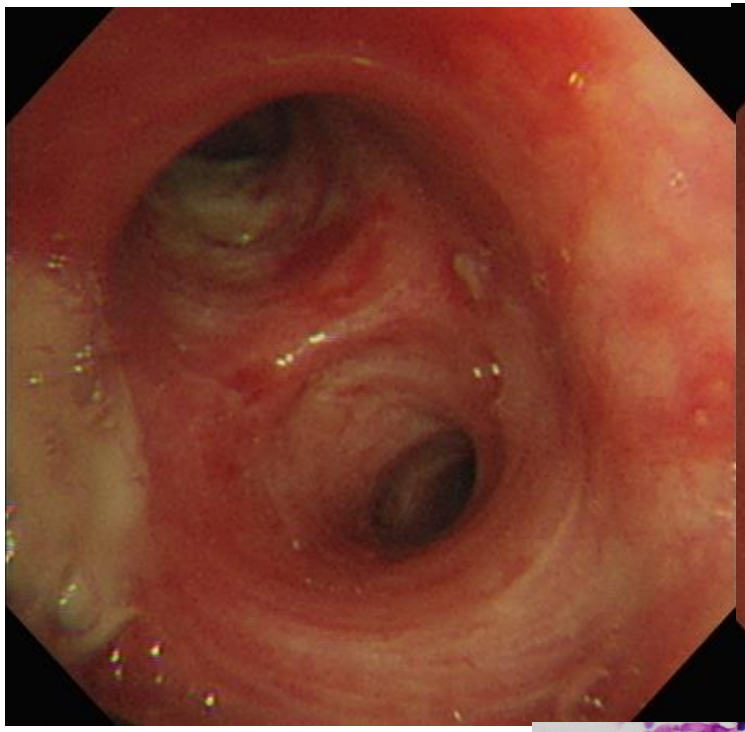
ICU

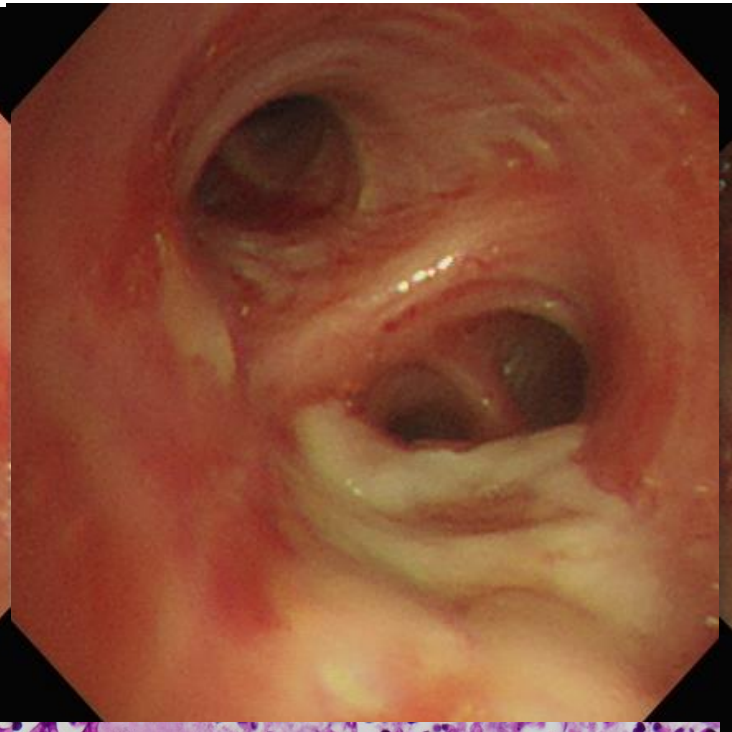
Day 7 Elevated D-dimer (>10000)
Heparin for susp. immunothrombosis

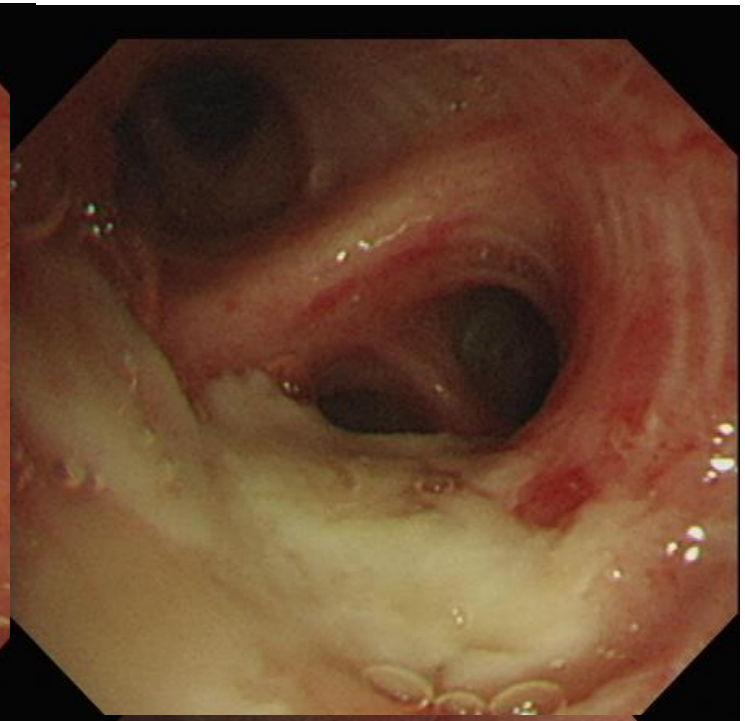
Day 12 Hemosputum noted

CXR: bil. diffuse infiltrates, P/F ratio 144
COVID-19 pneumonia with severe ARDS
Started lung-protective ventilation strategy

IATB

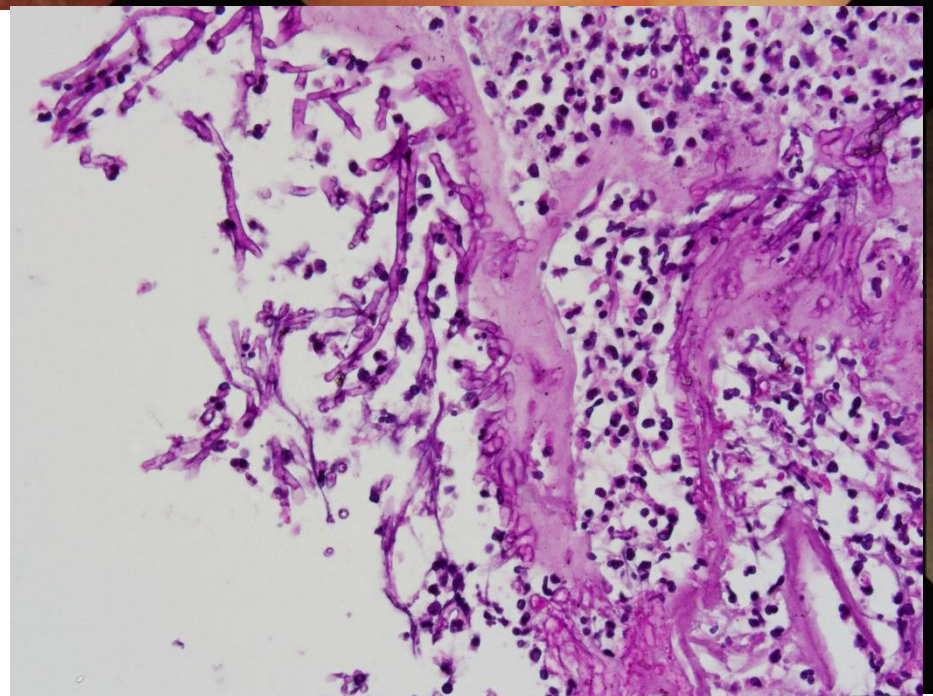


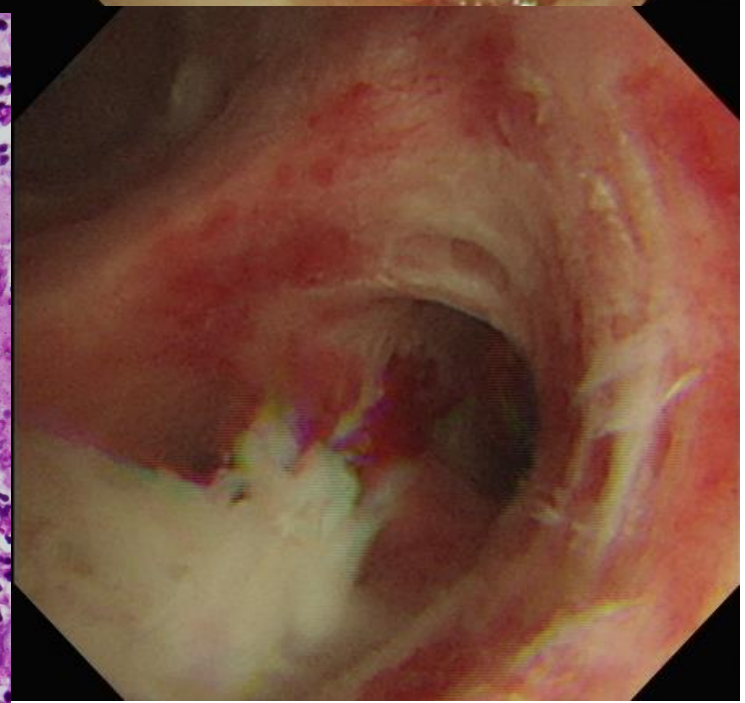




Bronchial biopsy

Some filament-like material is noticed and PAS staining is positive, which depicts branched and septate hyphae, suggestive of aspergillus.





Epidemiology of CAPA

CAPA

2020-2~2020-3 : Southern Netherlands
6 CAPA/31 ICU MV support patients (19.4%)

Patient	Sex and Age in Years	Medical History	Days after Symptom Onset to CAPA Onset	APACHE-II at ICU Admission	Days after ICU Admission to CAPA Onset	Bronchoscopy Findings	Microbiological Findings (Days after Symptom Onset of Sample Acquisition)	CAPA Classification (10)	Outcome (Days after Symptom Onset)
1	M, 83	Cardiomyopathy; prednisolon 0.13 mg/kg/d for 28 d preadmission	10	16	3	Not performed	Tracheal aspirate–cultured *Aspergillus fumigatus* (7); serum GM index 0.4 (8)	Possible	Died (12)
2	M, 67	COPD GOLD III; Post-RTx NSCLC 2014; prednisolon 0.37 mg/kg/d for 2 d preadmission	10	16	3	Not performed	Tracheal aspirate–cultured *Aspergillus fumigatus* (5)	Possible	Died (11)
3	M, 75	COPD GOLD IIa	8	15	5	Mucoid white sputum left bronchus	BAL-cultured *Aspergillus fumigatus* (8); BAL GM index 4.0 (8)	Probable	Died (12)
4	M, 43	None	21	10	14	Unrevealing	BAL GM index 3.8 (18); serum GM index 0.1 (16)	Probable	Survived
5	M, 57	Bronchial asthma; fluticason 1.94 mcg/kg/d for 1 mo preadmission	13	15	5	Unrevealing	BAL-cultured *Aspergillus fumigatus* (11); BAL GM index 1.6 (11); serum GM index 0.1 (13)	Probable	Died (20)
6	M, 58	None	42	15	28	Not performed	Sputum-cultured *Aspergillus fumigatus* (36, 40, 43, 47, and 50)	Possible	Survived
Median	—	—	11.5	15	5	—	—	—	12 d

Parameter	Presumed CAPA (*n* = 6)	Non-CAPA (*n* = 25)	*P* Value
Age, yr, median (range)	62.5 (43–83)	67 (16–79)	0.942
Sex, M, *n* (%)	6/6 (100)	20/25 (80)	0.553
EORTC/MSGERC host risk factors, *n* (%)	0/6 (0)	3/25 (12)	1
Interval from symptom onset to ICU admission, median (range), d	7 (3–14)	9 (3–15)	0.268
Interval from ICU admission to ICU discharge, median (range), d	10.5 (4–47)	14 (2–42)	1
Interval from symptom onset to death, median (range), d	12 (11–20)	17.5 (9–37)	0.570
Systemic corticosteroid use, *n* (%)	2/6 (33.3)	3/25 (12)	0.241
BAL performed, *n* (%)	1/6 (16.7)	6/25 (24)	1
Mortality, *n* (%)	4/6 (66.7)	8/25 (32)	0.174

American Journal of Respiratory and Critical Care Medicine. 2020; 202(1): 132-133.

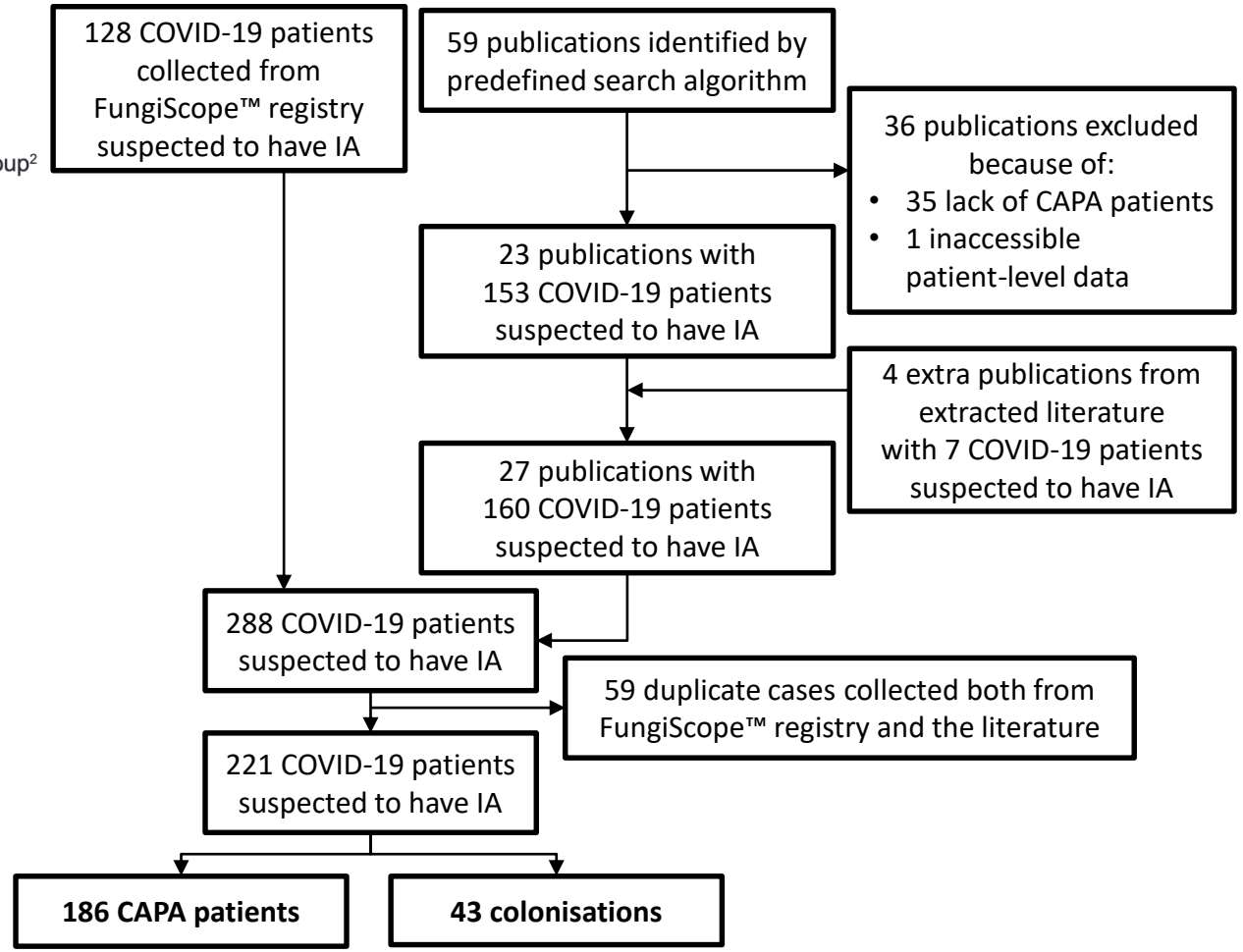
COVID-19–Associated Pulmonary Aspergillosis, March–August 2020

Jon Salmanton-García, Rosanne Sprute, Jannik Stemler, Michele Bartoletti, Damien Dupont, Maricela Valerio, Carolina Garcia-Vidal, Iker Falces-Romero, Marina Machado, Sofía de la Villa, Maria Schroeder, Irma Hoyo, Frank Hanses, Kennio Ferreira-Paim, Daniele Roberto Giacobbe, Jacques F. Meis, Jean-Pierre Gangneux, Azucena Rodríguez-Guardado, Spinello Antinori, Ertan Sal, Xhorxha Malaj, Danila Seidel, Oliver A. Cornely,[1] Philipp Koehler,[1] The FungiScope European Confederation of Medical Mycology/The International Society for Human and Animal Mycology Working Group[2]

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 27, No. 4, April 2021

221 suspected cases

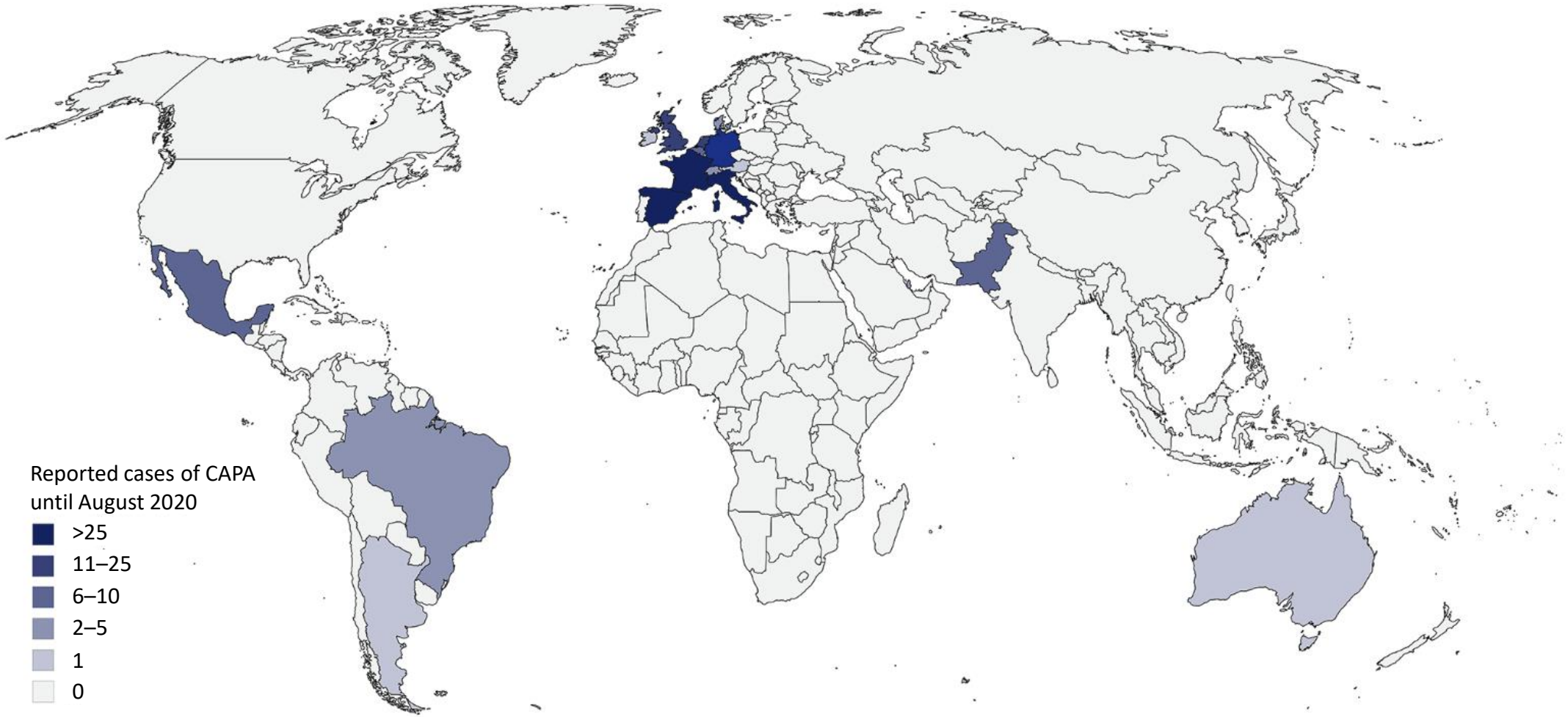
n=186 CAPA
n=43 colonisation



CAPA, COVID-19-associated pulmonary aspergillosis; IA, invasive aspergillosis

Salmanton-García J, *et al. Emerg Infect Dis.* 2021;27(4):1077–86.

