COVID-19 associated invasive fungal infections

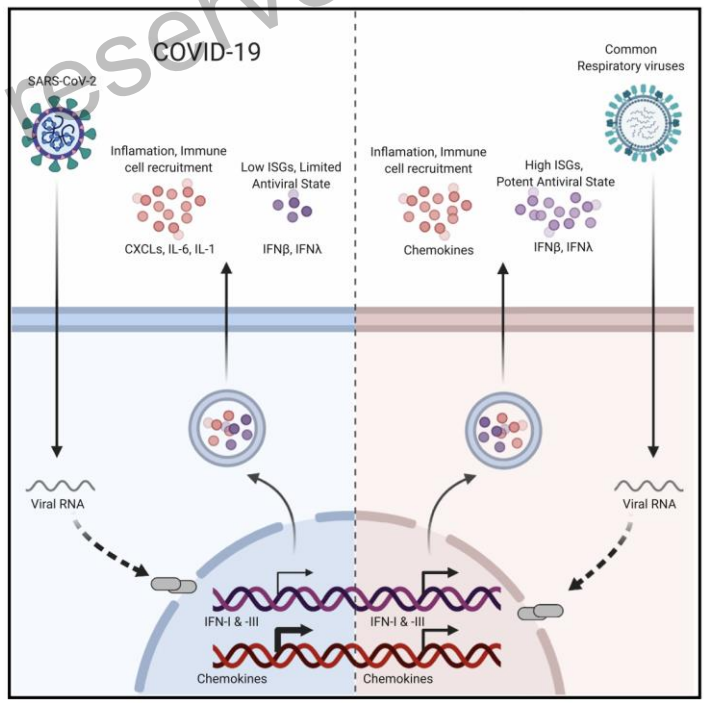
Arunaloke Chakrabarti
Director, Doodhdhari Burfani Hospital, Haridwar, India
Ex-Head & Professor, Medical Microbiology, PGIMER, Chandigarh
Past-President, International Society for Human & Animal Mycology

Devastating pandemic ever mankind suffered

- **Till July, 2023 - ~700,000,000 Coronavirus cases & ~6,902,000 deaths**

Why fungal infections in CIVID-19?

- Respiratory viruses cause **damage of airway epithelium, hampers ciliary clearance** enabling invasion of fungal spores (Short KR, *et al*. European Respir J 2016; 47: 954)
- **Immune dysfunction/dysregulation** due to viral infection helps further invasion of fungi (Herold S, *et al*. European Respir J 2015; 45: 1463)
- **Exuberant inflammatory cytokine production** are the defining & driving features of COVID-19 (Blanco-Melo D, *et al.* Cell 2020;181: 1036)
- COVID-19 - **release of danger-associated molecular pattern (DAMPs)** - an endogenous signal exacerbating inflammatory response leading to lung injury (Arastehfar A, *et al*. J Fungi 2020; 6)
- **DAMPs also play central role in pathogenesis of fungal diseases** (Cunha C, *et al.* Front Immunol 2012; 3: 286)



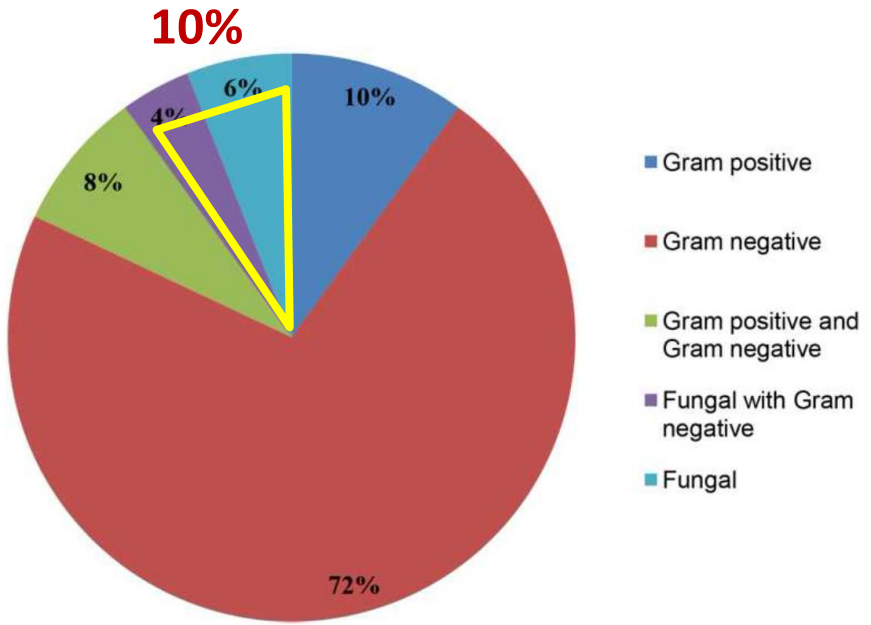
- **Corticosteroid & anti-IL6 antibody** also help fungal invasion
- **Compromise in infection control, antibiotics, steroids, CVC, surgery** – help in invasive candidiasis

Fungal infections in COVID-19

- Patients in **intensive care unit (ICU),** are particularly vulnerable **(incidence 5%-26.7%)**
  - **Covid associated invasive candidiasis (CAC)**
  - **Covid associated pulmonary aspergillosis (CAPA)**
  - **Covid associated mucormycosis (CAM)**
  - Rarely fusariosis, pneumocystosis, *Saccharomyces* fungemia, cryptococcosis

Multi-centre study, India: 17,534 COVID-19 patients

- ***Candida* – 6%** [67% from blood; **21.3% *C. auris***]; ***Aspergillus* – 1.6%**
- **Fungal infections contributed – 10% mortality**



Hoenigl M. Clin Infect Dis 2020, Sep 5; CDC report: https://www.cdc.gov/fungal/covid-fungal.html; Ezeokoli O, *et al.* J Fungi 2021; 7: 545; Vijay S, *et al.* Infect Drug Res 2021; 14: 1893-1903; Rovina N, *et al.* J Clin Med 2022; 11: 2017

Challenges we faced for diagnosis

- **Sepsis** – bacterial or fungal??
- **Pulmonary mycoses** - symptoms & radiology **similar to those of COVID-19; how to diagnose?**
- **How to distinguish CAPA & CAPM?**

- **So, what happened?**

Experience from Chelsea & Westminster Hospital, London, UK

- If patient in ICU fever not responding to antibacterial therapy, given antifungal
- **42% (24/57) received LAMB** (median treatment 6 days) **& majority empirical**
- 50% had fungi only in superficial samples (tracheal aspirate, sputum etc.), 58% BDG negative
- **21% with LAMB develop acute kidney injury; Need targeted therapy with improved diagnosis**

Heard KL, *et al.* Lancet Microbe 2020; 1: e107

COVID 19 associated candidiasis (CAC)