Epidemiology of CAPA



CAPA, COVID-19-associated pulmonary aspergillosis

Salmanton-García J, *et al. Emerg Infect Dis.* 2021;27(4):1077–86.

Epidemiology of CAPA

Country, site no.	CAPA cases, no.	Denominator, no. (% CAPA)			Timeframe
		COVID-19 patients	COVID-19 patients in ICU	COVID-19 patients on mechanical ventilation	
Argentina, I	2	673 (0.3)	163 (1.2)	69 (2.9)	Mar–Aug
Belgium, I	4	274 (1.5)	46 (8.7)	32 (12.5)	Mar–Aug
Belgium, II	4	NA	34 (11.8)	20 (20.0)	Mar–Apr
France, I	2	519 (0.4)	113 (1.8)	45 (4.4)	Mar–Aug
Germany, I	1	83 (1.2)	18 (5.6)	15 (6.7)	Mar–Aug
Germany, II	11	231 (4.8)	64 (17.2)	56 (19.6)	Mar–Aug
Germany, III	9	93 (9.7)	38 (23.7)	27 (33.3)	Mar–Aug
Germany, IV	7	123 (5.7)	76 (9.2)	57 (12.3)	Mar–Aug
Ireland, I	3	181 (1.7)	15 (20.0)	14 (21.4)	Mar–Aug
Italy, I	2	1,279 (0.2)	196 (1.0)	188 (1.1)	Mar–Aug
Italy, II	8	1,055 (0.8)	144 (5.6)	142 (5.6)	Mar–Aug
Mexico, I	6	312 (1.9)	131 (4.6)	115 (5.2)	Mar–Aug
Netherlands, I	9	NA	NA	53 (17.0)	Apr
Netherlands, II	6	483 (1.2)	118 (5.1)	NA	Mar–Aug
Pakistan, I	9	147 (6.1)	23 (39.1)	19 (47.4)	Mar–Apr
Spain, I	8	1,543 (0.5)	348 (2.3)	146 (5.5)	Mar–Aug
Spain, II	8	7,880 (0.1)	NA	NA	Mar–Aug
Spain, III	10	5,890 (0.2)	NA	NA	Mar–Aug
Switzerland, I	3	NA	118 (2.5)	80 (3.8)	Mar–May
United Kingdom, I	19	14,615 (0.1)	257 (7.4)	200 (9.5)	Mar–May
Total	131	35,381 (0.4)	1,902 (6.9)	1,278 (10.3)	Mar–Aug

CAPA, COVID-19-associated pulmonary aspergillosis; ICU, intensive care unit; NA, not available

Salmanton-García J, *et al. Emerg Infect Dis.* 2021;27(4):1077–86.

Clinical Infectious Diseases

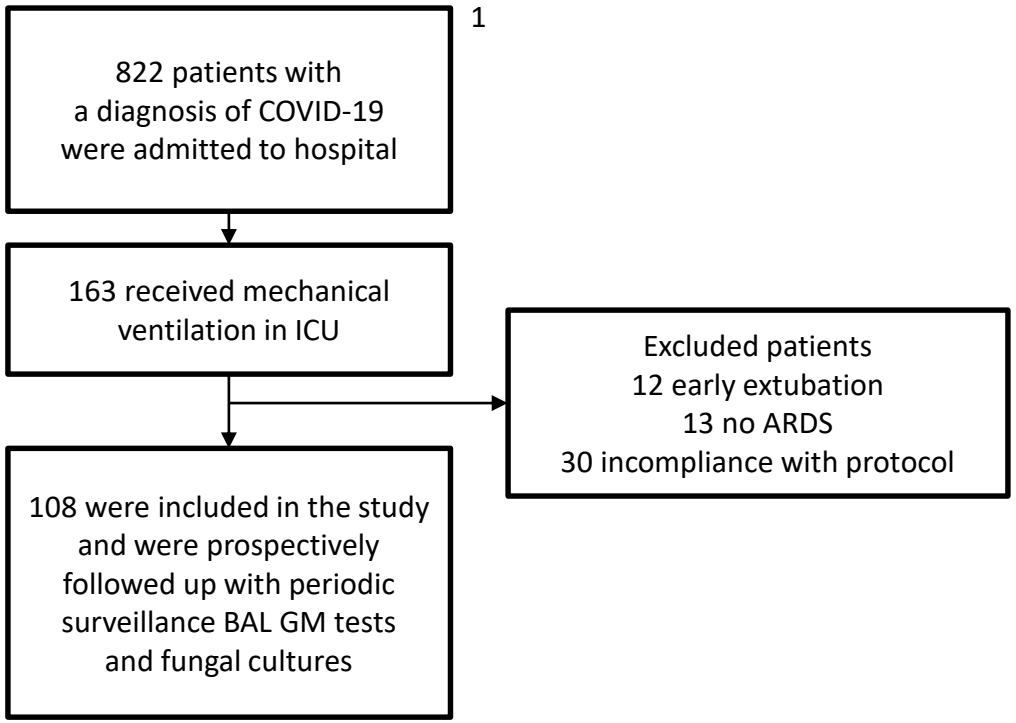
MAJOR ARTICLE

IDSA Infectious Diseases Society of America | hivma hiv medicine association | OXFORD [1]

Feb 22, 2020~Apr 20, 2020

Epidemiology of Invasive Pulmonary Aspergillosis Among Intubated Patients With COVID-19: A Prospective Study

Michele Bartoletti,[1] Renato Pascale,[1] Monica Cricca,[2] Matteo Rinaldi,[1] Angelo Maccaro,[1] Linda Bussini,[1] Giacomo Fornaro,[1] Tommaso Tonetti,[3] Giacinto Pizzilli,[3] Eugenia Francalanci,[1] Lorenzo Giuntoli,[4] Arianna Rubin,[1] Alessandra Moroni,[2] Simone Ambretti,[2] Filippo Trapani,[1] Oana Vatamanu,[1] Vito Marco Ranieri,[3] Andrea Castelli,[5] Massimo Baiocchi,[5] Russell Lewis,[1] Maddalena Giannella,[1] and Pierluigi Viale[1]; for the PREDICO Study Group[a]



BAL at admission 0–2 days[1]
BAL at 1 week ±2 days of MV[1]
BAL upon clinical worsening[1]

Definition IAPA (CAPA):[1]

- Positive culture in BAL
- BAL GM >1.0
- Serum GM >0.5
- Cavitating infiltrate (not attributed to another cause)

Definition *Asp*ICU (PIPA):[2]

- Positive culture + compatible signs and symptoms + abnormal medical imaging + host risk factors or positive BAL culture plus positive microscopy

ARDS, acute respiratory distress syndrome; BAL, bronchoalveolar lavage; CAPA, COVID-19-associated pulmonary aspergillosis; GM, galactomannan; HIVMA, Human Immunodeficiency Virus Medicine Association; IAPA, influenza-associated pulmonary aspergillosis; ICU, intensive care unit; IDSA, Infectious Diseases Society of America; MV, mechanical ventilation; PIPA, putative invasive pulmonary aspergillosis

1. Bartoletti M, *et al. Clin Infect Dis.* 2020. [Epub ahead of print];
2. Blot SI, *et al. Am J Respir Crit Care Med.* 2012;186(1):56–64.

30/108 cases = 27.8% prevalence of CAPA

Test	Total, N=108 No. (%)	CAPA, n=30[a] No. (%)	PIPA, n=19[a] No. (%)	Colonisation or no aspergillosis, n=77 No. (%)
Cultures *A. fumigatus* *A. niger* *A. flavus*	20 (18) 16 (15) 3 (3) 1 (1)	19 (63) 15 (50) 3 (10) 1 (3)	19 (100) 15 (79) 3 (16) 1 (5)	1 (1) 1 (1) 0 (0) 0 (0)
BAL-positive GM (index >1) Positive BAL GM on first determination (Day 0–2) Positive BAL GM on second determination (Day 5–9) Other BAL GM determination	30 (28) 14 (13) 9 (8) 5 (5)	30 (100) 14 (47) 9 (30) 7 (23)	18 (95) 11 (58) 4 (21) 4 (21)	0 (0) 0 (0) 0 (0) 0 (0)
BAL GM value, index, median (IQR)	0.14 (0.09–1.27)	3.5 (1.72–4.7)	3.73 (1.76–5.07)	0.09 (0.07–0.18)
Positive serum GM (index >0.5)	1 (1)	1 (3)	1 (5)	0 (0)
Serum GM value, index, median (IQR)[b]	0.06 (0.03–0.09)	0.06 (0.03–0.11)	0.06 (0.04–0.18)	0.06 (0.03–0.08)
Positive *Aspergillus* PCR[c]	26/67 (38)	20/30 (67)	19/19 (100)	5/36 (14)

6/30 patients with invasive *Aspergillus* tracheobronchitis (IATB)

BAL, bronchoalveolar lavage; CAPA, COVID-19-associated pulmonary aspergillosis; GM, galactomannan; ICU, intensive care unit; IQR, interquartile range; PIPA, putative invasive pulmonary aspergillosis; PCR, polymerase chain reaction

Bartoletti M, *et al. Clin Infect Dis.* 2020. [Epub ahead of print].

Risk factors for CAPA

Epidemiology of Invasive Pulmonary Aspergillosis Among Intubated Patients With COVID-19: A Prospective Study

Michele Bartoletti,[1,] Renato Pascale,[1] Monica Cricca,[2] Matteo Rinaldi,[1] Angelo Maccaro,[1] Linda Bussini,[1] Giacomo Fornaro,[1] Tommaso Tonetti,[3] Giacinto Pizzilli,[3] Eugenia Francalanci,[1] Lorenzo Giuntoli,[4] Arianna Rubin,[1] Alessandra Moroni,[2] Simone Ambretti,[2] Filippo Trapani,[1] Oana Vatamanu,[1] Vito Marco Ranieri,[3] Andrea Castelli,[5] Massimo Baiocchi,[5] Russell Lewis,[1] Maddalena Giannella,[1] and Pierluigi Viale[1]; for the PREDICO Study Group[a]

Underlying diseases	CAPA (n=30)	No CAPA (n=73)	p value
Obesity, n (%) BMI, median (IQR), kg/m^2	10 (37) 28 (26–31)	34 (49) 29 (26–31)	0.36 0.92
Hypertension, n (%)	16 (59)	49 (65)	0.64
Diabetes mellitus, n (%)	5 (17)	13 (17)	0.99
Coronary disease, n (%)	3 (10)	9 (11)	0.99
Cerebrovascular disease, n (%)	3 (10)	1 (1.4)	0.06
Chronic kidney disease, n (%)	6 (20)	6 (8)	0.08
COPD, n (%)	4 (13)	13 (17.8)	0.10
Malignancies, n (%)	2 (7)	5 (6)	0.99
Solid-organ transplant, n (%)	1 (3)	4 (5)	0.99
Chronic steroid treatment, n (%)	**5 (17)**	**2 (3)**	**0.02**
Haemodialysis, n (%)	3 (12)	3 (5)	0.36
Charlson index, median (IQR)	3 (1–4)	2 (1–4)	0.51

BMI, body mass index; CAPA, COVID-19-associated pulmonary aspergillosis; COPD, chronic obstructive pulmonary disease; IQR, interquartile range

Bartoletti M, *et al. Clin Infect Dis.* 2020. [Epub ahead of print].

Risk factors for CAPA

Research Note

Risk factors associated with COVID-19-associated pulmonary aspergillosis in ICU patients: a French multicentric retrospective cohort

Sarah Dellière [1, 2, †], Emmanuel Dudoignon [3, †], Sofiane Fodil [4, †], Sebastian Voicu [5, †], Magalie Collet [3, †], Pierre-Antoine Oillic [6], Maud Salmona [7], François Dépret [3, 8, 9], Théo Ghelfenstein-Ferreira [1], Benoit Plaud [3], Benjamin Chousterman [3], Stéphane Bretagne [1, 2], Elie Azoulay [4, †], Alexandre Mebazaa [3, 8, 9, †], Bruno Megarbane [5, †], Alexandre Alanio [1, 2, *, †]

21 CAPA /108 ICU COVID-19 patients with clinical deterioration

Therapy before sampling in patients with severe COVID-19 without and with IPA

Therapy with cumulative dose before sampling	Total (N=108)	Without IPA (n=87)	With IPA (n=21)	OR	95% CI
Azithromycin >1,500 mg total dose, n (%)	**26 (24.1)**	**17 (19.5)**	**9 (42.9)**	**3.1**	**1.1–8.5**
Dexamethasone >1,000 mg, n (%)	**16 (14.8)**	**10 (11.5)**	**6 (28.6)**	**3.1**	**1.0–9.8**
Any β-lactam >3 days, n (%)	90 (83.3)	74 (85.1)	16 (76.2)	0.6	0.2–1.8

Incidence of patients who develop IPA if prescribed azithromycin, dexamethasone, both or none

Azithromycin >1,500 mg	Dexamethasone >100 mg	Number of IPA /total (%)
+	+	**4/10 (40.0%)**
+	–	**5/16 (31.2%)**
–	+	**2/6 (33.3%)**
–	–	10/76 (13.2%)

CAPA, COVID-19-associated pulmonary aspergillosis; CI, confidence interval; EORTC, European Organisation for Research and Treatment of Cancer; ICU, intensive care unit; IPA, invasive pulmonary aspergillosis; MSGERC, Mycoses Study Group Education and Research Consortium; OR, odds ratio

Dellière S, *et al. Clin Microbiol Infect.* 2021;27(5):790.e1–790.e5.

Risk factors for CAPA

	Total patients in ICU	Patients tested for CAPA	Number of cases (%)	Median days from admission for CAPA diagnosis	Risk factors	Mortality (CAPA vs COVID-19)
Bartoletti, *et al*. Italy[2]	822	108	30 (27.8%)	4 days	**Steroids >16 mg/day >2 weeks**	44% vs 19%
White, *et al*. Wales[1]	257	135	19 (14.1%)	8 days	**High-dose corticosteroids; Chronic respiratory disease**	58% vs 38%
Dellière, *et al*. France[3]	366	108	21 (19.4%)	6 days	**Azithromycin ≥1,500 mg**	71% vs 37%
Permpalung, *et al*. Baltimore, USA[4*]	753	396	39 (9.85%)		**Corticosteroids use during admission**	

* Retrospective study

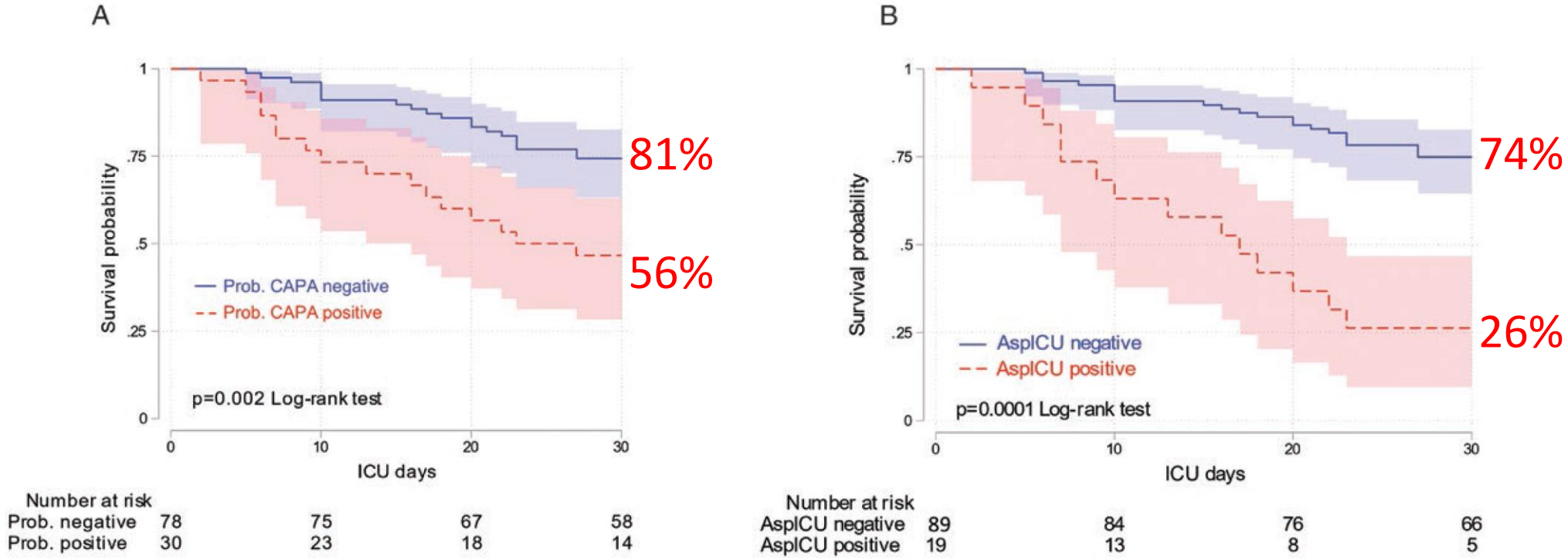
CAPA, COVID-19-associated pulmonary aspergillosis; ICU, intensive care unit

1. White PL, *et al. Clin Infect Dis.* 2020. [Epub ahead of print]; 2. Bartoletti M, *et al. Clin Infect Dis.* 2020. [Epub ahead of print]; 3. Dellière S, *et al. Clin Microb Infect.* 2021;27(5):790.e1–790.e5. 4. Permpalung N, et al. 2021. Clin Infect Dis. https:// doi. org/ 10. 1093/ cid/ ciab2 23

Survival of CAPA

Epidemiology of Invasive Pulmonary Aspergillosis Among Intubated Patients With COVID-19: A Prospective Study

Michele Bartoletti,[1] Renato Pascale,[1] Monica Cricca,[2] Matteo Rinaldi,[1] Angelo Maccaro,[1] Linda Bussini,[1] Giacomo Fornaro,[1] Tommaso Tonetti,[3] Giacinto Pizzilli,[3] Eugenia Francalanci,[1] Lorenzo Giuntoli,[4] Arianna Rubin,[1] Alessandra Moroni,[2] Simone Ambretti,[2] Filippo Trapani,[1] Oana Vatamanu,[1] Vito Marco Ranieri,[3] Andrea Castelli,[5] Massimo Baiocchi,[5] Russell Lewis,[1] Maddalena Giannella,[1] and Pierluigi Viale[1]; for the PREDICO Study Group[a]

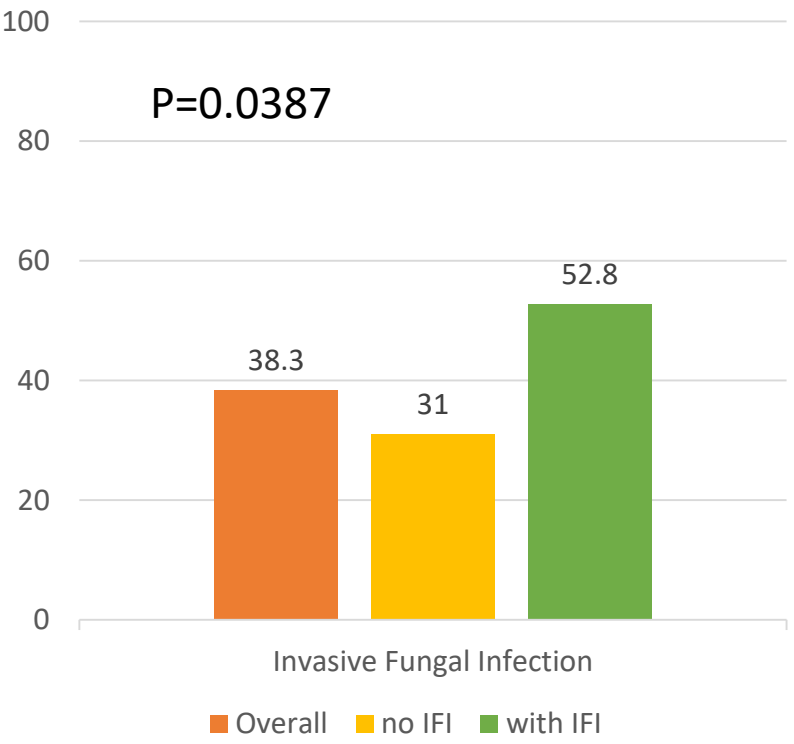


Clin Infect Dis. 2020 Jul 28;ciaa1065. doi:10.1093/cid/ciaa1065.

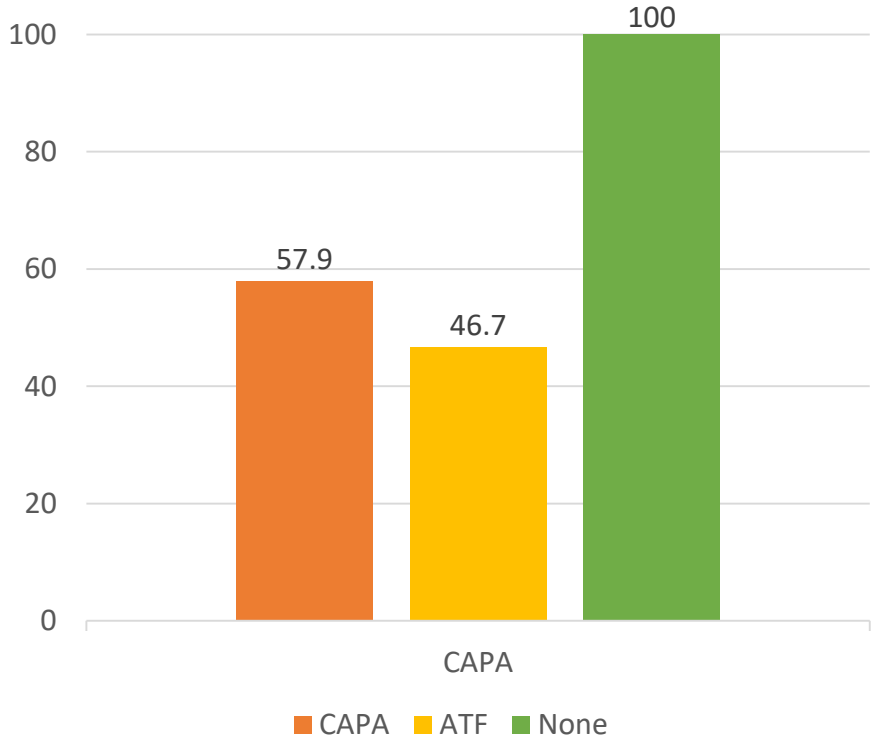
A National Strategy to Diagnose Coronavirus Disease 2019–Associated Invasive Fungal Disease in the Intensive Care Unit

P. Lewis White,[1] Rishi Dhillon,[1] Alan Cordey,[1] Harriet Hughes,[1] Federica Faggian,[1] Shuchita Soni,[1] Manish Pandey,[2] Harriet Whitaker,[3] Alex May,[1] Matt Morgan,[2] Matthew P. Wise,[2] Brendan Healy,[4] Ian Blyth,[4] Jessica S. Price,[1] Lorna Vale,[1] Raquel Posso,[1] Joanna Kronda,[1] Adam Blackwood,[1] Hannah Rafferty,[1] Amy Moffitt,[1] Alexandra Tsitsopoulou,[5] Soma Gaur,[6] Tom Holmes,[2] and Matthijs Backx[1]

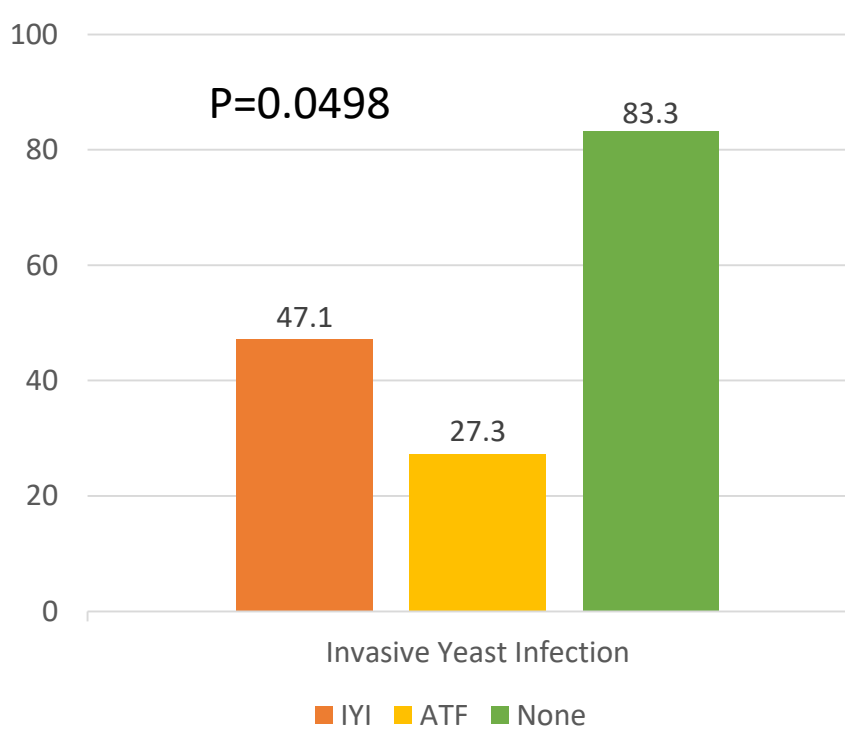
Mortality Rate of Invasive Fungal Infection (IFI) in COVID-19 patients



Mortality Rate in CAPA with and without AFT



Mortality Rate in IYI with and without AFT

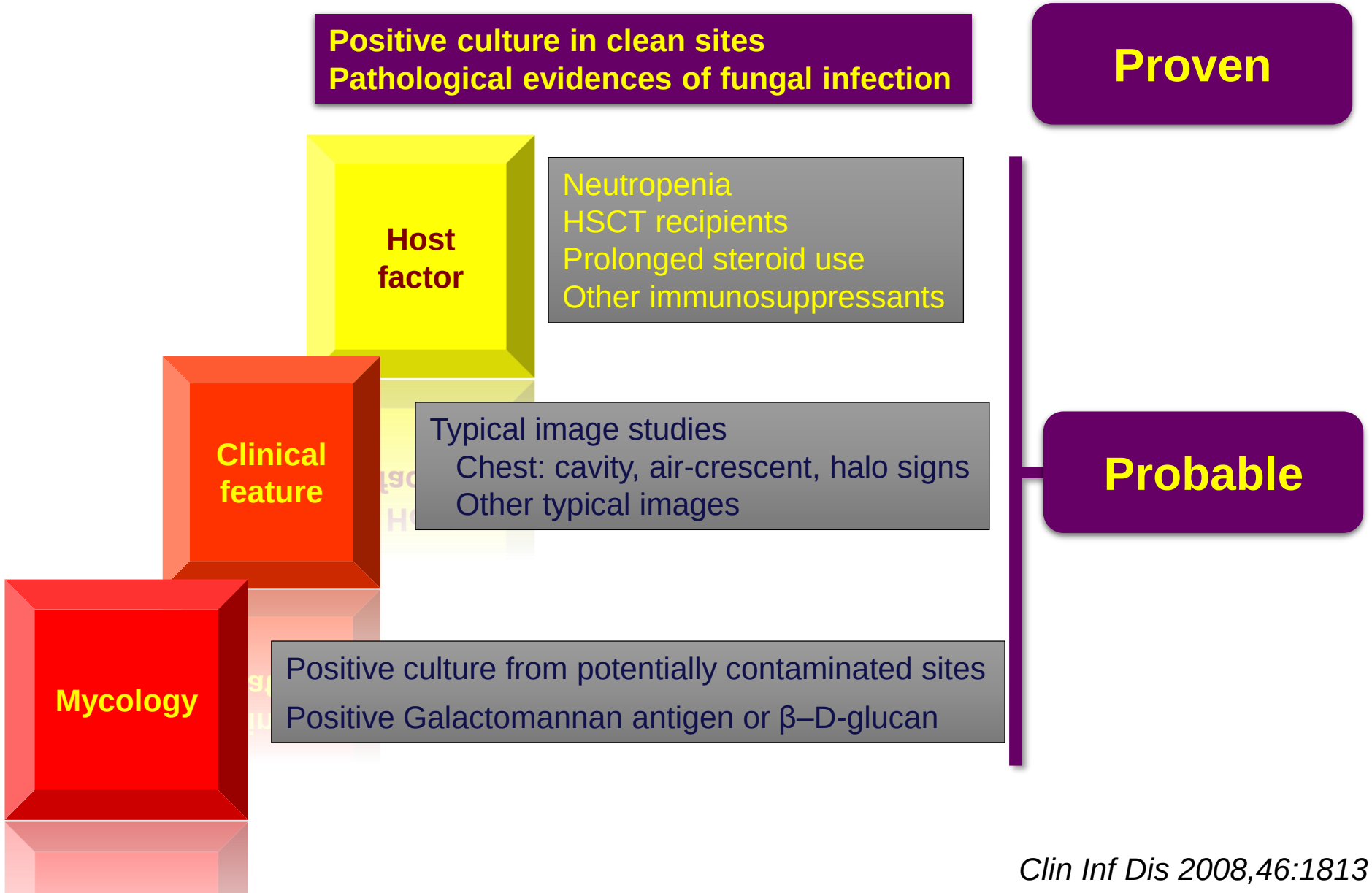


CAPA : COVID-19 associated pulmonary aspergillosis , IFI : invasive fungal infections, AFT: antifungal therapy, IYI: invasive yeast infection

Clin Infect Dis . 2020 Aug 29;ciaa1298. doi: 10.1093/cid/ciaa1298. Online ahead of print.

Diagnosis of CAPA in ICU

Diagnosis for invasive fungal disease:
EORTC/MSG 2008 criteria



Clin Inf Dis 2008,46:1813

Revised 2020 EORTC-MSG criteria

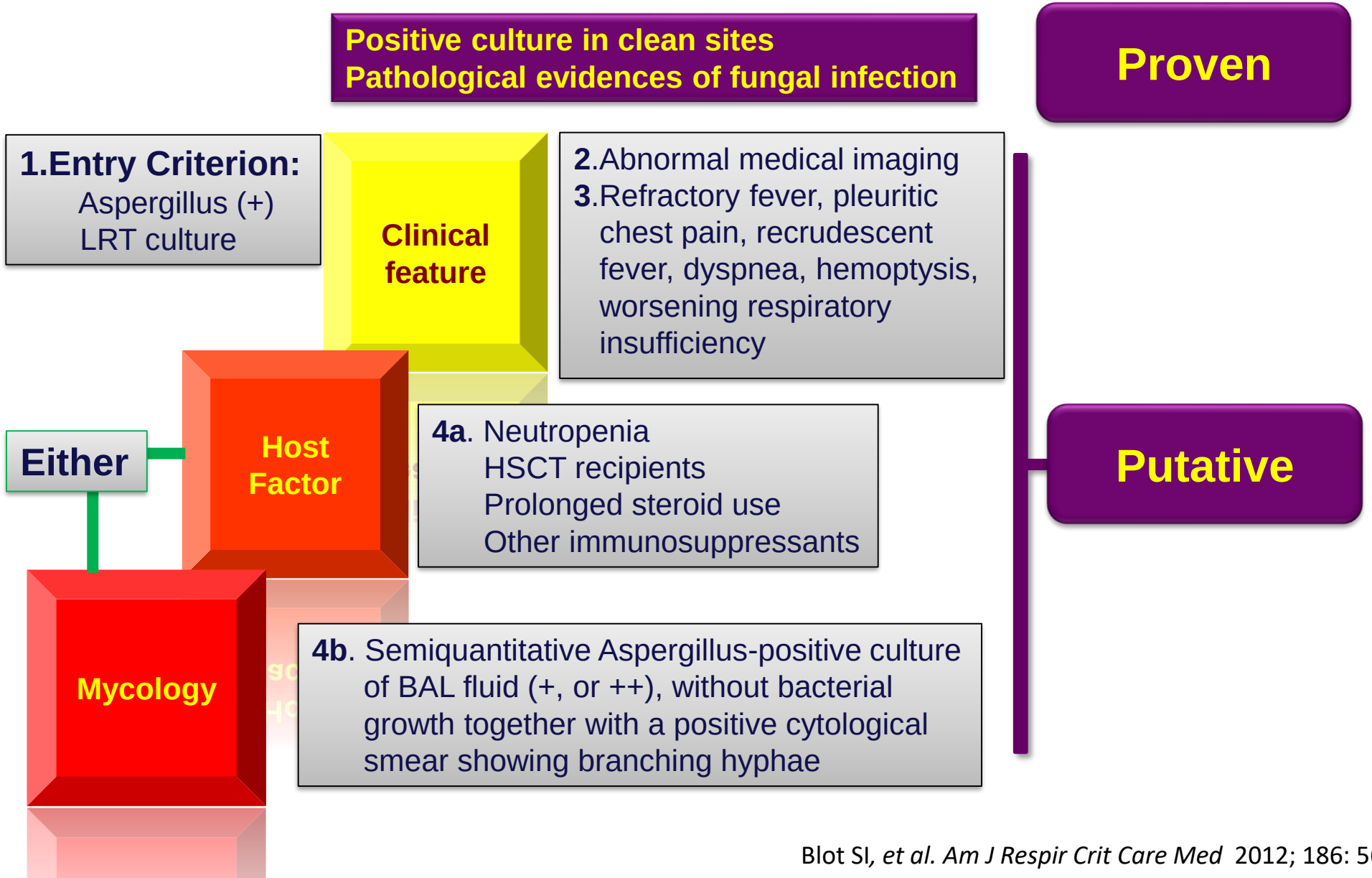
Host factors
Recent history of neutropenia (<0.5 × 10^9 neutrophils/L [<500 neutrophils/mm^3] for >10 days) temporally related to the onset of invasive fungal disease
Hematologic malignancy[a]
Receipt of an allogeneic stem cell transplant
Receipt of a solid organ transplant
Prolonged use of corticosteroids (excluding among patients with allergic bronchopulmonary aspergillosis) at a therapeutic dose of ≥0.3 mg/kg corticosteroids for ≥3 weeks in the past 60 days
Treatment with other recognized T-cell immunosuppressants, such as calcineurin inhibitors, tumor necrosis factor-a 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

Clinical features
Pulmonary aspergillosis
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
Sino-nasal diseases
Acute localized pain (including pain radiating to the eye)
Nasal ulcer with black eschar
Extension from the paranasal sinus across bony barriers, including into the orbit
Central nervous system infection
1 of the following 2 signs:
Focal lesions on imaging
Meningeal enhancement on magnetic resonance imaging or CT

Clin Infect Dis. 2020 ;71(6):1367-1376.