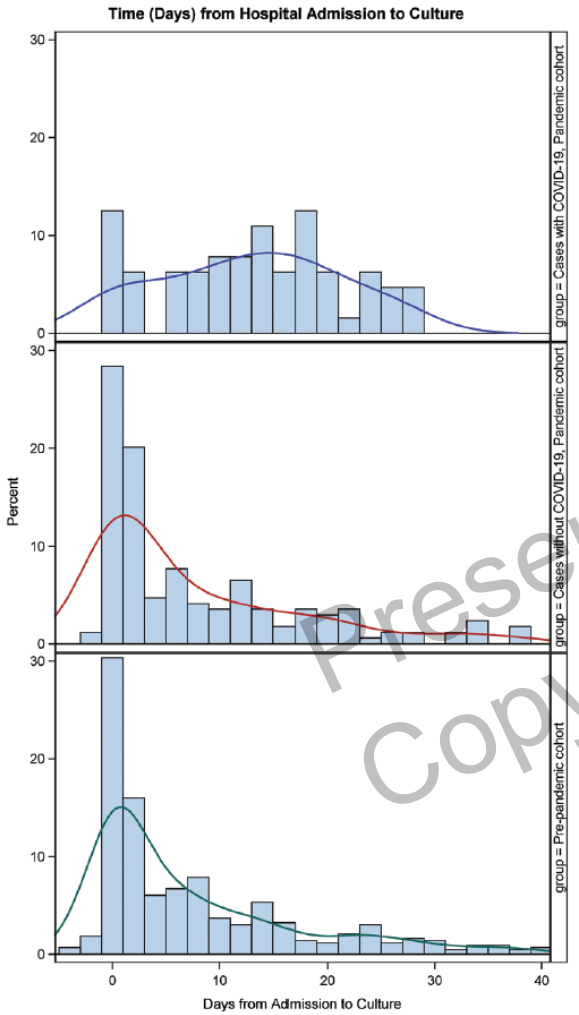
COVID-19 associated candidiasis

Hoenigl M, *et al*. Nature Microbiol 2022; 7: 1127-1140

5-10-fold rise in invasive candidiasis reported in ICUs

Mastrangelo A, *et al*. Clin Infect Dis 2020, Oct 30; ciaa1594

University Hospital Italy



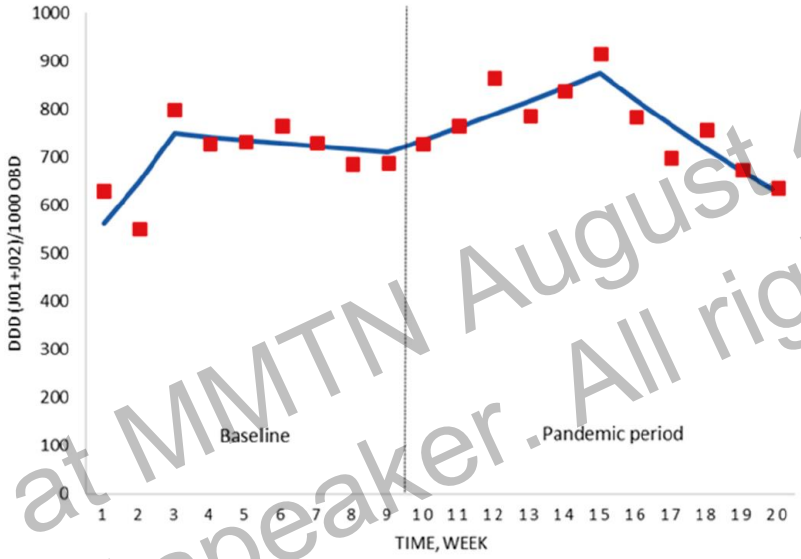
Significant risk factors	COVID-19 (n=21)	Non-COVID-19 (n=51)	P-value
ICU stay	**66.7%**	**29.4%**	**<0.003**
Prior antibiotics	**100%**	**82.4%**	**0.050**
Immunosuppression	**61.1%**	**32.7%**	**<0.035**
Candidemia/10,000 patient days follow up	**10.97** (6.79-16.76)	**1.48** (1.10-1.95)	**<0.001**

- **50-80% of CAC are health-care associated**
- Rise in CAC noted due to **co-morbidities, indiscriminate use of antibiotics, glucocorticoids**, & **lapses in infection control** (Seaton RA, *et al*. J Infect 2020; 81; 952)

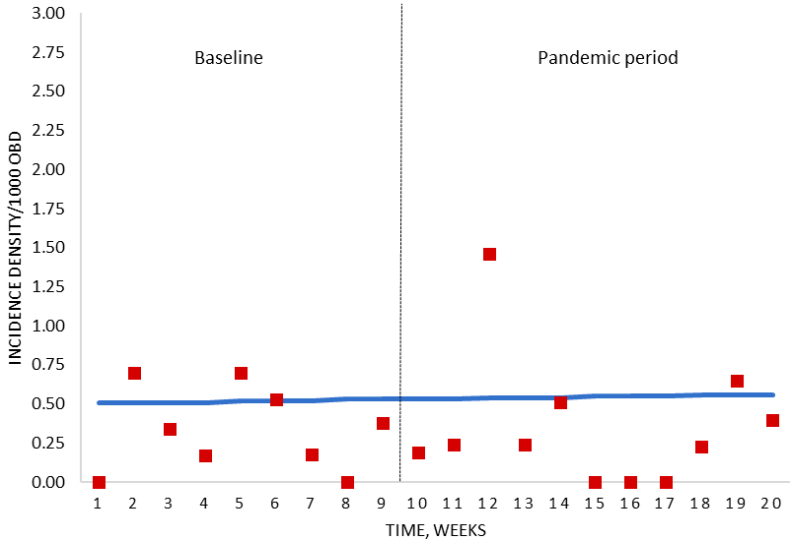
Seagle EE, *et al*. Clin Infect Dis 2021; ciab 562

Is the rise linked with more antibiotic use?

University Hospital in Spain



Antibiotic consumption

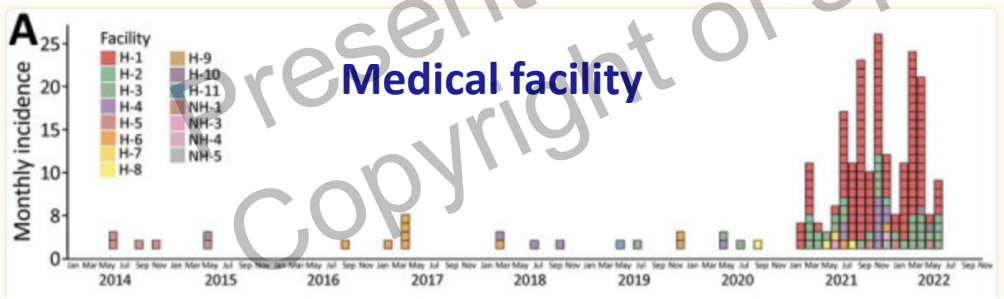


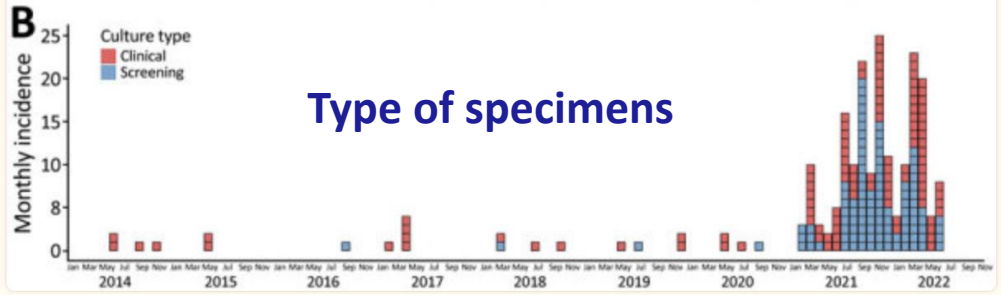
Hospital acquired candidemia & MDR bacterial BSI

Guisado-Gil AB, *et al*. Antibiotics 2020; 9: 816

Nationwide outbreak of *C. auris* driven by COVID-19 in Israel

- During May 2014–May 2022, 209 patients with *C. auris* infection/colonization
- ***C. auris* incidence rate increased 30-fold in 2021 (p = 0.00015),** corresponding with surges of COVID-19–related hospitalization.
- Multilocus sequence typing revealed clade III clone, accounted for 48.8% of isolates after January 2021 & was more frequently **resistant to fluconazole (100% vs. 63%; p = 0.00017) and voriconazole (74% vs. 5.2%; p<0.0001)** than were non–clade III isolates.





Biran R, *et al*. Emerg Infect Dis 2023; 29: 1302-1311

What about South Asia?