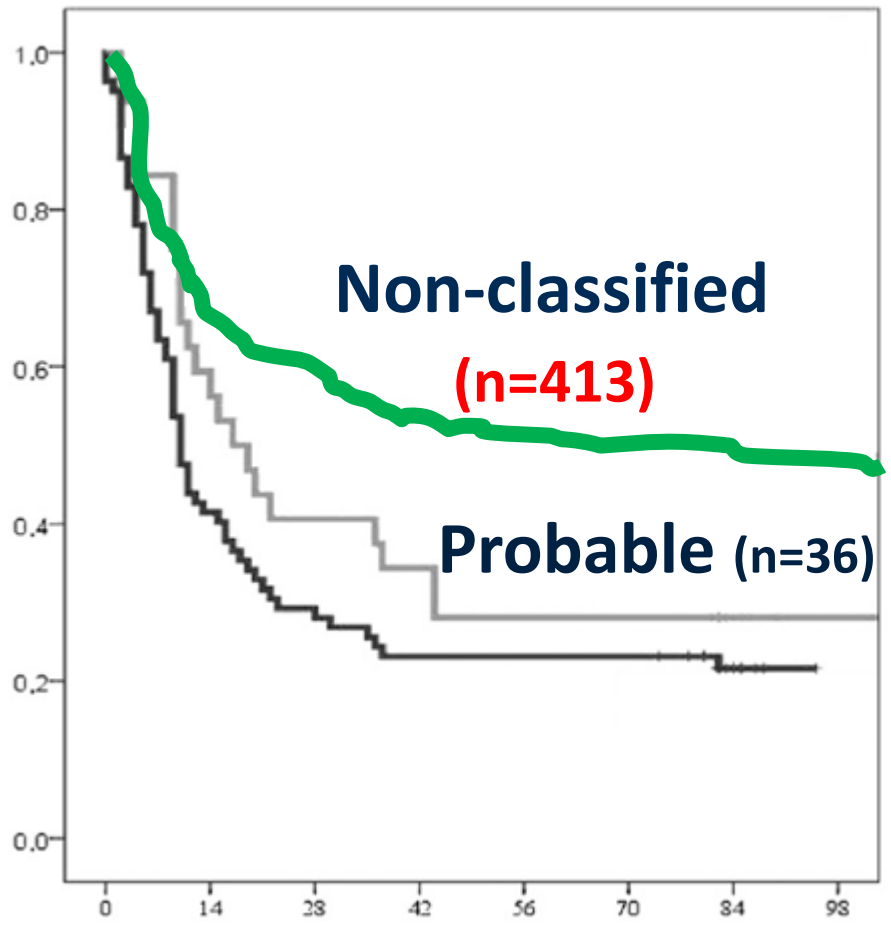
Diagnosis for invasive fungal disease:

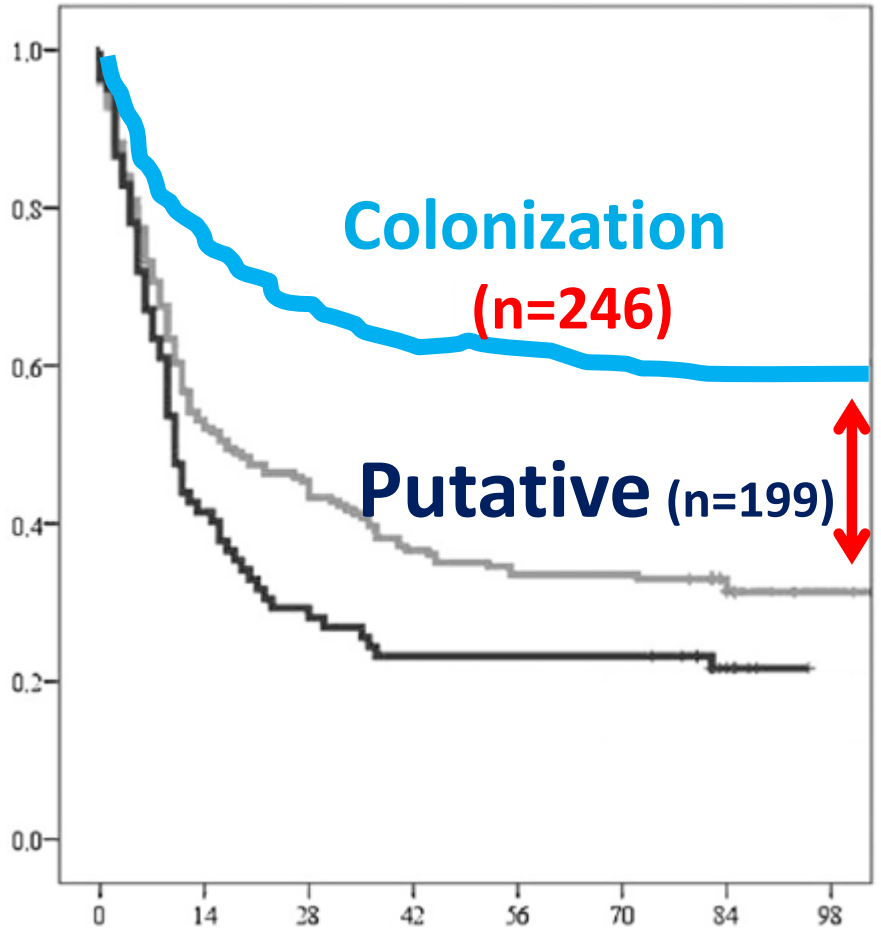
*Asp*ICU criteria



Blot SI, *et al. Am J Respir Crit Care Med* 2012; 186: 56–64.

Survival





EORTC/MSG **Time (days)** ***Asp* ICU**

- Sensitivity: 92%.
- Specificity: 61%.

Blot SI, *et al. Am J Respir Crit Care Med* 2012; 186: 56–64.

Influenza Associated Pulmonary Aspergillosis (IAPA)

Review of influenza-associated pulmonary aspergillosis in ICU patients and proposal for a case definition: an expert opinion

Paul E. Verweij[1,2*], Bart J. A. Rijnders[3], Roger J. M. Brüggemann[2,4], Elie Azoulay[5], Matteo Bassetti[6,7], Stijn Blot[8,9], Thierry Calandra[10], Cornelius J. Clancy[11,12], Oliver A. Cornely[13,14,15], Tom Chiller[16], Pieter Depuydt[17], Daniele Roberto Giacobbe[6,18], Nico A. F. Janssen[2,19], Bart-Jan Kullberg[2,19], Katrien Lagrou[20,21], Cornelia Lass-Flörl[22], Russell E. Lewis[23], Peter Wei-Lun Liu[24,25], Olivier Lortholary[26,27], Johan Maertens[20,28], Ignacio Martin-Loeches[29,30], M. Hong Nguyen[11,12], Thomas F. Patterson[31,32], Thomas R. Rogers[33], Jeroen A. Schouten[34,35], Isabel Spriet[36], Lore Vanderbeke[20,37], Joost Wauters[37] and Frank L. van de Veerdonk[2,19]

EORTIC IFI criteria > non-classifiable

AspICU criteria for "putative" aspergillosis: pure *Aspergillus* in BAL > non-classifiable

Intensive Care Med 2020 Aug;46(8):1524-1535.

Influenza-Associated Pulmonary Aspergillosis in ICU - Proposed Case Definition

Tracheobronchitis: tracheal/bronchial ulcerations, nodules, pseudomembranes or plaques visualized at bronchoscopy

Entry criteria: influenza-like illness + positive influenza PCR or antigen + temporally relationship		
	***Aspergillus* tracheobronchitis**	**IAPA in patients without documented *Aspergillus* tracheobronchitis**
Proven	Biopsy or brush specimen of airway plaque, pseudomembrane or ulcer showing hyphal elements and *Aspergillus* growth on culture or positive *Aspergillus* PCR in tissue	Lung biopsy showing invasive fungal elements and *Aspergillus* growth on culture or positive *Aspergillus* PCR in tissue
Probable	Airway plaque, pseudomembrane or ulcer and at least one of the following: Serum GM index > 0.5 *or* BAL GM index ≥ 1.0 *or* Positive BAL culture *or* Positive tracheal aspirate culture *or* Positive sputum culture *or* Hyphae consistent with *Aspergillus*	**A**: Pulmonary infiltrate and at least one of the following: Serum GM index > 0.5 *or* BAL GM index ≥ 1.0 *or* Positive BAL culture ***OR*** **B**: Cavitating infiltrate (not attributed to another cause) and at least one of the following: Positive sputum culture *or* Positive tracheal aspirate culture

Intensive Care Med 2020 Aug;46(8):1524-1535.

Defining CAPA

CORRECTED PROOF

A National Strategy to Diagnose Coronavirus Disease 2019–Associated Invasive Fungal Disease in the Intensive Care Unit FREE

P Lewis White ✉, Rishi Dhillon, Alan Cordey, Harriet Hughes, Federica Faggian, Shuchita Soni, Manish Pandey, Harriet Whitaker, Alex May, Matt Morgan ... Show more

*Asp*ICU	IAPA	CAPA-specific

Putative:
• Positive culture from lower respiratory tract specimen in a patient with host risk factors (neutropenia, underlying haematological/oncological malignancy, corticosteroids [20 mg/day], congenital/acquired immunodeficiency, COPD, decompensated cirrhosis)
• Semi-quantitative positive culture from BAL with a positive cytological smear in the absence of bacterial growth in patient without host factors
	Putative:
	• Positive culture from BAL
	• Positive GM-EIA in BAL ≥1.0
	• Positive GM-EIA in serum ≥0.5
		Putative:
		• Non-specific radiology:[a]
		• **Two or more** positives across different test types or multiple positives within one test type, from the following:
		  • **Positive culture from NBL/BAL**
		  • **Positive GM-EIA in NBL/BAL ≥1.0**
		  • **Positive GM-EIA in serum ≥0.5**
		  • **Positive *Aspergillus* PCR in BAL or blood**
		  • **Positive BDG in serum/plasma**

[a]If radiology typical of invasive aspergillosis, one positive mycological test required, unless the typical radiological signs can be attributed to a different underlying infection. In this scenario, multiple positive results would be required to attain a diagnosis of putative invasive pulmonary aspergillosis.

BAL, bronchoalveolar lavage; BDG, β(1,3)-D-glucan; CAPA, COVID-19-associated pulmonary aspergillosis; COPD, chronic obstructive pulmonary disease; GM-EIA, galactomannan enzyme immunoassay; IAPA, influenza-associated pulmonary aspergillosis; NBL, non-directed bronchial lavage; PCR, polymerase chain reaction

White PL, *et al. Clin Infect Dis.* 2020. [Epub ahead of print].

CAPA incidence differs depending on the diagnostic criteria used

CORRECTED PROOF

A National Strategy to Diagnose Coronavirus Disease 2019–Associated Invasive Fungal Disease in the Intensive Care Unit FREE

P Lewis White ✉, Rishi Dhillon, Alan Cordey, Harriet Hughes, Federica Faggian, Shuchita Soni, Manish Pandey, Harriet Whitaker, Alex May, Matt Morgan ... Show more

25 CAPA out of 135 ICU patients (18.5%)
(among the 3 methods)

	***Asp*ICU**	**IAPA**	**CAPA-specific**
Number of CAPA patients	8/135 (5.9%)	20/135 (14.8%)	19/135 (14.1%)
≥2 positive mycological criteria	7/8 (87.5%)	15/20 (75.0%)	18/19 (84.2%)

CAPA, COVID-19-associated pulmonary aspergillosis; IAPA, influenza-associated pulmonary aspergillosis

White PL, *et al. Clin Infect Dis.* 2020. [Epub ahead of print].

COVID-19–Associated Pulmonary Aspergillosis, March–August 2020

Jon Salmanton-García, Rosanne Sprute, Jannik Stemler, Michele Bartoletti, Damien Dupont, Maricela Valerio, Carolina Garcia-Vidal, Iker Falces-Romero, Marina Machado, Sofía de la Villa, Maria Schroeder, Irma Hoyo, Frank Hanses, Kennio Ferreira-Paim, Daniele Roberto Giacobbe, Jacques F. Meis, Jean-Pierre Gangneux, Azucena Rodríguez-Guardado, Spinello Antinori, Ertan Sal, Xhorxha Malaj, Danila Seidel, Oliver A. Cornely,[1] Philipp Koehler,[1] The FungiScope European Confederation of Medical Mycology/The International Society for Human and Animal Mycology Working Group[2]

Classification of CAPA patients

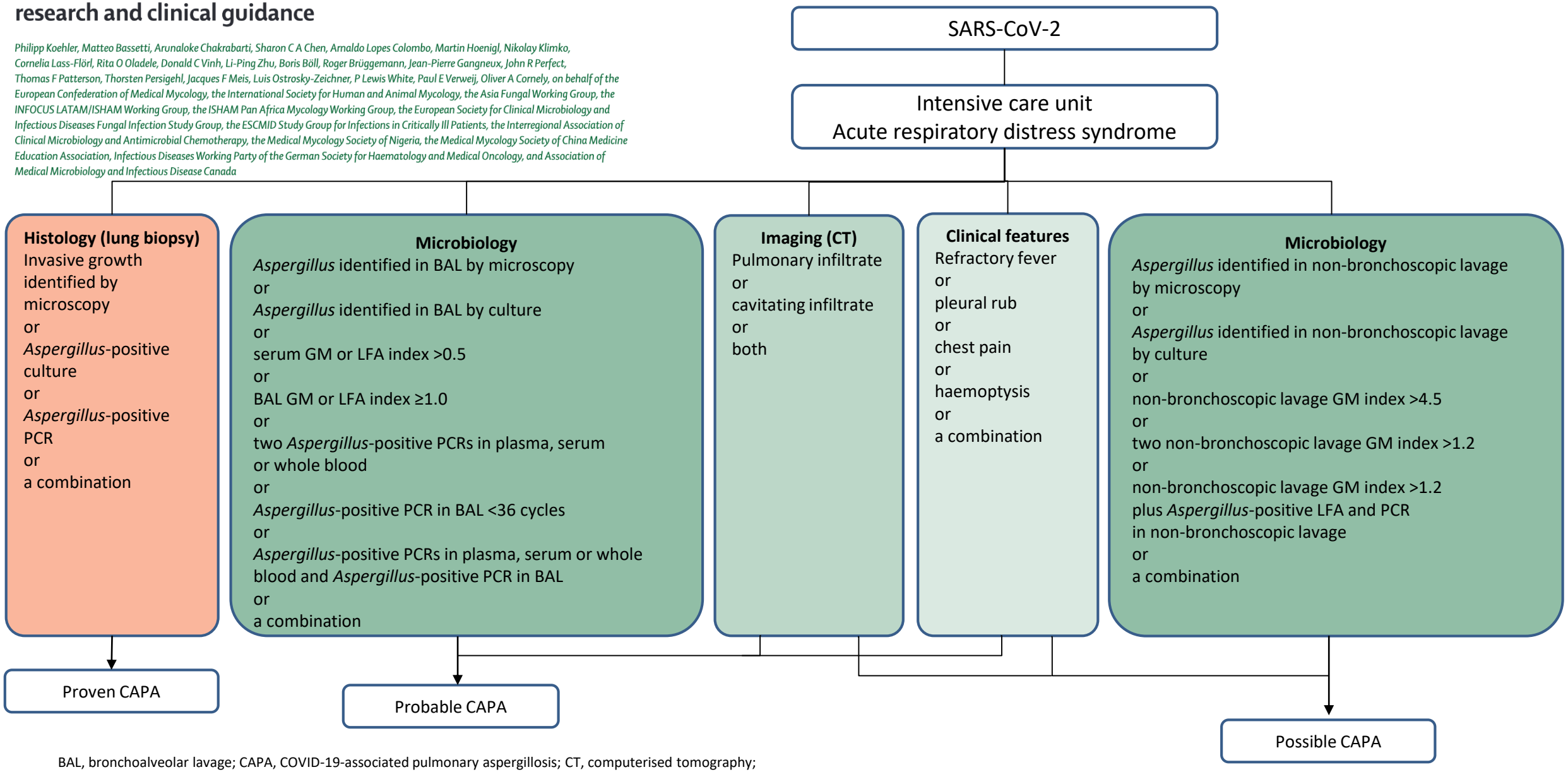
Case definition	N=186 No. (%)
EORTC/MSGERC criteria	
Proven	7 (3.8)
Probable	10 (5.4)
Non-classifiable	**169 (90.9)**
*Asp*ICU algorithm	
Proven	7 (3.8)
Putative	**142 (76.3)**
Colonisation	34 (18.3)
Non-classifiable	3 (1.6)
Consensus definition	
Proven	7 (3.8)
Probable	**82 (44.1)**
Possible	19 (10.2)
Non-classifiable	78 (41.9)

CAPA, COVID-19-associated pulmonary aspergillosis; EORTC, European Organisation for Research and Treatment of Cancer; IMD, invasive mould disease; MSGERC, Mycoses Study Group Education and Research Consortium

Salmanton-García J, *et al. Emerg Infect Dis.* 2021;27(4):1077–86.

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

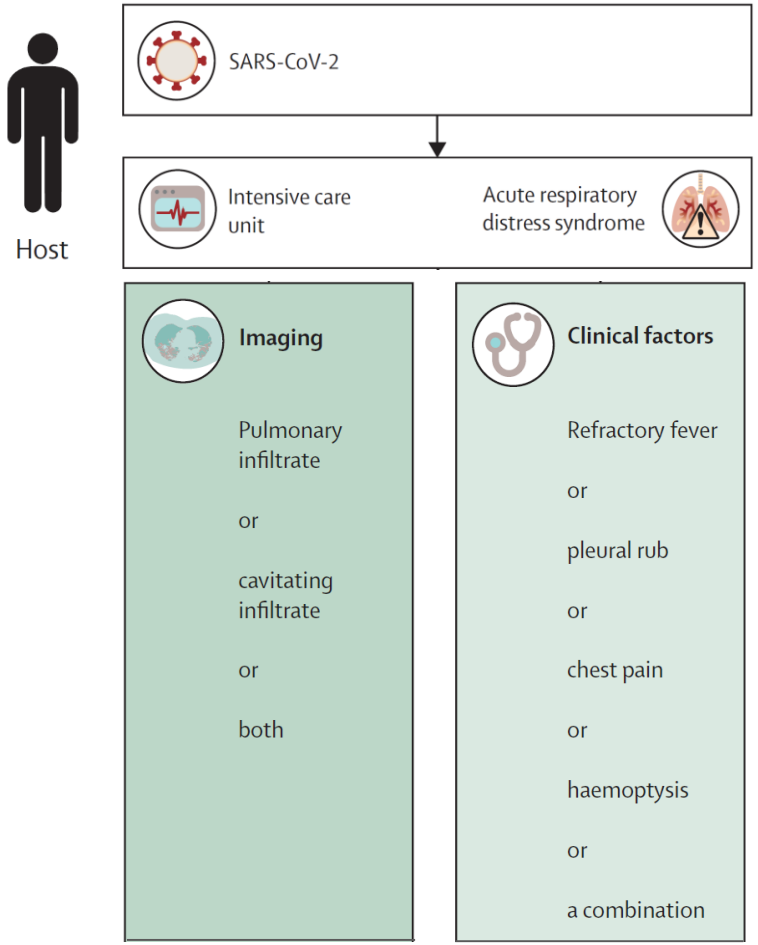
Philipp Koehler, Matteo Bassetti, Arunaloke Chakrabarti, Sharon C A Chen, Arnaldo Lopes Colombo, Martin Hoenigl, Nikolay Klimko, Cornelia Lass-Flörl, Rita O Oladele, Donald C Vinh, Li-Ping Zhu, Boris Böll, Roger Brüggemann, Jean-Pierre Gangneux, John R Perfect, Thomas F Patterson, Thorsten Persigehl, Jacques F Meis, Luis Ostrosky-Zeichner, P Lewis White, Paul E Verweij, Oliver A Cornely, on behalf of the European Confederation of Medical Mycology, the International Society for Human and Animal Mycology, the Asia Fungal Working Group, the INFOCUS LATAM/ISHAM Working Group, the ISHAM Pan Africa Mycology Working Group, the European Society for Clinical Microbiology and Infectious Diseases Fungal Infection Study Group, the ESCMID Study Group for Infections in Critically Ill Patients, the Interregional Association of Clinical Microbiology and Antimicrobial Chemotherapy, the Medical Mycology Society of Nigeria, the Medical Mycology Society of China Medicine Education Association, Infectious Diseases Working Party of the German Society for Haematology and Medical Oncology, and Association of Medical Microbiology and Infectious Disease Canada



BAL, bronchoalveolar lavage; CAPA, COVID-19-associated pulmonary aspergillosis; CT, computerised tomography; ECMM, European Confederation of Medical Mycology; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; GM, galactomannan; INFOCUS LATAM, Latin American Forum of Fungal Infections in Clinical Practice; ISHAM, The International Society for Human and Animal Mycology; LFA, lateral flow assay; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Koehler P, *et al. Lancet Infect Dis.* 2020;21(6)e149–e162.

Defining and Diagnosing CAPA



CAPA Proven

Visualisation of invasive fungal element in **tissue**
or
Positive culture
or microscopy or histology
or PCR from a **biopsy**
or a material obtained
by **sterile aspiration**

CAPA Probable

BAL
Microscopy or culture
or GM BAL ≥1 or LFA BAL ≥1
or positive PCR Cq <36

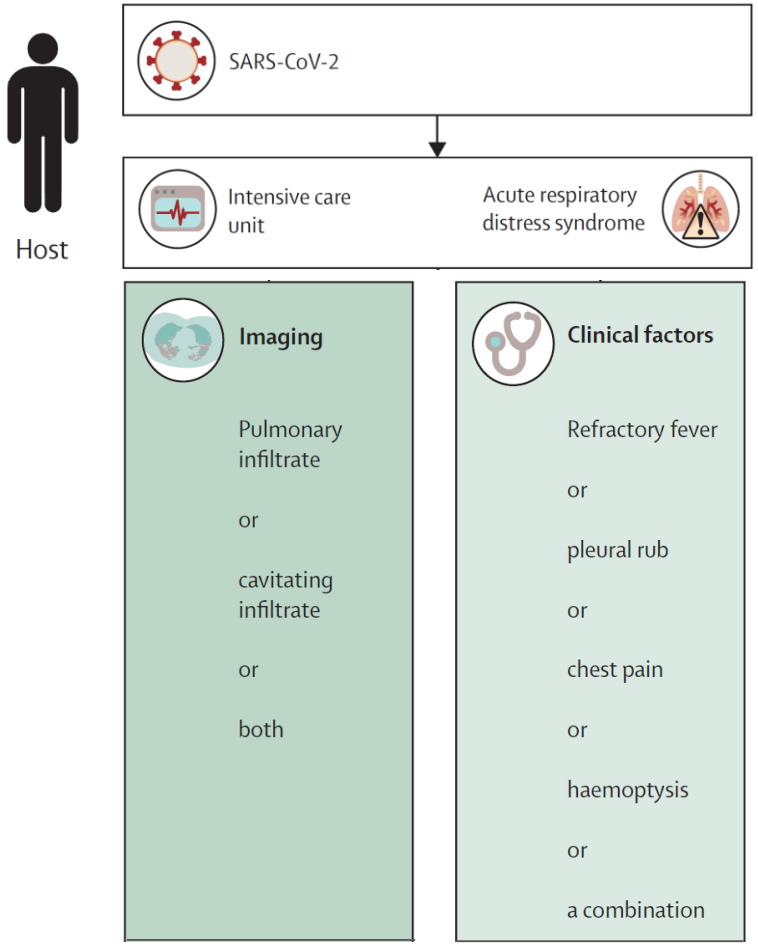
Serum
GM >0.5 or LFA >0.5
or 2 or more positive PCR

1 PCR positive in serum and in BAL

BAL, bronchoalveolar lavage; CAPA, COVID-19-associated pulmonary aspergillosis; Cq, quantitation cycle; ECMM, European Confederation of Medical Mycology; GM, galactomannan; ISHAM, The International Society for Human and Animal Mycology; LFA, lateral flow assay; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Koehler P, *et al. Lancet Infect Dis.* 2020;21(6)e149–e162.

Defining and Diagnosing CAPA



CAPA POSSIBLE

NBL

Microscopy or culture

or GM NBL >4.5

or 2 GM NBL >1.2

or 1 GM NBL >1.2 + another NBL mycology test positive

CAPA, COVID-19-associated pulmonary aspergillosis; ECMM, European Confederation of Medical Mycology; GM, galactomannan; ISHAM, The International Society for Human and Animal Mycology; NBL, non-directed bronchial lavage; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Koehler P, *et al. Lancet Infect Dis.* 2020;21(6)e149–e162.

Non-directed Bronchoalveolar Lavage

CORRESPONDENCE

Detection of Invasive Pulmonary Aspergillosis in COVID-19 with Nondirected BAL

To the Editor:

Invasive pulmonary aspergillosis (IPA) can complicate influenza pneumonia in critically ill patients owing to viral destruction of bronchial mucosa, facilitating invasion of *Aspergillus* species, and compromised host defenses to *Aspergillus* (1). Given the association between IPA and increased mortality in influenza, rapid diagnostic investigations and early (preemptive) treatment of IPA are recommended in critically ill patients with influenza (2). In ICU patients with coronavirus disease (COVID-19), the same principles may apply as in influenza. A high incidence of IPA in patients with COVID-19 admitted to the ICU has been reported in small cohorts of patients, some of which appeared online (3–7). However, in 3-week time frame in April 2020. The institutional review board of the Amsterdam University Medical Center considered the study as not requiring informed consent. The clinical AspICU algorithm can be used to distinguish IPA from colonization in critically ill patients (9), but as viral infection is not a classified host risk factor in this definition, the host factor was omitted. The IPA definition used in this paper is based on nondirected BAL GM testing with a cutoff of 1 optical density index, for which sensitivity and specificity are 86% and 95%, respectively, combined with worsening clinical symptoms (i.e., increase in C-reactive protein, worsening Pa_{O_2}/FI_{O_2} ratio, persistent or rising fever). Nondirected BAL was performed at a median of 2 days (range, 0–8 d) after ICU admission, in nonparalyzed patients, by advancing a 12-F suction catheter with a length of 54 cm via a closed circuit until bronchial wedging (Halyard Turbo-cleaning closed suction system for adults). Then, 2 × 20 ml of sterile NaCl 0.9% was given via the closed circuit and retrieved via the suction catheter.

Patient No.	Sex	Age (*yr*)	APACHE IV Pred Mort. (%)	BMI (kg/m^2)	LOS at IPA Diagnosis (*d*)	GM in BAL at Diagnosis (*ODI*)	Fungal Culture
1	M	39	12.55	34.57	19	3.14	No growth
2	F	76	25.73	39.34	4	>4.00	*A. fumigatus*
3	F	73	14.73	29.78	3	>4.00	*A. fumigatus*
4	M	64	21.49	27.76	3	1.10	*A. fumigatus*
5	M	74	12.22	23.15	1	>4.00	*A. fumigatus*
6	F	72	18.45	29.70	1	>4.00	*A. fumigatus*
7	M	76	30.67	27.78	1	>4.00	*A. flavus*
8	M	64	12.80	31.46	6	2.60	No growth
9	M	73	28.62	26.32	3	3.35	*A. terreus*

- nonparalyzed patients
- advancing a 12-F suction catheter with a length of 54 cm via a closed circuit until bronchial wedging
- 2 X 20 ml of sterile NaCl 0.9% was given via the closed circuit and retrieved via the suction catheter.

Concordance between GM index >1.0 and positive Aspergillus cultures: 7/9 (77.8%).

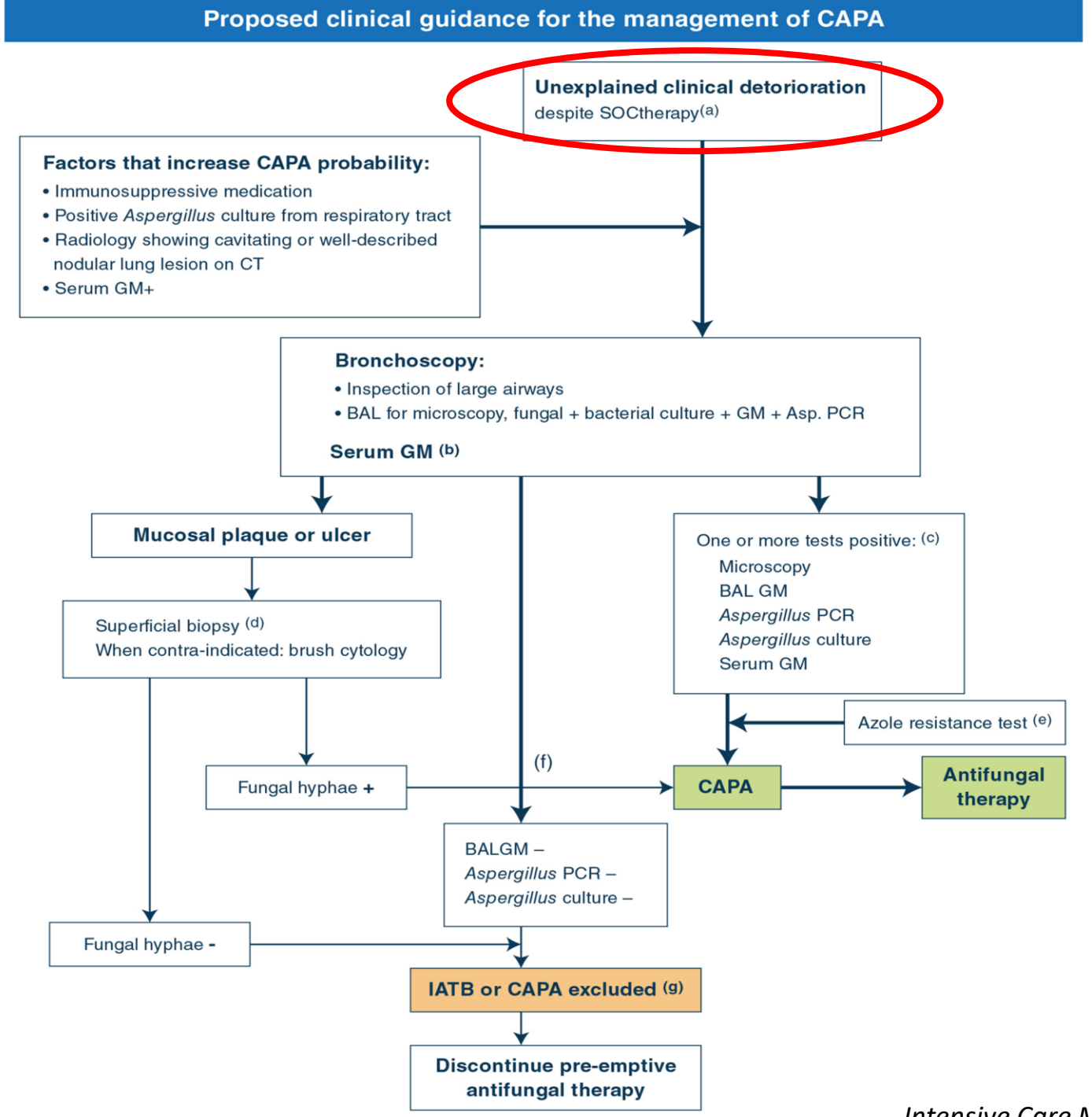
Van Biesen S, et al. Detection of invasive pulmonary aspergillosis in COVID-19 with non-directed bronchoalveolar lavage. Am J Respir Crit Care Med 2020; 202:1171–1173.

COVID-19 Associated Pulmonary Aspergillosis (CAPA)

Taskforce report on the diagnosis and clinical management of COVID-19 associated pulmonary aspergillosis

Paul E. Verweij[1,2,3*], Roger J. M. Brüggemann[2,4], Elie Azoulay[5], Matteo Bassetti[6,7], Stijn Blot[8,9], Jochem B. Buil[1,2], Thierry Calandra[10], Tom Chiller[11], Cornelius J. Clancy[12], Oliver A. Cornely[13,14,15], Pieter Depuydt[16], Philipp Koehler[13,14], Katrien Lagrou[17,18], Dylan de Lange[19], Cornelia Lass-Flörl[20], Russell E. Lewis[21], Olivier Lortholary[22,23], Peter-Wei Lun Liu[24,25], Johan Maertens[26], M. Hong Nguyen[12], Thomas F. Patterson[27,28], Bart J. A. Rijnders[29], Alejandro Rodriguez[30], Thomas R. Rogers[31], Jeroen A. Schouten[32,33], Joost Wauters[34], Frank L. van de Veerdonk[35] and Ignacio Martin-Loeches[36,37,38*]

Intensive Care Med 2021 Aug;47(8):819-834.



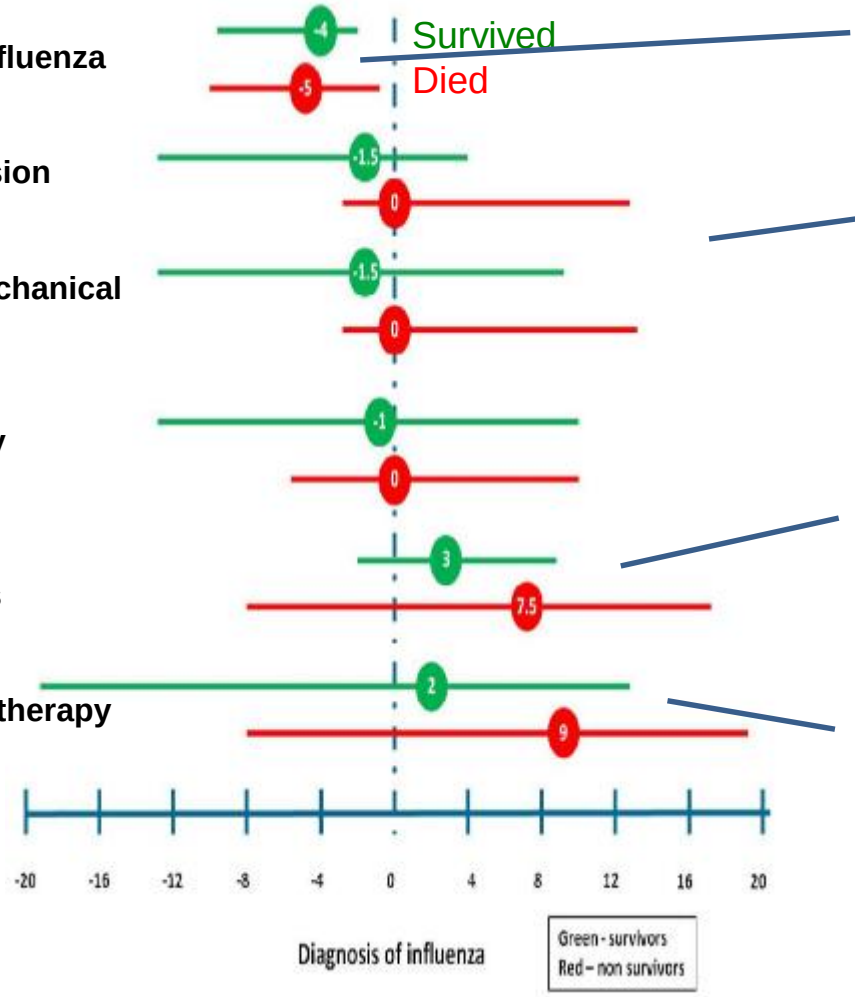
Intensive Care Med 2021 Aug;47(8):819-834.

Treatment Strategy:

Early initiation of first-line therapy is mandatory

Influenza and Invasive Aspergillosis in the ICU

- **Onset of influenza**
- **ICU admission**
- **Start of Mechanical Ventilation**
- **Chest X-ray infiltrate**
- **Aspergillus diagnosis**
- **Antifungal therapy**



Only sick for a few days

ICU & ventilated right from admission

Aspergillosis diagnosed within a few days

Treatment delay associated with mortality

van de Veerdonk FL, et al. *Am J Respir Crit Care Med*. 2017 Aug 15; 196(4):524-527.

Guidelines for Management of Aspergillosis

Recommendations	Strength of recommendation	Quality of evidence
Primary treatment with voriconazole	**Strong**	**High**
Patients with strongly suspected IPA warrant early initiation of antifungal therapy, whilst awaiting diagnostic evaluation	**Strong**	**High**
Alternative treatment with liposomal AmB	Strong	Moderate
Primary therapy with echinocandin is not recommended	Strong	Moderate
Alternative treatment with isavuconazole	**Strong**	**Moderate**
For select patients with documented IPA, combination antifungal therapy with voriconazole and an echinocandin may be considered	Weak	Moderate
Echinocandins (micafungin or caspofungin) can be used in settings in which azole or polyene antifungals are contraindicated	Weak	Moderate

Clin Infect Dis. 2016 Aug 15;63(4):e1-e60

A National Strategy to Diagnose Coronavirus Disease 2019–Associated Invasive Fungal Disease in the Intensive Care Unit FREE

P Lewis White ✉, Rishi Dhillon, Alan Cordey, Harriet Hughes, Federica Faggian, Shuchita Soni, Manish Pandey, Harriet Whitaker, Alex May, Matt Morgan ... Show more

Clinical Infectious Diseases, ciaa1298,
https://doi.org/10.1093/cid/ciaa1298

Clinical risk factors associated with CAPA:

- Chronic respiratory diseases
- The use of corticosteroids

- The administration of antifungal therapy (AFT) on the basis of radiology typical of IPA or positive mycology represents an improvement over empirical AFT use.
- Cavity, nodules, tree-in-bud, progression of non-specific CT image

White PL, *et al. Clin Infect Dis.* 2020. [Epub ahead of print].