2 ICUs in Delhi & Jaipur
August 2020 to January 2021

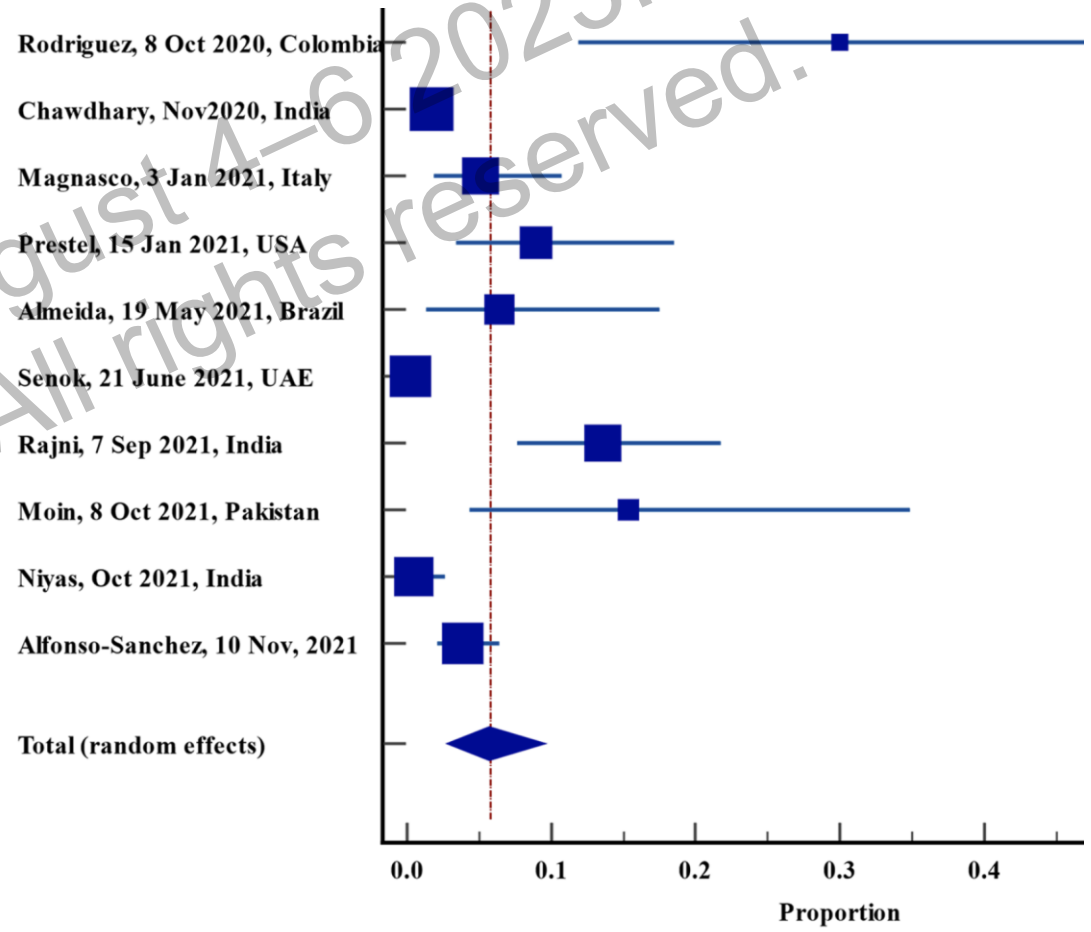
2018-2019	Aug 20-Jan21	2018-2019	Aug 20-Jan21
5/1000 admission	14/1000 admission	7/1000 admission	15/1000 admission

- **2-fold rise** in incidence of candidemia in COVID-19 patients vs. non-COVID-19 patients
- ***C. auris* – 42% (100% resistant to flu & 21% AmB),** *C. tropicalis* – 21%, *C. albicans* - 18%
- **Tocilizumab (67% vs, 20%) , duration of ICU stay (24 vs. 14 days)** – independent predictor for COVID-19 associated candidemia

Rajni E, *et al*. OFID 2021; 8: ofa452

Global prevalence of COVID-19 associated *C. auris* infection (CACa)

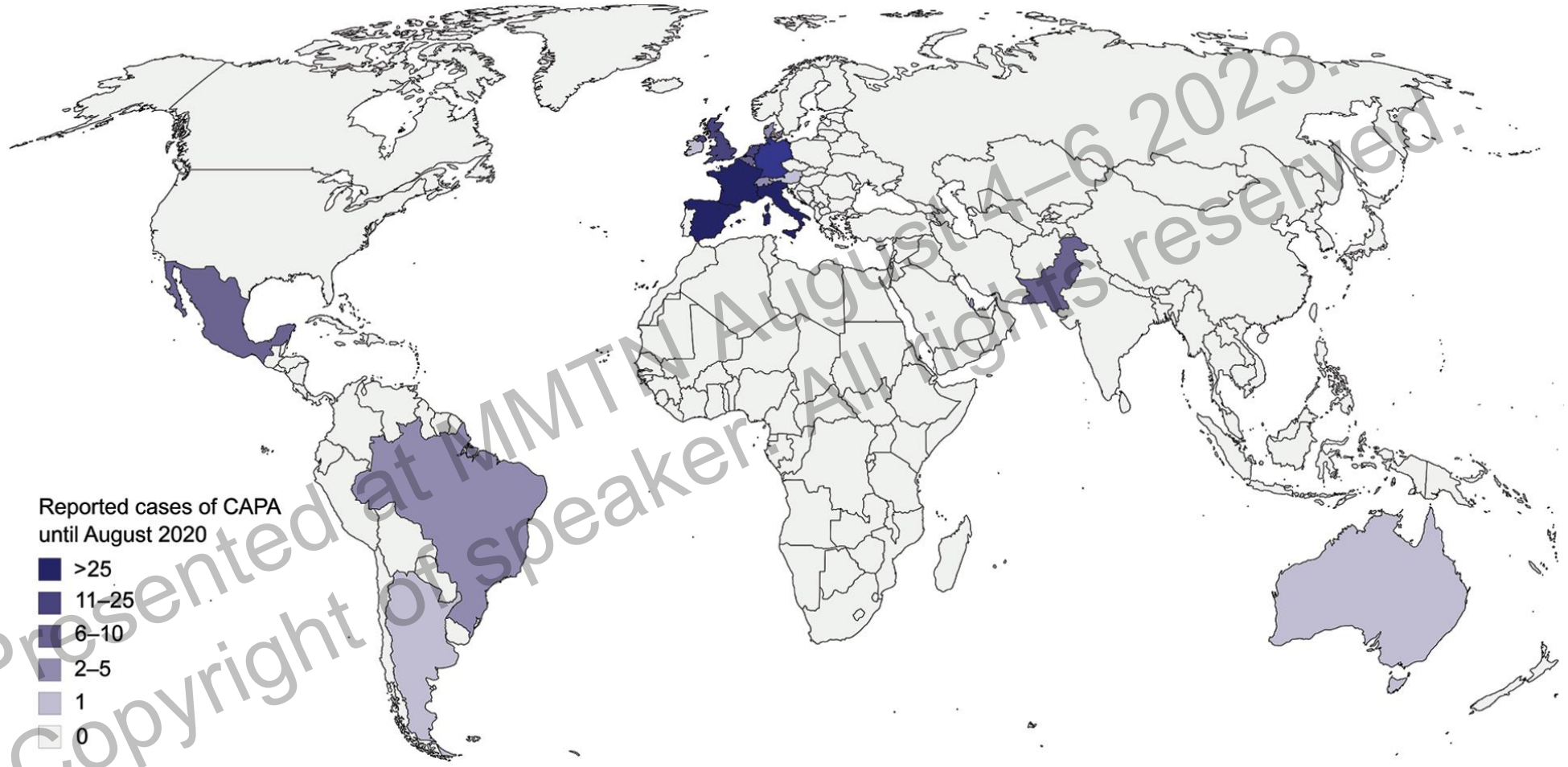
- 10 studies, 1942 hospitalized COVID-19 patients during December 2019 & April 2022
- **Overall pooled prevalence – 5.7%**
- **Mortality rate at 67.8%**
- Hypertension, diabetes, & cardiovascular diseases are prevalent co-morbidity
- Men with prevalence rate of 80.0% were 3.27 (OR) times more prone to getting infected by *C. auris*