Invasive Aspergillosis as an Under-recognized Superinfection in COVID-19

George R. Thompson III,[1,2] Oliver A. Cornely,[3,4,5,6] Peter G. Pappas,[7] Thomas F. Patterson,[8,9] Martin Hoenigl,[10,11] Jeffrey D. Jenks,[10] Cornelius J. Clancy,[12,13] and M. Hong Nguyen[13]; on behalf of the Mycoses Study Group (MSG) and European Confederation of Medical Mycology (ECMM)

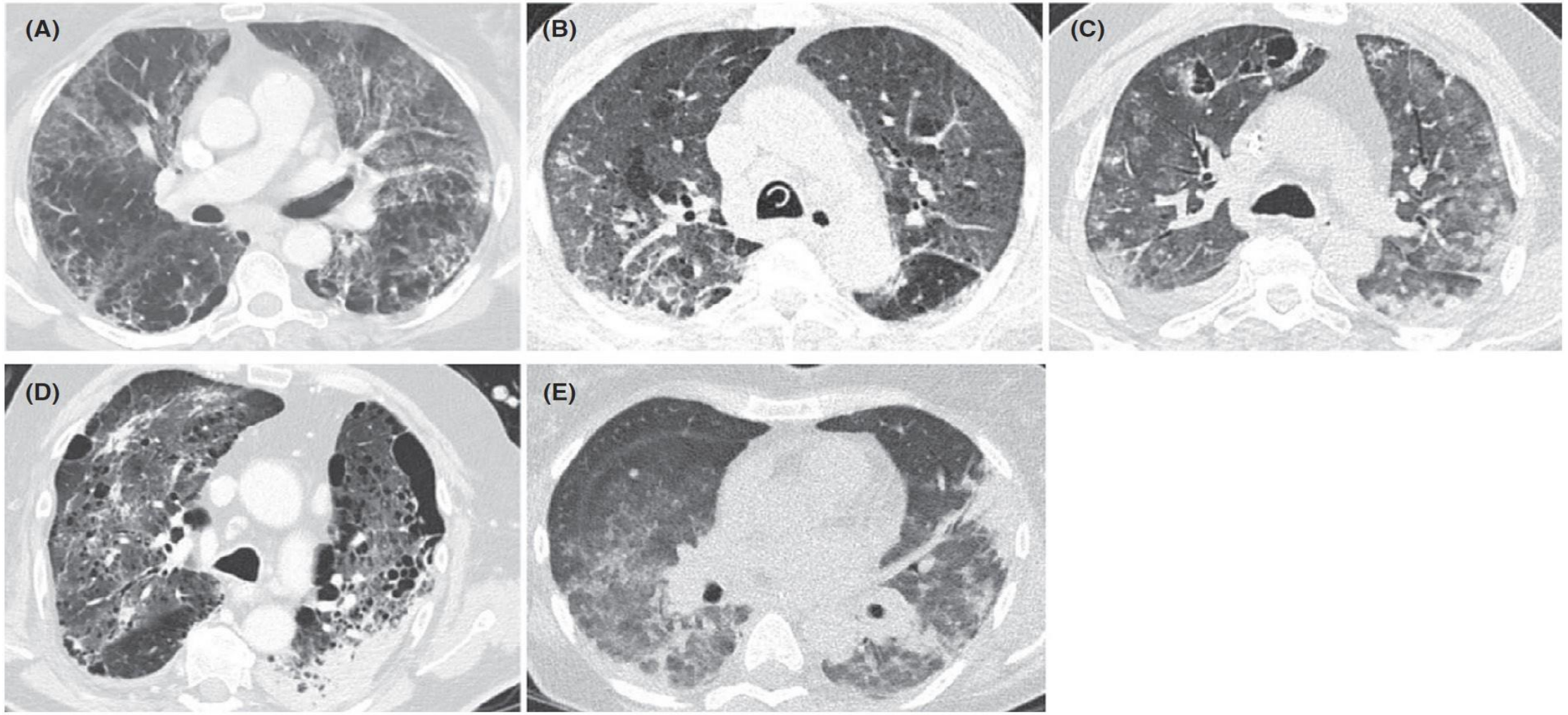
- Recommend consideration of aspergillosis as a cause of superinfection in COVID-19 patients with worsening clinical or radiographic findings.

- Positive endotracheal cultures may be the major predictive laboratory finding and should be scrutinized in an attempt to delineate putative aspergillosis from *Aspergillus* colonization.

- In those deemed to have active infection, antifungal therapy with voriconazole or isavuconazole should be initiated to optimize patient outcomes.

Thompson GR, *et al. Open Forum Infect Dis.* 2020. [Epub ahead of print].

CT Image of CAPA



Köhler P, *et al. Mycoses.* 2020;63(6):528–34.

Treatment of Invasive Aspergillosis

Treatment duration:

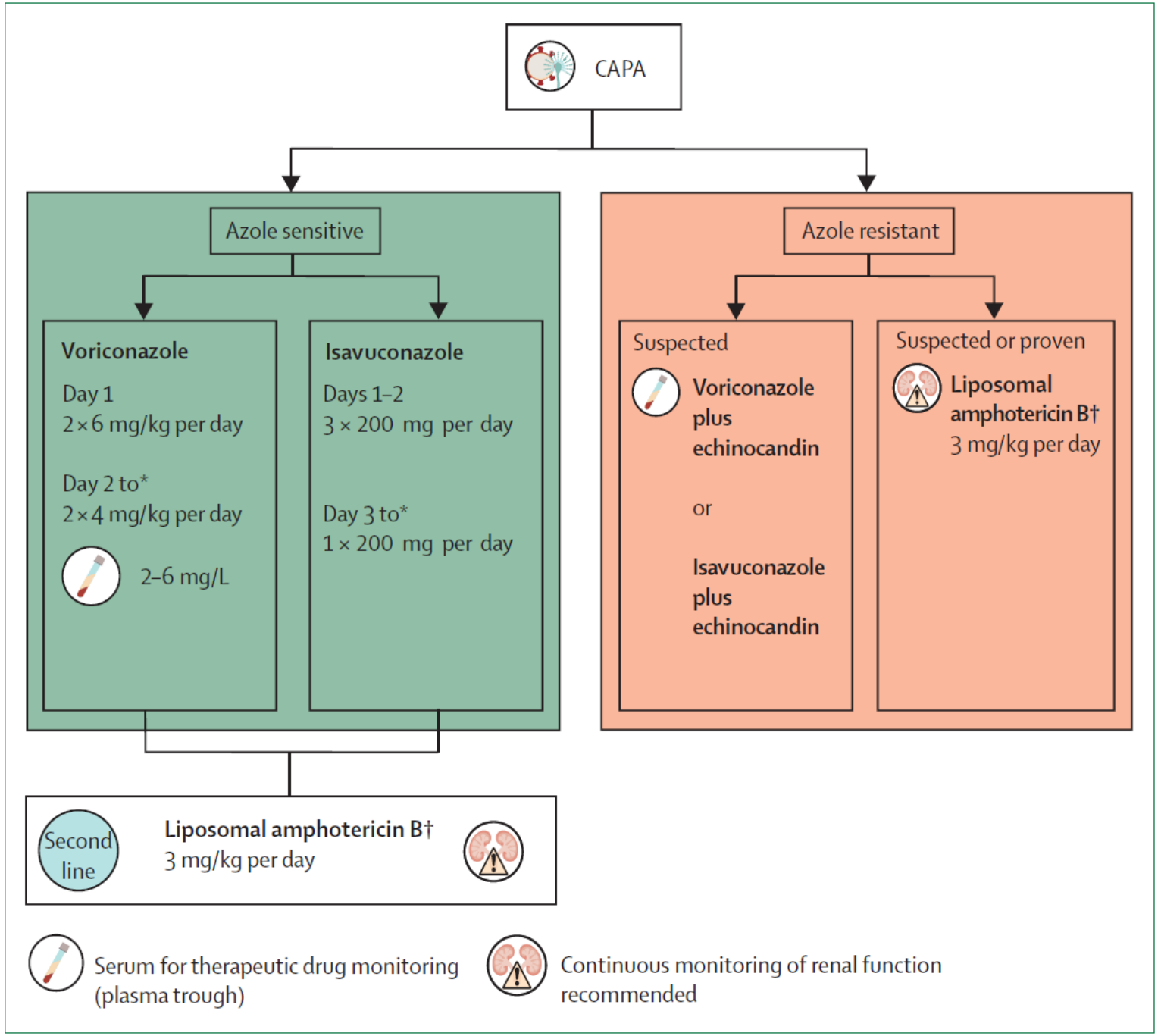
- Minimum of 6–12 weeks

Depends on:

- The degree and duration of immunosuppression
- Site of disease
- Evidence of disease improvement

Clin Infect Dis. 2016 Aug 15;63(4):e1-e60

Recommended Treatment for CAPA



Koehler P et al. Lancet ID 2020.

Take-home messages

- IPA in COVID-19 patients admitted to ICU is not rare (10–30%)
- Host/risk factors: high dose or long administration of corticosteroid, an EORTC/MSGERC host/risk factor, and structural lung disease
- Integrating all mycological tests would be useful (including GM, LFA, qPCR)
- A diagnostic work-up for CAPA is recommended in clinically deteriorating patients with no other explanation or with cavitary and/or nodular lesions on CT scan.
- First-line treatment: voriconazole or isavuconazole
- Salvage/azole-resistance: liposomal amphotericin B

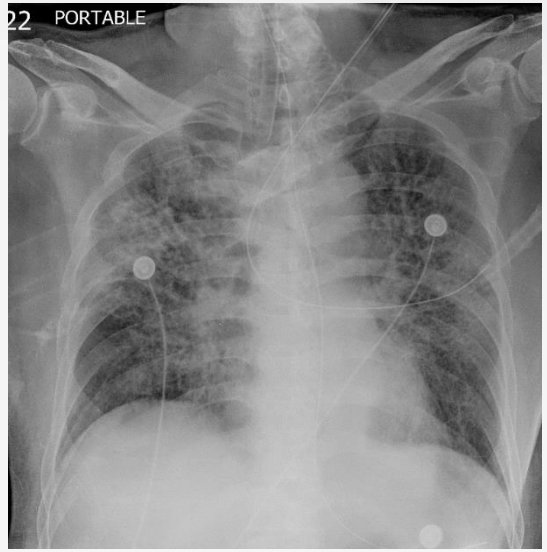
ORTC, European Organisation for Research and Treatment of Cancer; IA, invasive aspergillosis; ICU, intensive care unit;
MSGERC, Mycoses Study Group Education and Research Consortium;
qPCR, quantitative real-time polymerase chain reaction

Intensive Care Med 2021 Aug;47(8):819-834.

Patient Scenario

70 y/o man

- **BPH**
- **40 pack-year heavy smoker**



Sputum with cough, fever and dyspnea 4 days

CXR: bil infiltrative change

ER → **ICU**

SPO2 drop to 80-86%, RR >28bpm, intubation with ventilator support, COVID PCR (+)

SARS-CoV-2 infectious pneumonia with ARDS, AKI

Patient Scenario

ETT with MV support

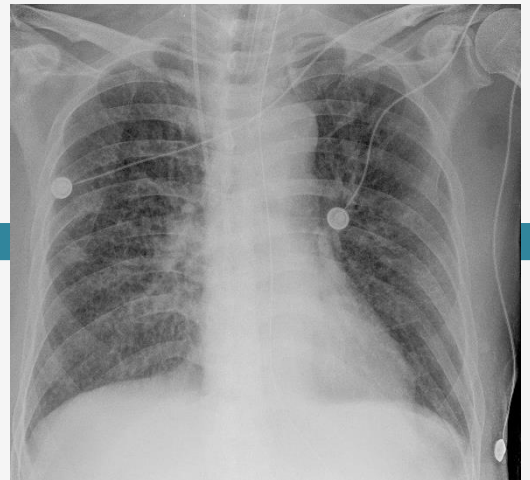
SARS-CoV-2 infectious pneumonia with severe ARDS (P/F ratio 84)

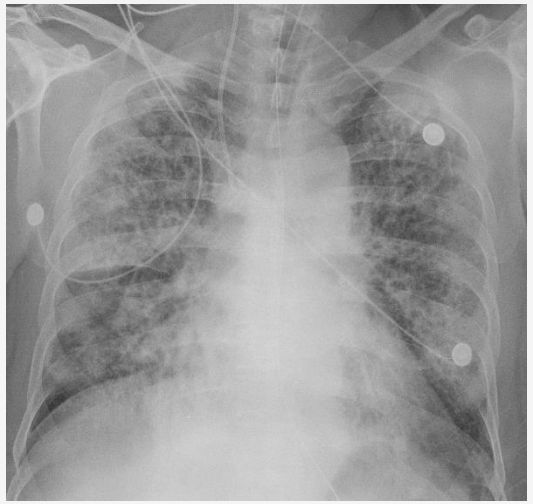
Aspergillus infection

Day 4 ETA Aspergillus Ag (LFA): 2.300 Positive
Day 6 ETA Aspergillus Ag (GM): 11.018 Positive
Day 9 ETA Aspergillus Ag (LFA): 5.430 Positive
Day 12 ETA Aspergillus Ag(LFA): **25.970 Positive**

Sputum culture

Day 6 Fungus S/C: Candida albicans, few Yeast-like



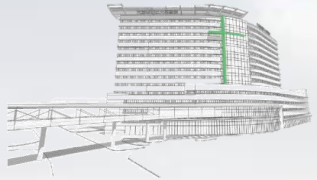


Prone position

Day 12-14 , CXR infiltration progress
Prone position twice

ICU Day 1

ICU Day 14



Cultures

5/25: S/C、B/C: negative

5/26: blood cultures (I/II): Staphylococcus hominis

5/31: Sputum culture: Candida albicans; few Aspergillus app.

6/2: S/C: Unidentified mold

6/7: S/C: Unidentified mold

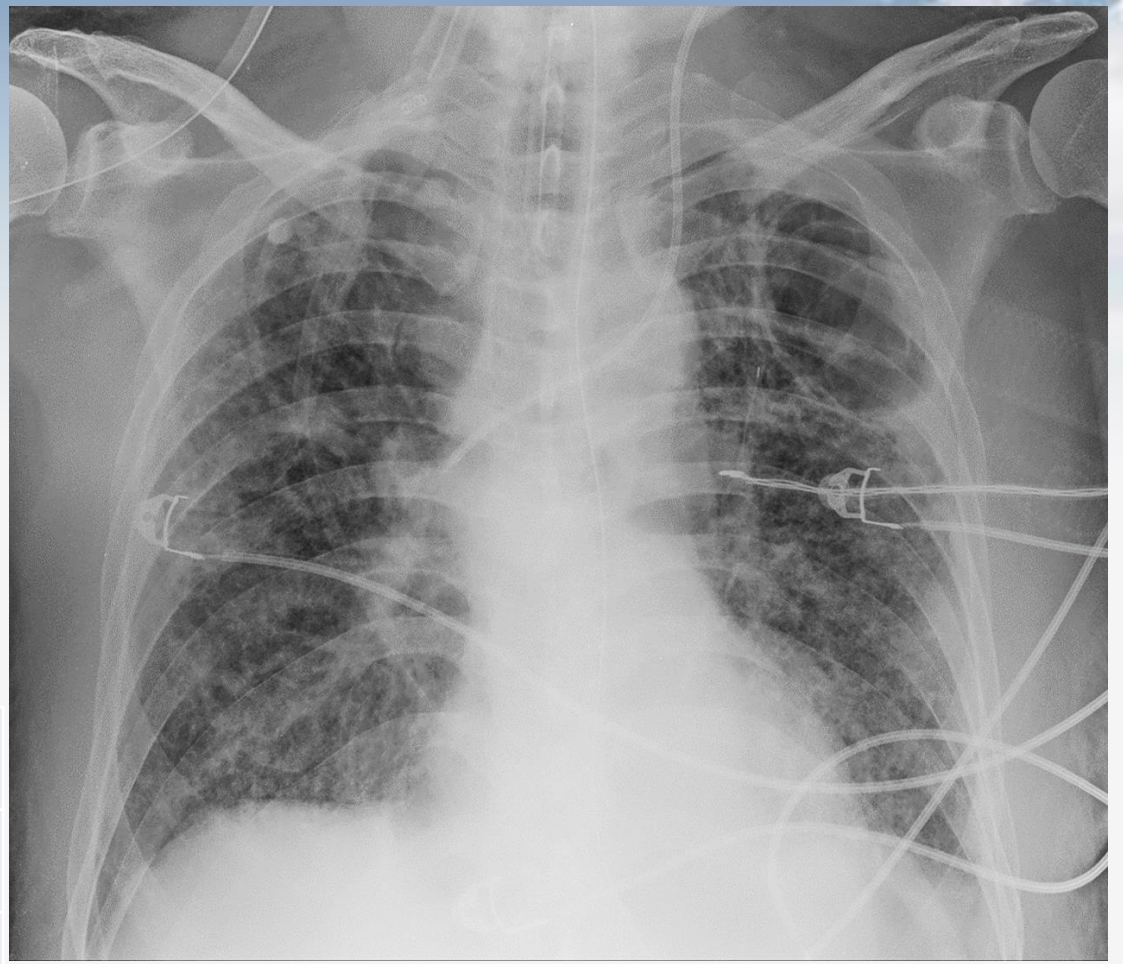
6/10: S/C: Unidentified mold

6/17: S/C: Unidentified mold

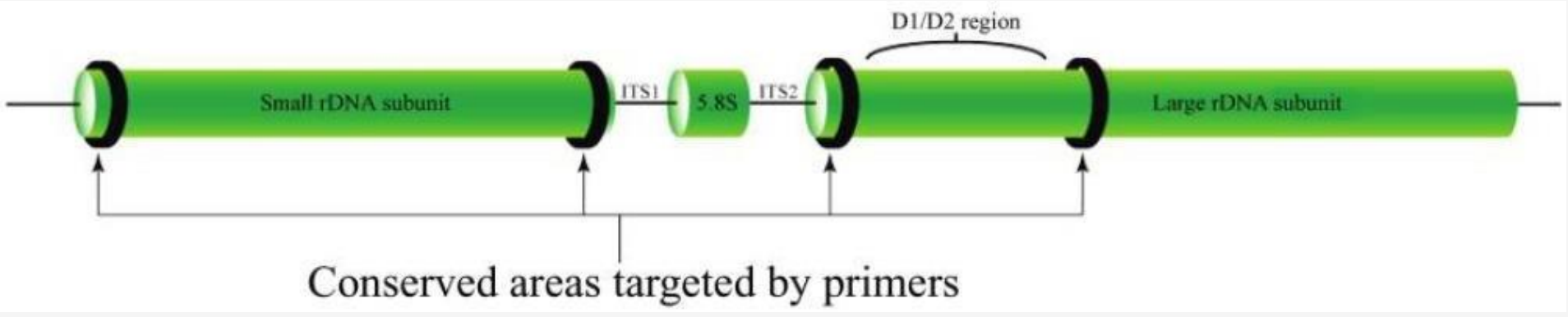
6/24: pleural effusion: Unidentified mold