Vaseghi N, *et al*. Mycoses 2022; 65: 683-703

COVID 19 associated pulmonary aspergillosis (CAPA)

Covid 19 associated pulmonary aspergillosis (CAPA)



March-August 2020 – 186 cases (majority cases from developing countries)

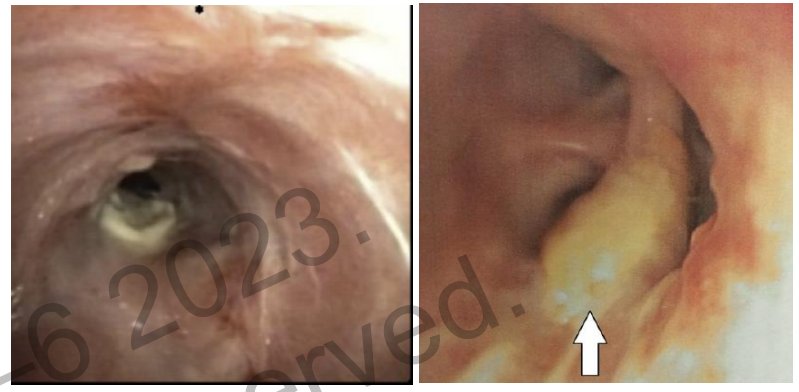
Incidence – 0.4% hospitalized COVID, 6.9% of ICU, 10.3% mechanically ventilated

Mortality – all-cause – 52.2%, attributed – 33%

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

Influenza-associated or COVID-19 associated pulmonary aspergillosis (IAPA)

Aspergillus **tracheobronchitis**



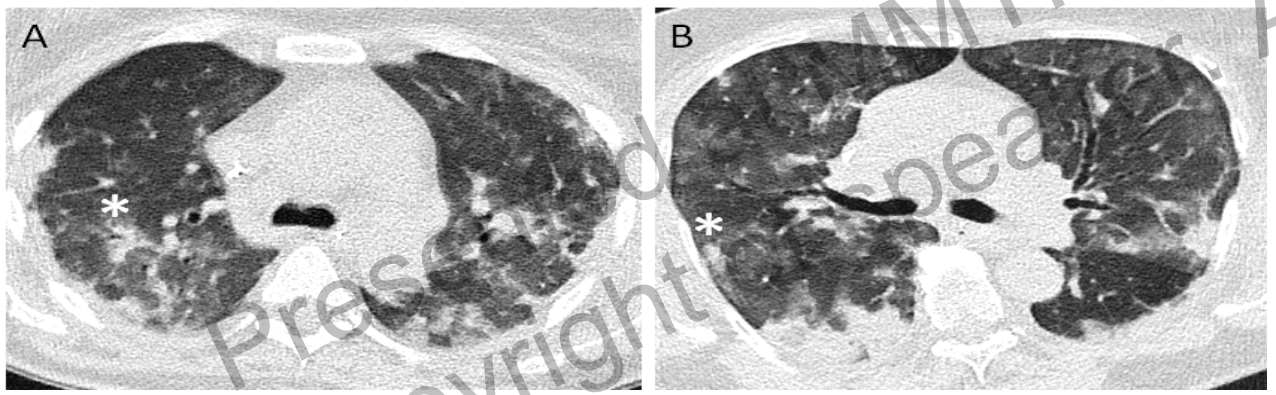
Factor	IAPA	CAPA
Incidence	**10% of ICU patients**	**6.9% of ICU, 10.3% mechanically ventilated**
Risk factors	male sex, smoking, chronic lung disease, corticosteroid (within 28d) , solid organ transplant & haematological malignancy	Old age, COPD, long term steroid use
Tracheobronchitis	**Up to 55% patients**	**Very few cases**
Aspergillus diagnostic	**BAL GM positive in > 88%**	**BAL GM commonly positive**
	Serum GM positive in 65%	**Serum GM positive in 21%**
Diagnostic algorithm	Consensus algorithm	4 algorithm with controversies
Mortality	51%	all-cause – 52.2%, attributed – 33%

Shi C, *et* al. Mycoses 2022; 65: 152-163; Verweij PE, *et al*. Intensive Care Med 2020; 46: 1524-1535; Chong WH, *et al*. Infection 2022; 50: 43-56; Rouze A, *et* al. Curr Opin Crit Care 2022; 28: 470-9; Salmanton-García J, *et al.* Emerg Infect Dis. 2021; 27: 1077–86

COVID-19 associated pulmonary aspergillosis (CAPA)

- **Diagnosis of CAPA is a big challenge** – lot of ambiguity (**histological evidence difficult**)
- As majority cases in ICU - clinicians tried to use **AspICU or IAPA guidelines**
- But, **bronchoscopy & processing of respiratory samples were avoided**

- **Non-specificity of clinical & radiological findings**



Confirmed aspergillosis **Without fungal infections**

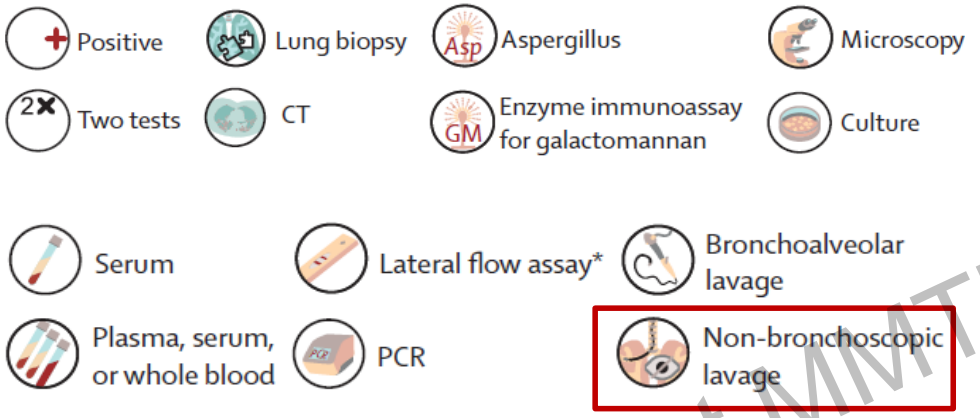
Four possible definitions

- Verweij PE, *et al.* Lancet Microbe 2020; 1: e53-5
- White PL, *et al.* Clin Infect Dis 2020: ciaa1298
- Koehler P, *et al.* Lancet Infect Dis 2021; 21: E149-E162
- Bassetti M, *et al.* Clin Infect Dis 2021; 72: 5121-7