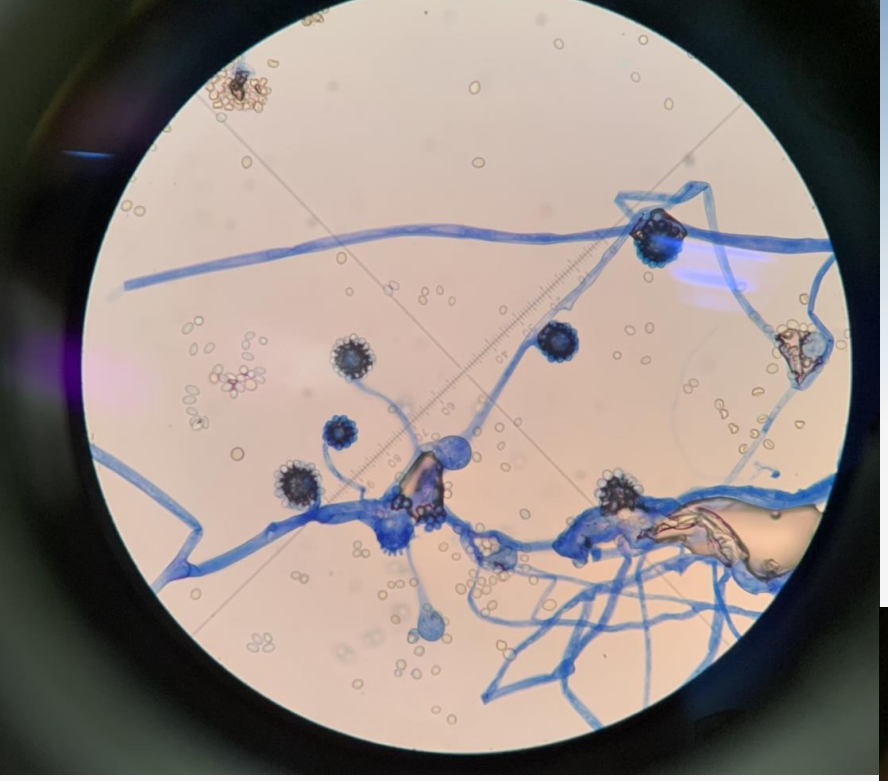
6/28: S/C: Light Mold

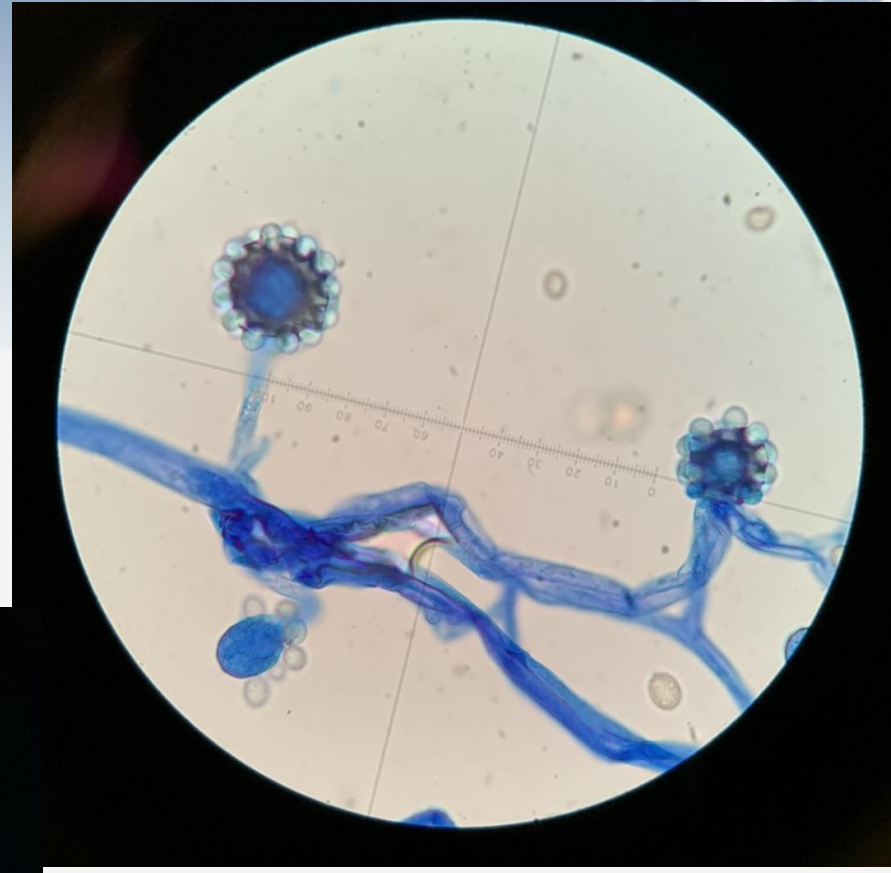
- Pleural effusion culture: Mold
- ITS (internal transcribed spacer, ITS) sequencing : ***Cunninghemella berthollectiae***
- Drug susceptibility test:



Final ID	藥敏方法	AmB MIC	ITC MIC	VRC MIC	PSC MIC	ISC MIC	AND MEC	AND MIC
Cunninghamella bertholletiae	CLSI M38-A2	2	> 16 (1)	>16	>8 (0.5)	>8	>8	>8
Aspergillus terreus	CLSI M38-A2	2	0.12	1	0.03	0.5	<0.004	>8







Cunninghemella berthollectiae

印度疫情：毛霉菌病讓新冠患者雪上加霜

莫妮卡·斯萊文（Monica Slavin），卡琳·瑟斯基（Karin Thursky）
本文最早發表於《對話》（The Conversation）

2021年6月6日

Coronavirus Disease–Associated Mucormycosis

EMERGING INFECTIOUS DISEASES®

ISSN: 1080-6059

EID Journal > Volume 27 > Early Release > Main Article

Volume 27, Number 9—September 2021

Research

Multicenter Epidemiologic Study of Coronavirus Disease–Associated Mucormycosis, India

Sept–Dec 2020

187 patients with CAM (0.27% of hospitalised COVID-19 patients)

Patient characteristics

Uncontrolled diabetes mellitus, COVID-19-related hypoxemia, inappropriate steroid treatment

CAM, COVID-19-associated mucormycosis; EID, Emerging Infectious Diseases

Patel A, *et al. Emerg Infect Dis.* 2021. [Epub ahead of print].

Coronavirus Disease–Associated Mucormycosis

Classified glucocorticoid use as:

- not indicated: any steroid was used for managing non-hypoxemic COVID-19
- appropriate when dexamethasone-equivalent doses of 6 mg/day were used for <10 days
- indicated but inappropriate when dexamethasone-equivalent doses >6 mg/day were used for ≥10 days.

Treatment : liposomal amphotericin B (5 mg/kg 1×/d for 4–6 weeks, or, if the patient had economic constraints, amphotericin B deoxycholate 1 mg/kg 1×/d for 6–8 weeks).

Patel A, Agarwal R, Rudramurthy SM, Shevkani M, Xess I, Sharma R, et al. Multicenter Epidemiologic Study of Coronavirus Disease–Associated Mucormycosis, India. Emerg Infect Dis. 2021;27(9). https://doi.org/10.3201/eid2709.210934

Coronavirus Disease–Associated Mucormycosis

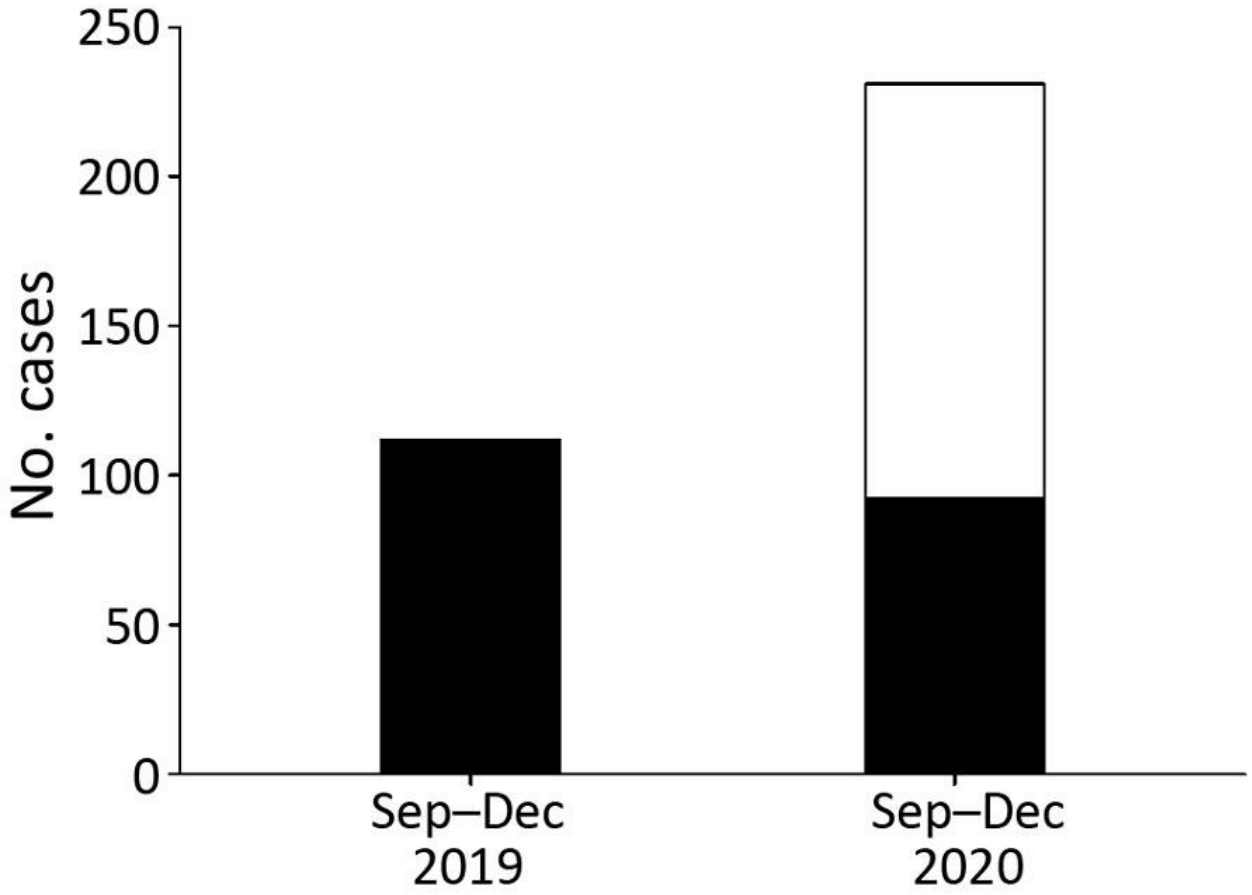


Figure 2. Cumulative number of mucormycosis cases during September–December 2019 and September–December 2020 in 10 health centers, India. White bar section indicates coronavirus disease–associated mucormycosis (CAM); black bar sections indicate non-CAM cases. During 2019, 112 cases of mucormycosis were detected, but a total of 231 cases, 92 non-CAM and 139 CAM, were detected in 2020.

Patel A, et al. Emerg Infect Dis. 2021;27(9).
https://doi.org/10.3201/eid2709.210934

Coronavirus Disease–Associated Mucormycosis

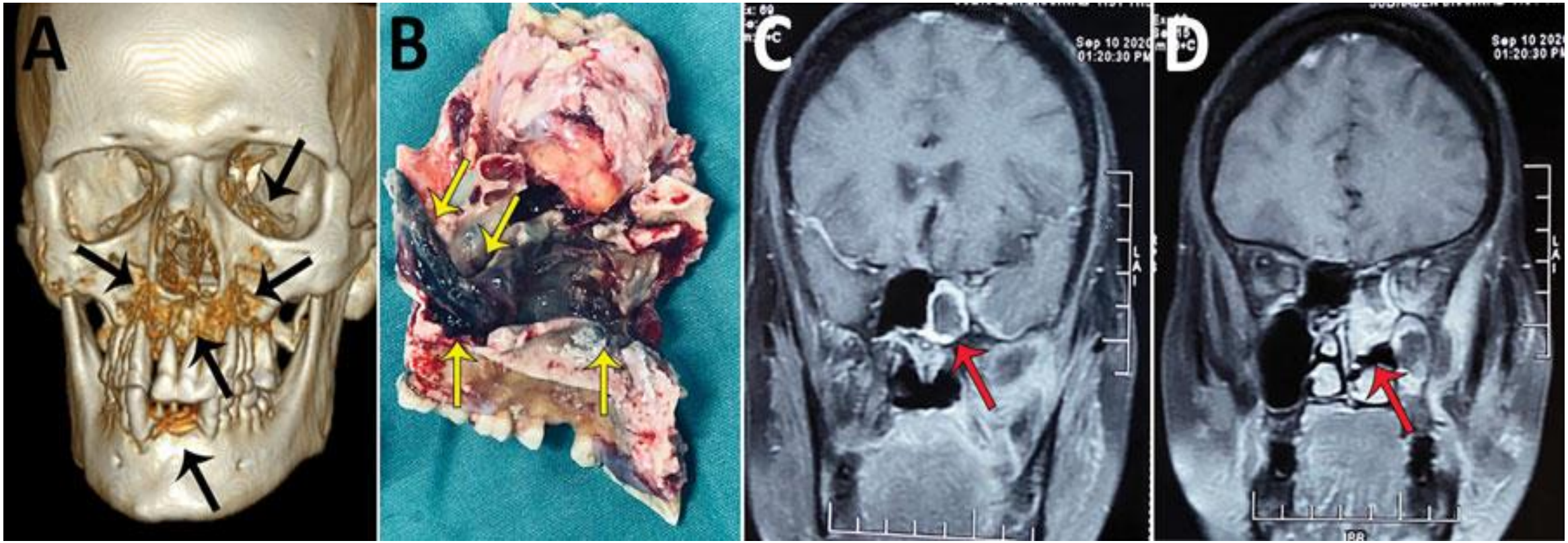


Figure 3. Radiographic images and surgical specimens demonstrating rhino-orbital-cerebral coronavirus disease–associated mucormycosis in patients from India, 2020. A) Three-dimensional reconstruction of computed tomography scan of 54-year-old male patient. Black arrows indicate patchy osteonecrosis involving the upper jaw, right orbital wall, and paranasal sinuses. B) Surgical specimen from the maxilla of 54-year-old male patient showing black necrotic paranasal sinus with palatal involvement indicated by yellow arrows. C, D) Magnetic resonance imaging (MRI) of coronal section of paranasal sinus and brain of 51-year-old female patient. Red arrow in panel C indicates enhancing cavernous sinus lesion; D) red arrow in panel D indicates right ethmoid and maxillary sinusitis. Scale bar indicates 7 cm.

Patel A, et al. Emerg Infect Dis. 2021;27(9).
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Coronavirus Disease–Associated Mucormycosis

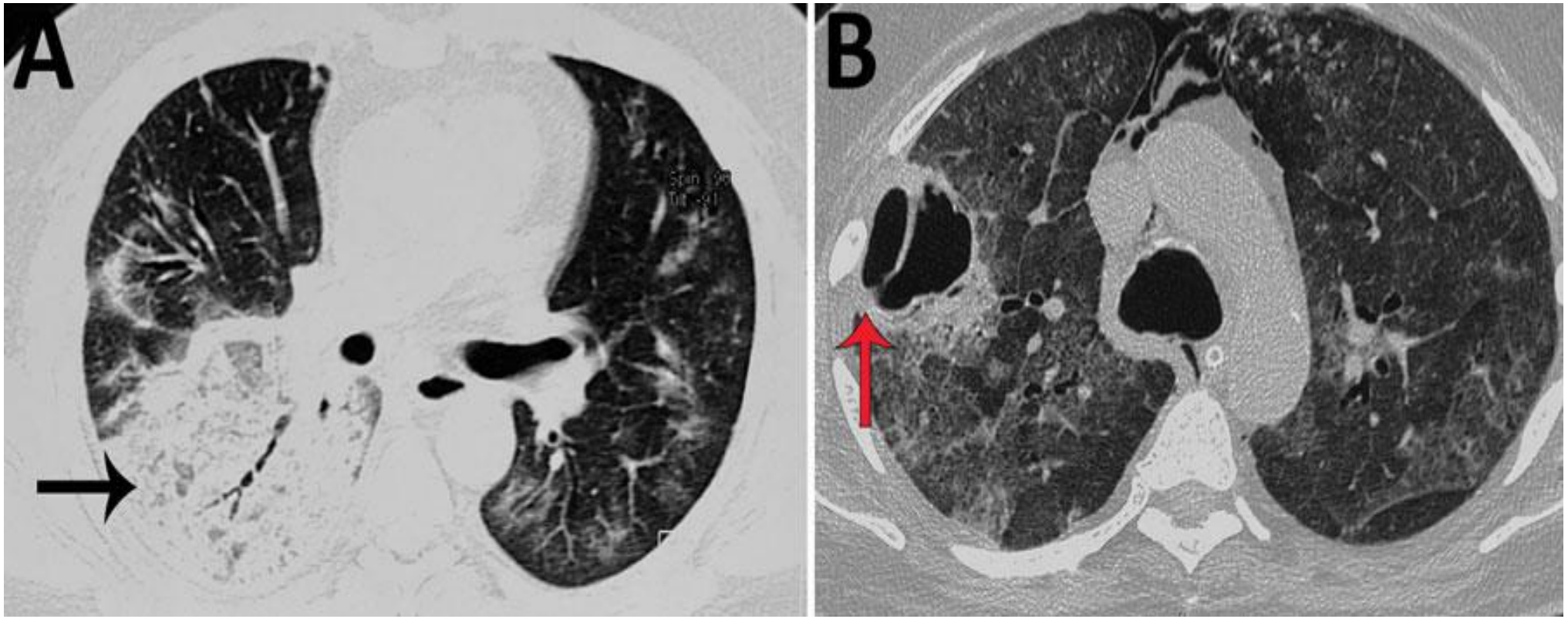

Figure 4. Noncontrast computed tomography scan of the thorax of a patient with coronavirus disease–associated mucormycosis, India, 2020. A) Pulmonary mucormycosis demonstrated as a large area of consolidations with patchy air trapping (black arrow), patchy ground-glass opacities, and septal thickening; B) large thick-walled cavity (red arrow) with surrounding ground-glass opacities.