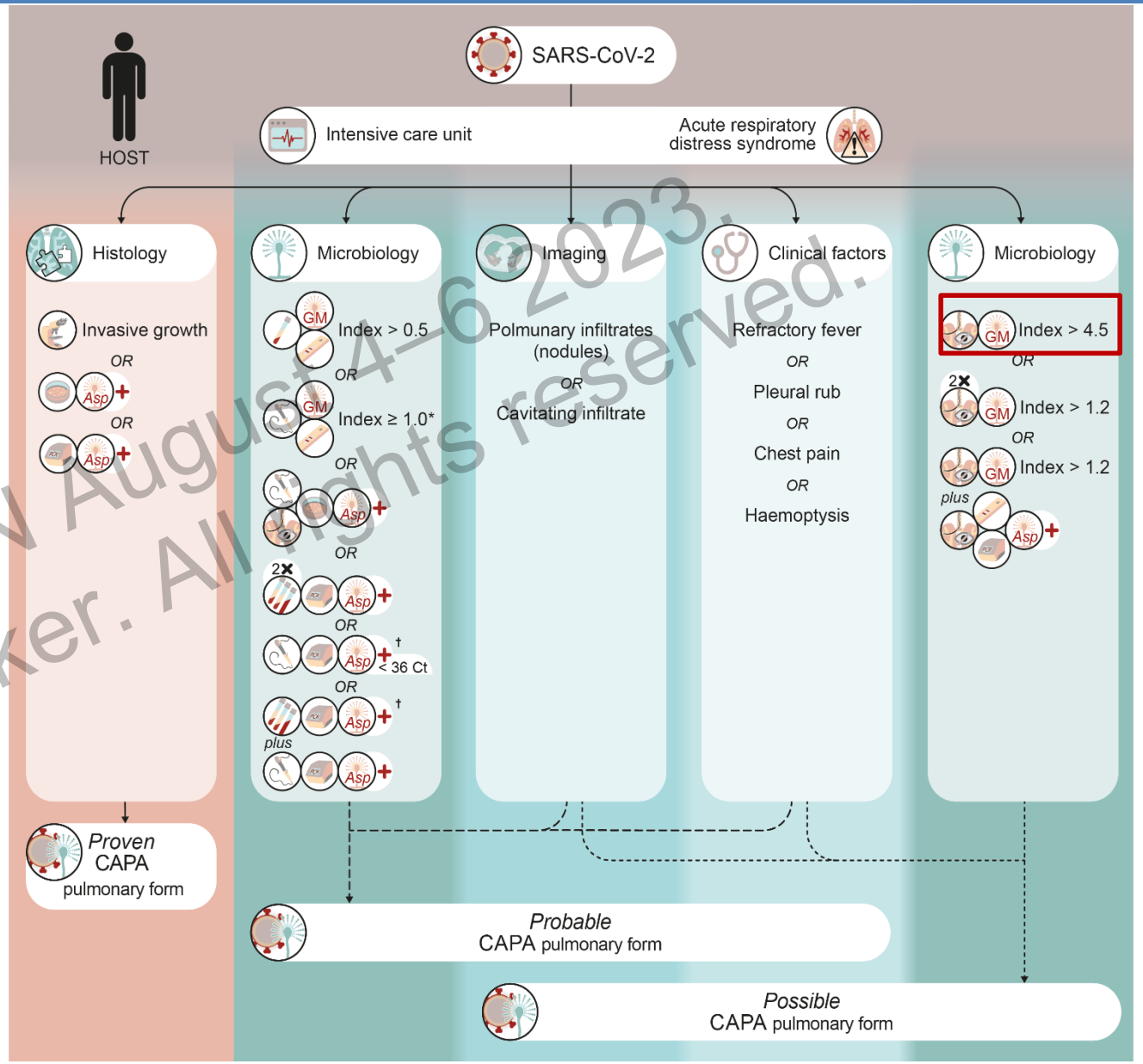
Koehler P, *et al*. Lancet Infect Dis 2021; 21: e149-62;
Köhler P, *et al. Mycoses.* 2020;63(6):528–34

Kariyawasam RM, *et al.* Clin Microbiol Infect 2022; 28: 920-927

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

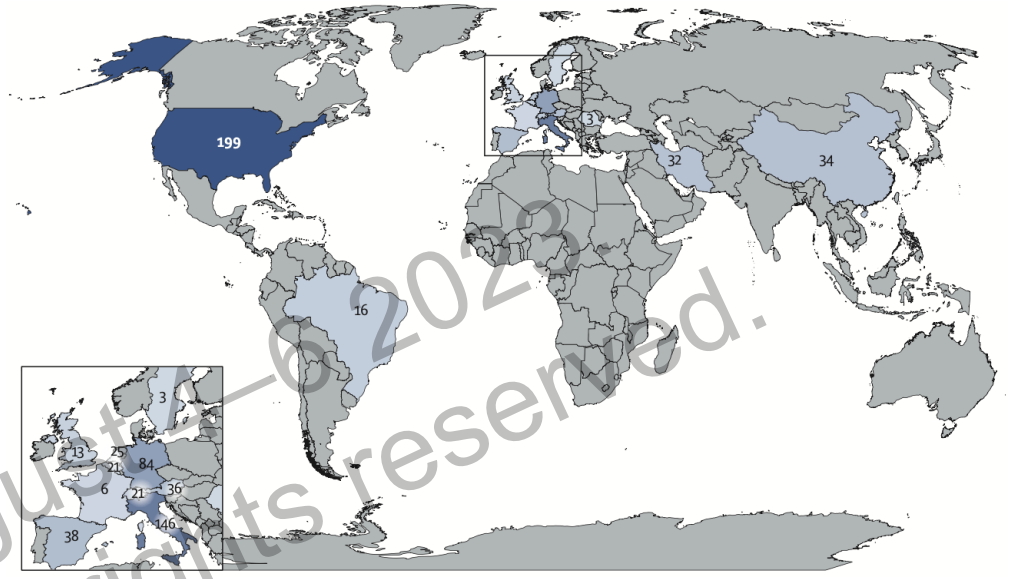


- **Microscopic detection of hyphae & culture**
- **Serum GM/LFA >0.5, BAL GM/LFA ≥1.0**
- **2 PCR +ve in blood**
- **BAL PCR <36 cycles**
- **PCR+ve in blood & BAL**



Koehler P, *et al.* Lancet Infect Dis 2021; 21: E149-E162

Autopsy data



- Jan, 2019 – Sept, 2020; Autopsy of 677 decedents
- 30% diabetes, 22% pre-existing lung disease, 6% immunosuppressed, 58% ventialation
- **IMD in 2% only – 8 CAPA, 2 unspecified IMD, 1 mucormycosis**
- **? CAPA is over-diagnosed**

	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%)

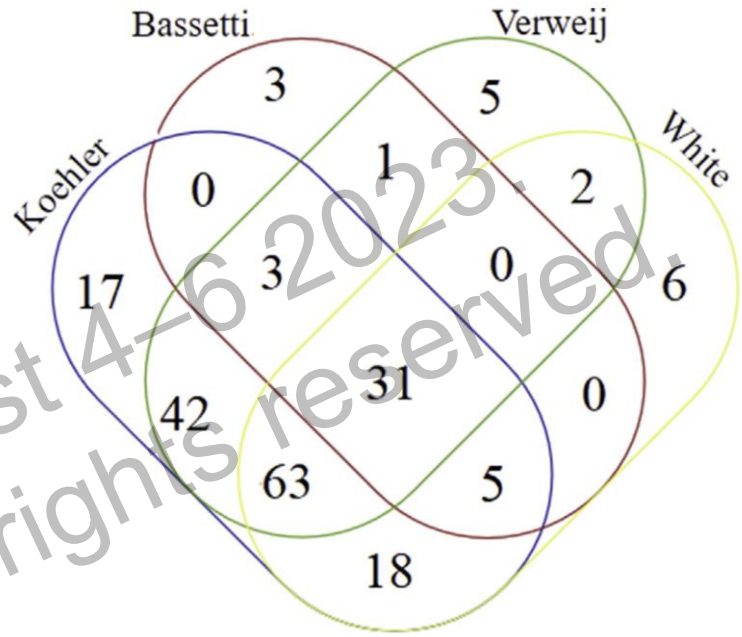
Data missing for *60 decedents, †3 decedents, ‡5 decedents, §112 decedents, ¶1 decedent, and ‖37 decedents.