Patel A, et al. Emerg Infect Dis. 2021;27(9).
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Coronavirus Disease–Associated Mucormycosis

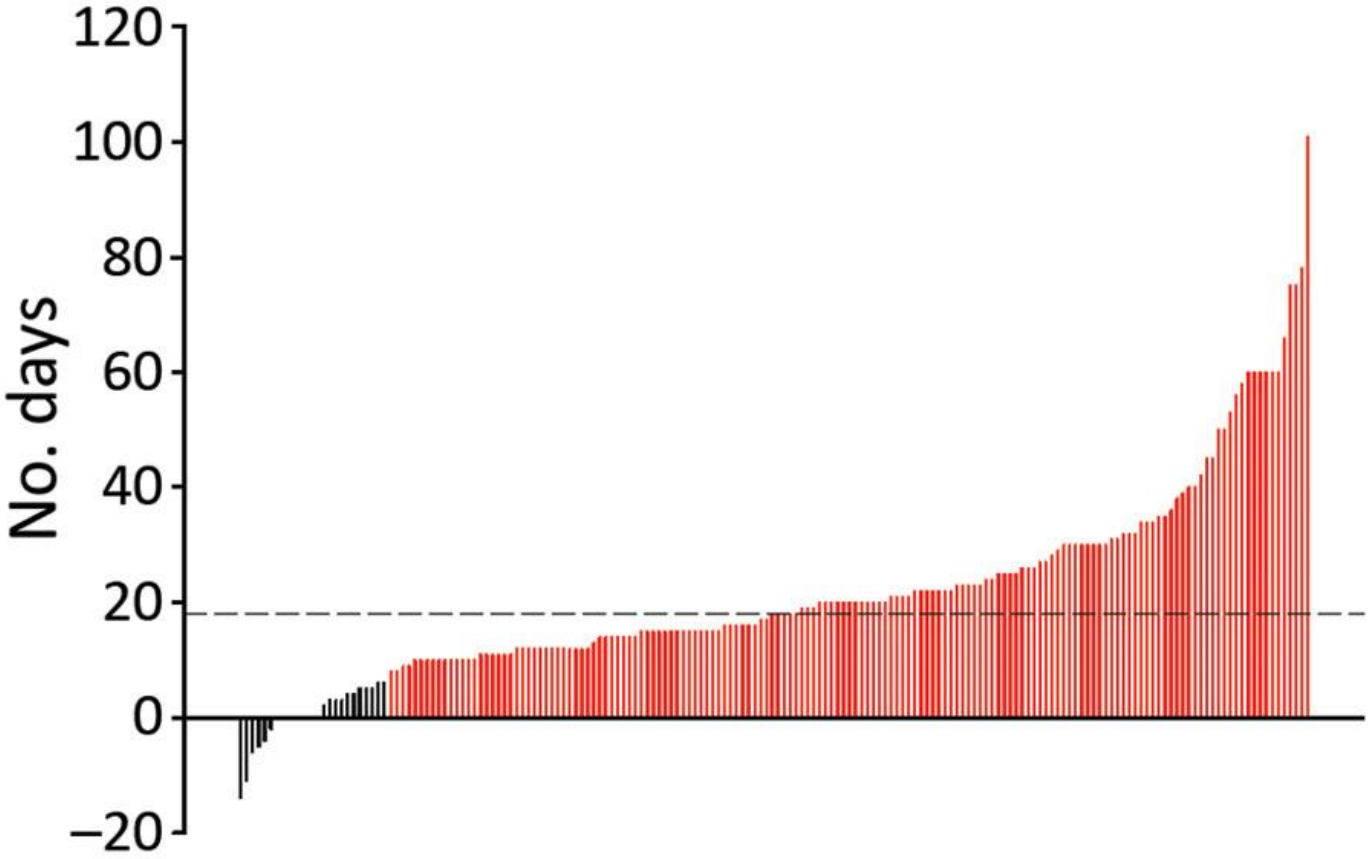

Figure 5. Waterfall plot showing the number of days between the diagnosis of coronavirus disease (COVID-19) and COVID-19–associated mucormycosis (CAM). Each vertical line represents a case-patient. Red indicates late CAM (mucormycosis developing >8 days after COVID-19 diagnosis); black indicates early CAM (mucormycosis developing <7 days of COVID-19 diagnosis). Among early CAM cases, mucormycosis was diagnosed before (n = 8), concurrently with (n = 8), or after (n = 13) COVID-19 diagnosis. Dotted line represents the median duration (18 days) after COVID-19 diagnosis for the diagnosis of CAM.

Patel A, et al. Emerg Infect Dis. 2021;27(9).
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Coronavirus Disease–Associated Mucormycosis

Variables	Early CAM, n = 29†	Late CAM, n = 158‡	p value
Mean age, y (SD)	51.8 (14.2)	57.8 (11.9)	0.015
Sex			0.10
F	9 (31.0)	28 (17.7)	
M	20 (69.0)	130 (82.3)	
Glucocorticoids	8 (27.6)	138 (87.3)	0.0001
Tocilizumab	0	5 (3.2)	0.33
Underlying diseases			0.52

Variables	Survivors, n = 177	Non-survivors, n = 110	Odds ratio (95% CI)	p value
Mean age, y (SD)	52.6 (15.1)	54.7 (14.0)	1.02 (1.00–1.04)	**0.03**
Underlying disease				
None	10 (5.6)	9 (8.2)	Referent	Referent
Isolated COVID-19	42 (23.7)	19 (17.3)	0.56 (0.17–1.83)	0.34
Diabetes mellitus	109 (61.6)	71 (64.5)	0.92 (0.32–2.64)	0.88
Traumatic inoculation	8 (4.5)	4 (3.6)	1.30 (0.25–6.80)	0.76
Others	5 (2.8)	3 (2.7)	1.20 (0.18–7.81)	0.85
Renal transplantation	1 (0.6)	2 (1.8)	6.87 (0.42–113.19)	0.18
Hematological malignancy	2 (1.1)	2 (1.8)	1.60 (0.14–18.72)	0.71
Site of involvement				
Rhino-orbital	117 (66.1)	50 (45.5)	Referent	Referent
Rhino-orbito-cerebral	39 (22)	39 (35.5)	2.39 (1.30–4.40)	**0.005**
Pulmonary	8 (4.5)	14 (12.7)	3.26 (1.05–10.11)	**0.04**
Other†	13 (7.3)	7 (6.4)	1.29 (0.43–3.86)	0.64
Admission to the intensive care unit	32 (18.1)	35 (31.8)	2.87 (1.43–5.75)	**0.003**
Combined medical surgical therapy	135 (76.3)	69 (62.7)	0.77 (0.41–1.45)	0.41
Combination of antifungals				
Single antifungal drug	95 (53.7)	88 (80)	Referent	Referent
Concurrent	9 (5.1)	5 (4.5)	0.37 (0.09–1.44)	0.15
Sequential	73 (41.2)	17 (15.5)	0.17 (0.87–0.35)	**0.0001**

Patel A, Agarwal R, Rudramurthy SM, Shevkani M, Xess I, Sharma R, et al. Emerg Infect Dis. 2021;27(9). https://doi.org/10.3201/eid2709.210934

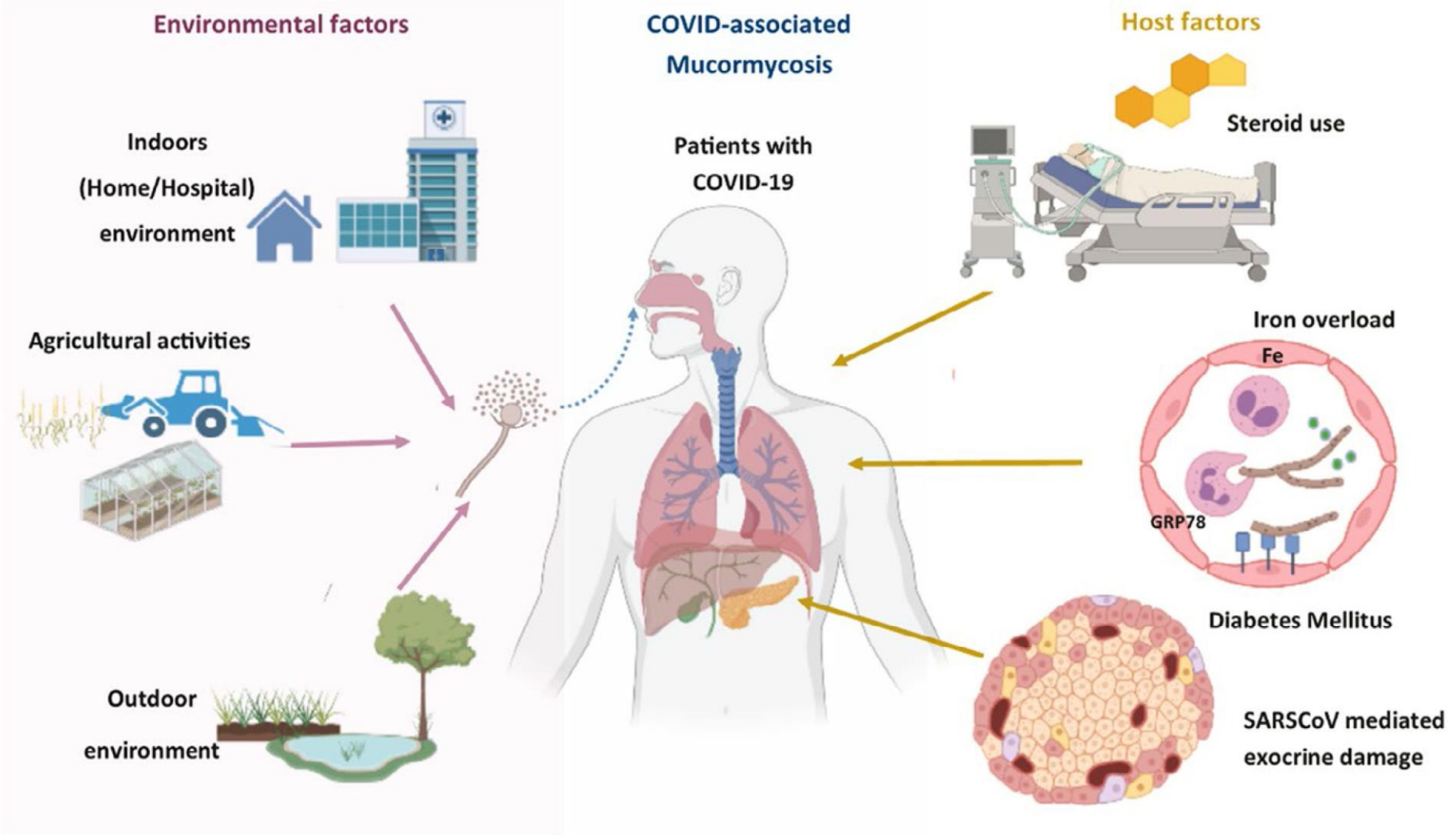
Risk Factors for Mycormycosis

Rhino-orbito-cerebral mucormycosis and pulmonary mucormycosis:

- Uncontrolled diabetes
- Immunosuppressive conditions, such as patients receiving corticosteroid treatment, cancer chemotherapy or immunotherapy
- Hematological stem cell transplants
- Prolonged neutropenia or solid organ transplants.

Mycoses. 2021 Jun 16.
doi:10.1111/myc.13335. Online ahead of print.

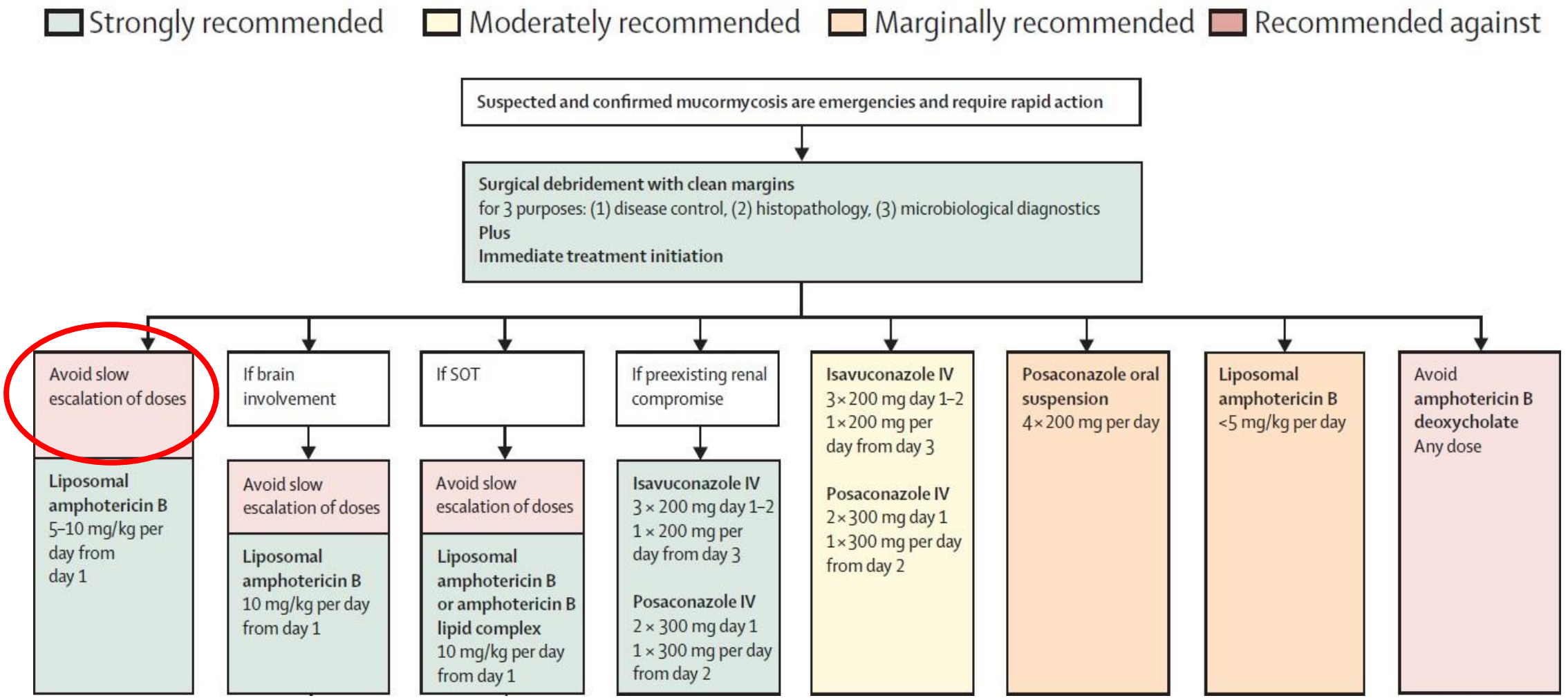
Risk Factors of COVID-associated Mycormycosis



Mycoses. 2021 Jun 16. doi:10.1111/myc.13335. Online ahead of print.

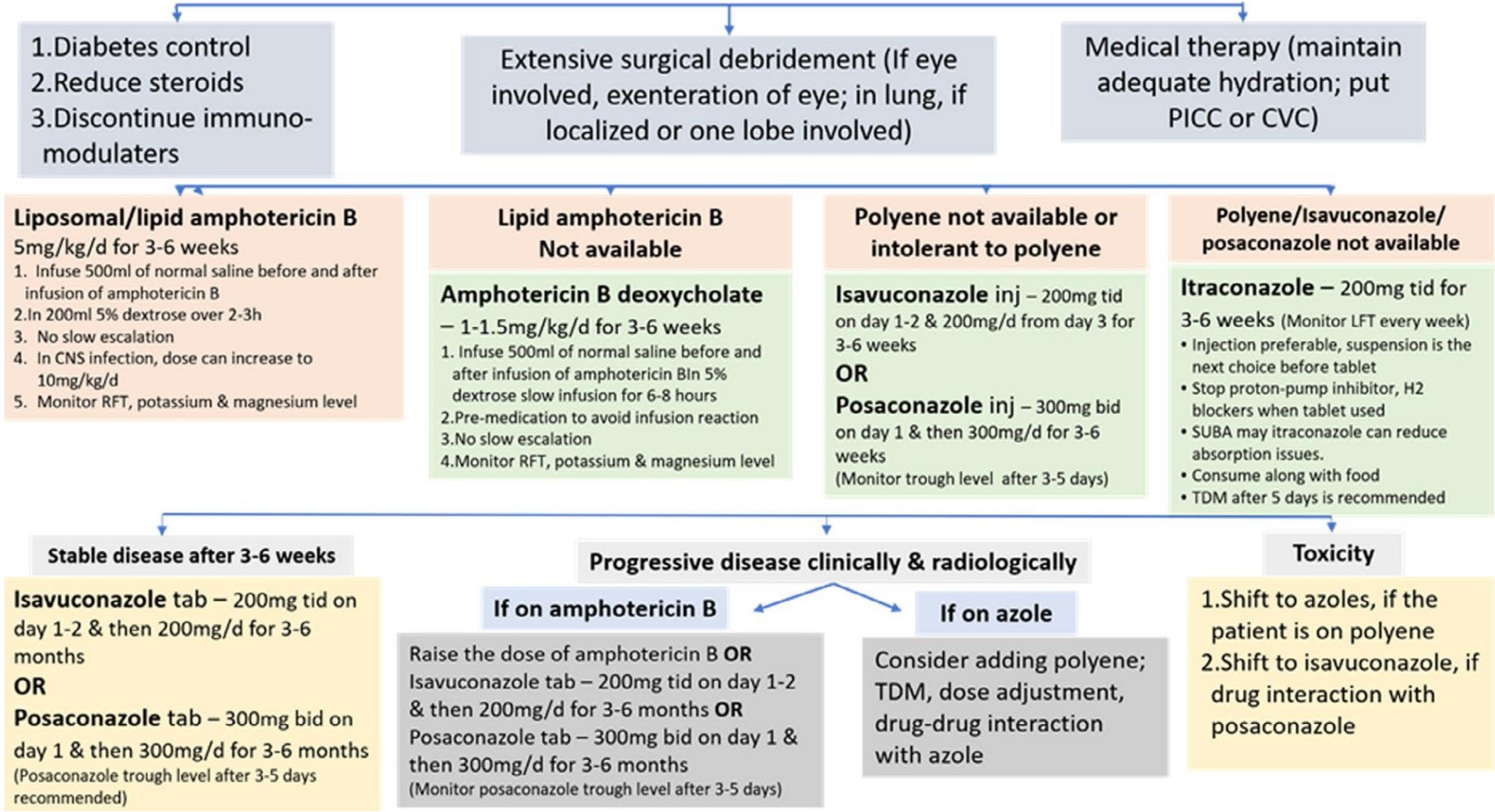
Optimal Treatment for Mucormycosis in Adults

when all treatment modalities and antifungal drugs are available



European Confederation of Medical Mycology (ECMM) guideline 2019. Lancet Infect Dis 2019

Treatment algorithm for CAM



Mycoses. 2021 Jun 16. doi:10.1111/myc.13335. Online ahead of print.

Do's

- **Maintain strict glycaemic control** during COVID-19 management.
- **Systemic corticosteroids should only be used in patients with hypoxemia** while ensuring glycaemic control.
- **Limit the dose and duration of steroid** therapy: dexamethasone (0.1mg/kg/day) for 5-10 days.
- **Use of surgical or three-layered linen mask,** both outdoor and indoor to reduce exposure to *Mucorales.*
- Advise all patients especially diabetics to **check for early signs of mucormycosis** (facial pain, nasal blockage, excessive discharge, loosening of teeth, chest pain, respiratory insufficiency) after discharge from COVID-19 wards.

Don'ts

- **Primary antifungal prophylaxis is not recommended** for diabetes associated mucormycosis including CAM.
- *Mucorales* are **intrinsically resistant to voriconazole, fluconazole, caspofungin, anidulafungin, micafungin, and 5-flurocytosine**. These drugs are not effective against mucormycosis and should not be used for treatment.
- **Breakthrough mucormycosis** is common with **voriconazole prophylaxis.**
- **Combination of antifungals is NOT recommended** for treating CAM.

Remember:

- The term '**Black Fungi**' should **NOT** be used for ***Mucorales*** or for the disease 'mucormycosis'. 'Black fungi' are a different group of fungi that produce melanin and have dark brown or black hyphae.
- Mucormycosis is **NOT contagious**. Human to human transmission does not occur.
- **Fungi are present in the indoor & outdoor environment** and spores enter the respiratory tract via air.
- **No antifungal prophylaxis** is recommended as the incidence is <10% in any COVID-19 cohort.

Mycoses. 2021 Jun 16. doi:10.1111/myc.13335. Online ahead of print.