Kula BE, *et al.* Lancet Microbe 2021; 2: e405-14

Correlation between definition

- PubMed search from inception to October 12, 2021
- 361 CAPA cases reported; 277 – patient data available

Definition	Total cases	No. classifiable	Proven	Probable/ putative
Verweij	277	147 (53.1%)	4	143
White	277	125 (45.1%)	4	77
Bassetti	237 (40 no radiology)	42 (17.7%)	4	38
Koehler	277	179 (64.6%)	4	137
Not meeting any definition – 94 (33.9%)				



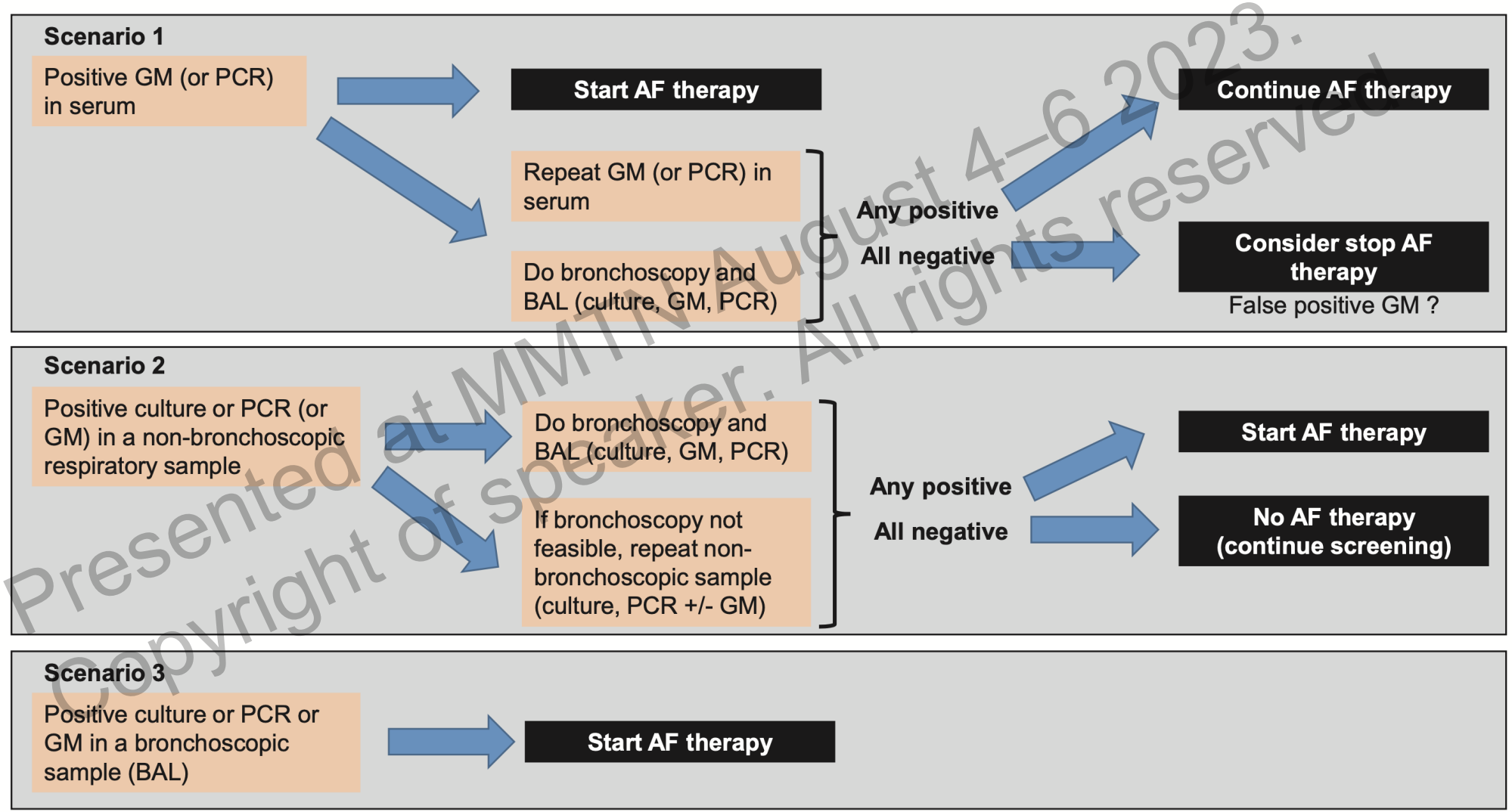
Diagnostic Test/Study	Sensitivity	Specificity
BAL GM ODI > 1.0	74% (77/104)	99% (268/272)
BAL Culture	53% (56/106)	100% (298/298)
BAL LFA ODI > 1.0	52% (15/29)	98% (60/61)
BAL PCR	42% (48/115)	100% (49/49)
Serum GM ODI > 0.5	19% (20/106)	100% (379/380)
Serum BDG ≥ 80 pg/mL	38% (8/21)	85% (29/188)

BAL, bronchioalveolar lavage; BDG, β-d-glucan; GM, galactomannan; ODI, optical density index.

Opinion of 28 expert group	
Not recommended	CT imaging, Serum GM or BDG; sputum or tracheal aspirate culture, LFA
Recommended	Maximum effort to perform bronchoscopy & BAL to diagnose CAPA

Kariyawasam RM, *et al.* Clin Microbiol Infect 2022; 28: 920-927 Egger M, *et al*. J Fungi 2022; 8: 390 Verweij PE, *et al*. Intensive Care Med 2021; 47: 819

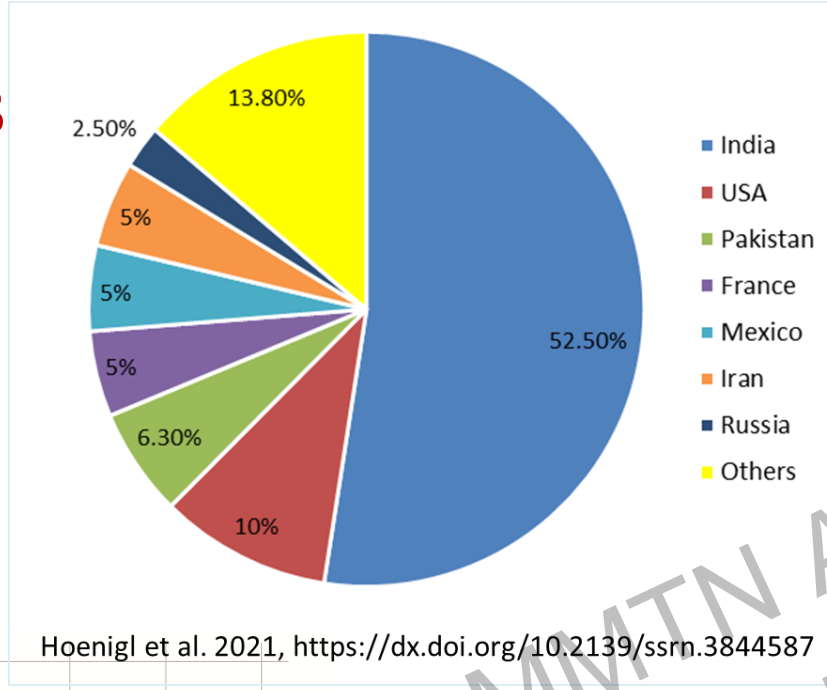
Practical approach



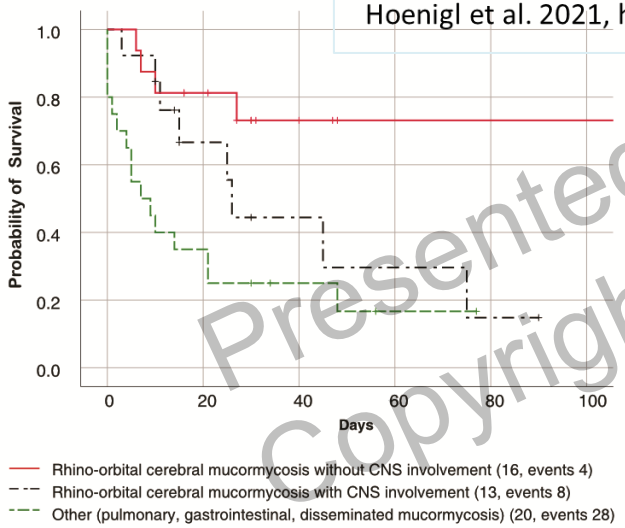
Lamoth F. Curr Opin Infect Dis 2022; 35: 163-169

COVID 19 associated mucormycosis (CAM)

CAM cases



Hoenigl et al. 2021, https://dx.doi.org/10.2139/ssrn.3844587



ROCM with vs without CNS P=0.074
ROCM with CNS vs Other P=0.116
ROCM without CNS vs Other P=0.001

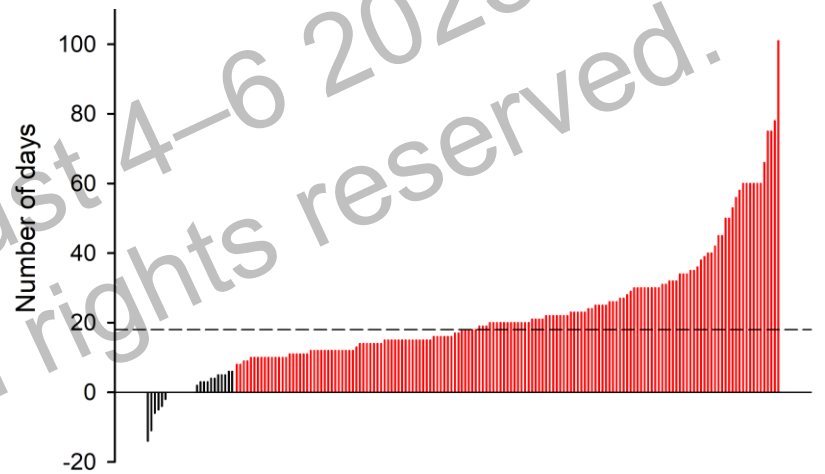
Rhino-orbito cerebral (n=59)	Pulomonary (n=20)
India (n=41) USA (n=4) Pakistan (n=1) France (n=2) Mexico (n=3) Iran (n=4) Russia (n=2) Bangladesh, Turkey (both n=1)	India (n=1) USA (n=4) Pakistan (n=4) France (n=2) Mexico (n=1) - - Austria, Chile, Czech republic, Germany, Italy, Kuwait, Lebanon, UK (all n=1)
Diabetes (n=55; uncontrolled n=46) Hematological malignancy (n=1)	Diabetes (n=17; uncontrolled n=7) Hematological malignancy (n=4)

Multicenter Epidemiologic Study of Coronavirus Disease–Associated Mucormycosis, India

EMERGING INFECTIOUS DISEASES® Volume 27, Number 9—September 2021

September – December 2020; 16 centers

- **>2-fold rise last year compared to 2019**
- **CAM prevalence – 0.27% (0.05-0.57%) in COVID 19; 1.6% (0.65-2.0%) treated in ICU**
- **86.1% naso-orbital mucormycosis, 23.5% brain involvement; 8.6% pulmonary, & 2.1% disseminated**
- **Diabetes – 62.7%; Steroid – 78.1%**
- **COVID19 alone was underlying disease – 32.6%, & 79% received steroid**
- **Majority (84.2%) of CAM were diagnosed ≥8 days (median 18 days) after COVID diagnosis**
- **Mortality – 6 weeks (38.3%), 12 weeks (45.7%)**
- **Multivariate analysis : Hypoxia (p=0.02), inappropriate steroid - 60.3% (p=0.0001)**

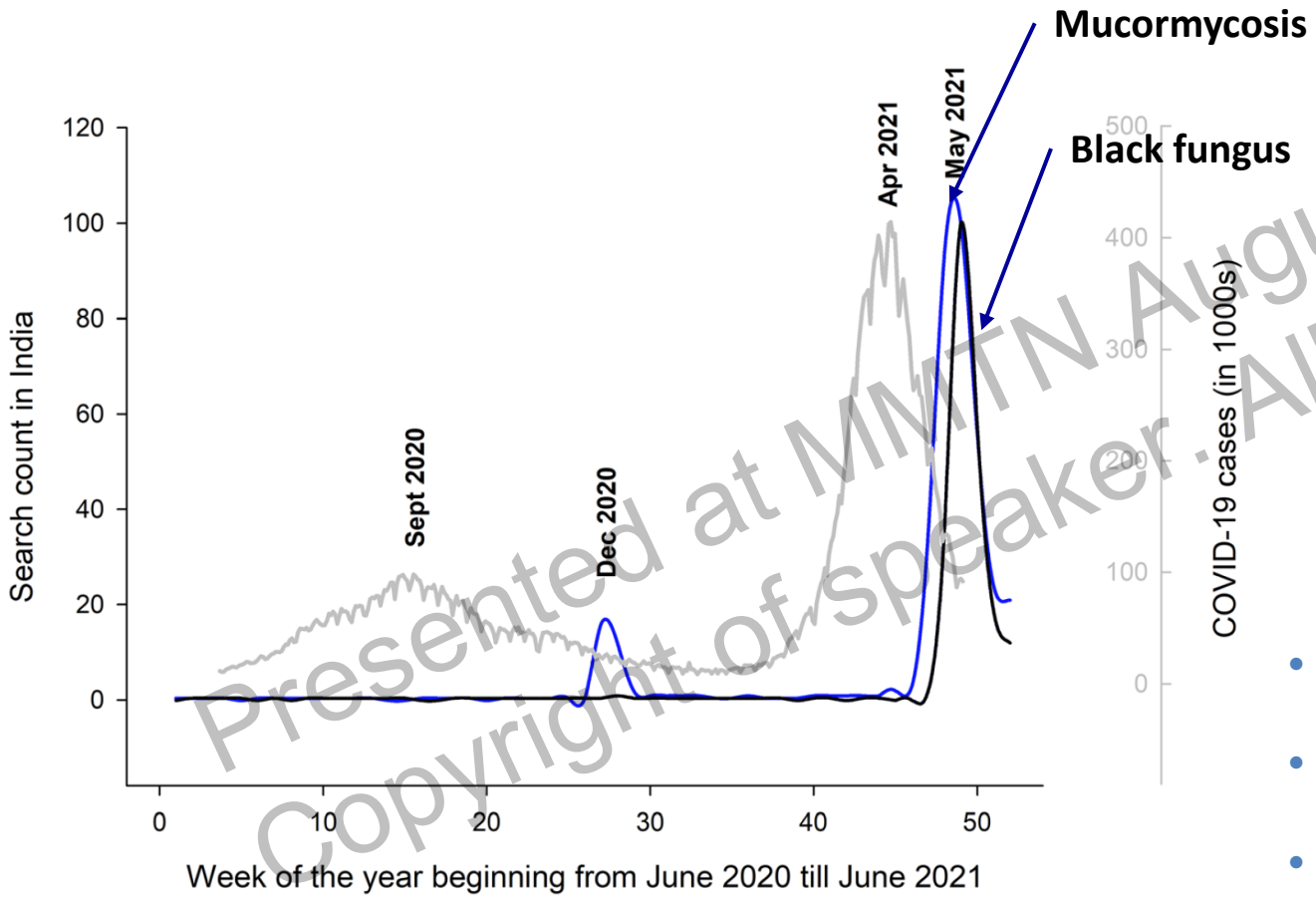


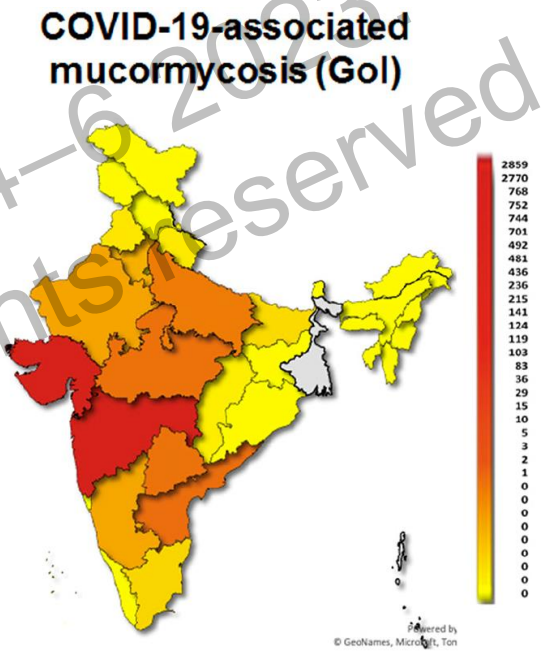
- 3-centre study **1.8%** of 2567 COVID-19 patients
- **after 12.1 ± 4.6 day COVID-19 diagnosis**
- **76.6% diabetic**
- **61.7% i.v. steroid &/95.7% oral steroid**

Selarka L, *et al*. Mycoses 2021; 64: 1253-1260

Patel A,…Chakrabarti A. Emerg Infect Dis 2021; 27: 2349-2359

Picture changed in second wave (March-May, 2021) of COVID-19 pandemic





- **2826 mucormycosis from eye specialties**
- Diabetes 78%, steroid 87% (21% >10d)
- **Orbit involved in 72%, orbital exenteration in 34%**

Muthu, Agarwal, Chakrabarti. Mycopathologia 2022; 187: 405-406

Sen M, *et al.* Indian J Opthalmol 2021; 69: 1670-92

COVID-19 associated mucormycosis in France: a rare but deadly complication

François Danion, Valérie Letscher-Bru, Juliette Guitard, Karine Sitbon, Sarah Dellière, Adela Angoulvant, Guillaume Desoubeaux, Francoise Botterel, Anne-Pauline Bellanger, Gilles Gargala ... Show more

Open Forum Infectious Diseases, ofab566,
https://doi.org/10.1093/ofid/ofab566
Published: 06 November 2021 **Article history**

- **17 cases reported nationwide**
- **Pulmonary-9**, GI-3, rhino-orbito-cerebral -2, disseminated -3
- Diabetes mellitus (47% in France versus up to 95% in India)
- Hematological malignancies (35% versus 1%)
- **88% mortality** versus <50%

Mycoses
Diagnosis, Therapy and Prophylaxis of Fungal Diseases

ORIGINAL ARTICLE | Open Access

Results from a national survey on COVID-19 associated mucormycosis in Germany: 13 patients from six tertiary hospitals

Danila Seidel, Michaela Simon, Rosanne Sprute, Matthias Lubnow, Katja Evert, Claudius Speer, Jessica Seeßle, Elham Khatamzas, Uta Merle, Christopher Behrens, Igor Wolfgang Blau ... See all authors

First published: 16 October 2021 | https://doi.org/10.1111/myc.13379

- **13 CAM cases – from 6 hospitals**
- prevalence – 0.58-0.67% of hospitalized & 0.15 -1.78% of ICU
- 5 were immunocompromised, 3 were diabetic.
- **Mortality was 53.8%**.

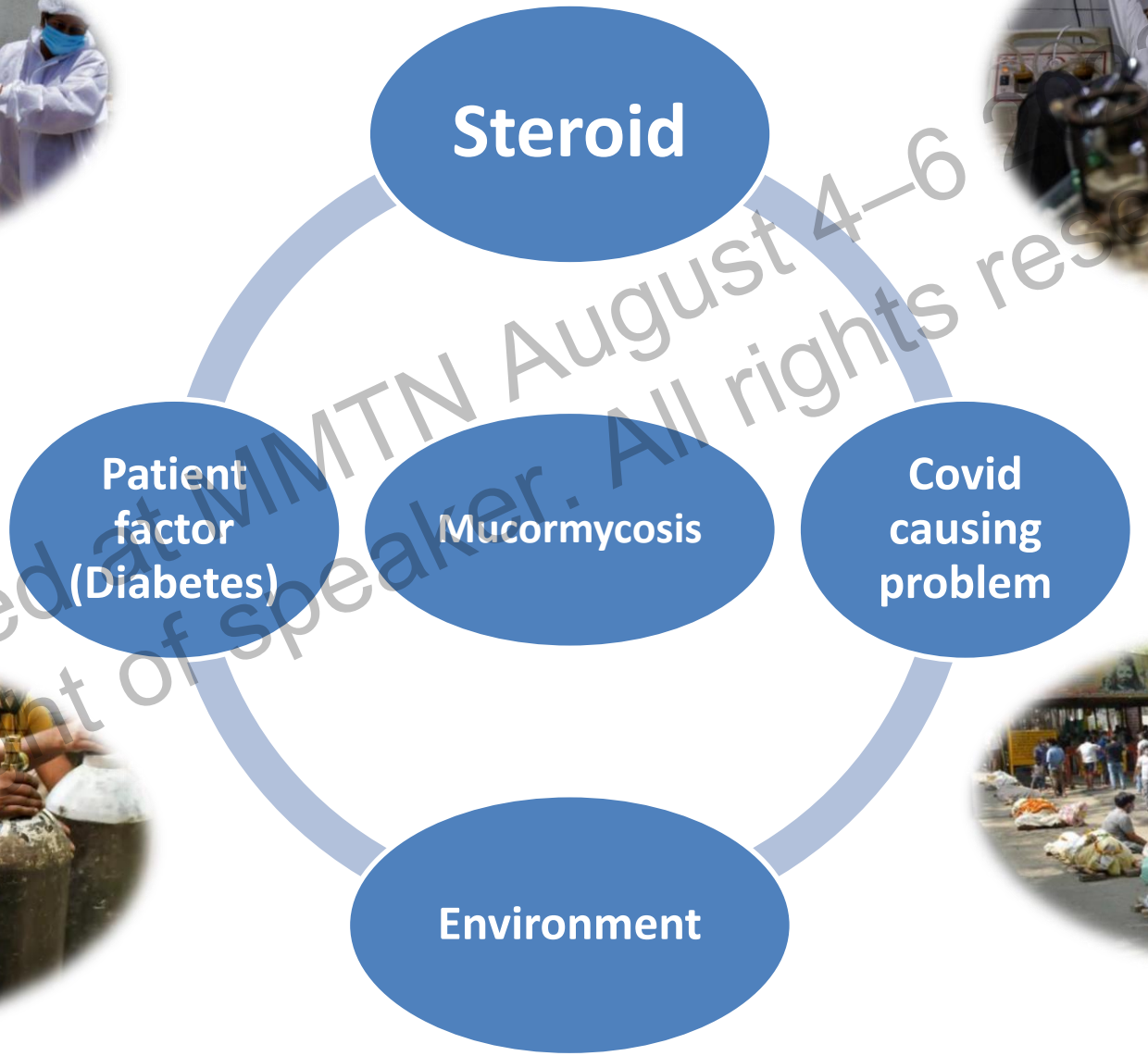
Multicenter Study > Mycoses. 2021 Oct;64(10):1238-1252. doi: 10.1111/myc.13334. Epub 2021 Jul 1.

Mucormycosis in patients with COVID-19: A cross-sectional descriptive multicentre study from Iran

Farzad Pakdel [1], Kazem Ahmadikia [2], Mohammadreza Salehi [3], Azin Tabari [4], Rozita Jafari [5], Golfam Mehrparvar [5], Yasaman Rezaie [3], Shahin Rajaeih [6], Neda Alijani [7], Aleksandra Barac [8], Alireza Abdollahi [9], Sadegh Khodavaisy [2]

- **15 CAM patients** with
- 13 **(86%) had diabetes mellitus**, while 7 (**46.6%**) received **intravenous corticosteroid**
- 5 patients (33%) underwent orbital exenteration, while 7 (**47%**) **patients died** from mucormycosis

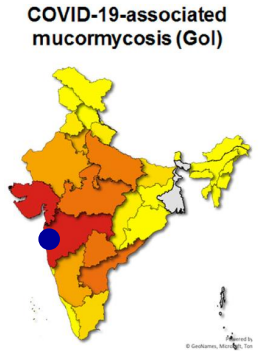
Second wave



Diabetes & Metabolic Syndrome: Clinical Research & Reviews 15 (2021) 102169

Absence of Case of Mucormycosis (March 2020–May 2021) under strict protocol driven management care in a COVID-19 specific tertiary care intensive care unit

Bindu Mulakavalupil [a], Charudatta Vaity [a], Shashank Joshi [b], Anoop Misra [c], Rahul Anil Pandit [a, *]



- 5248 patients were admitted in a tertiary-care hospital in Mumbai between **March 2020 to May 2021**; 1027 were in ICU and 4221 in wards
- Of the 1027 patients admitted in Intensive care unit, **915 received steroids & 417 had diabetes as existing co-morbidity.**

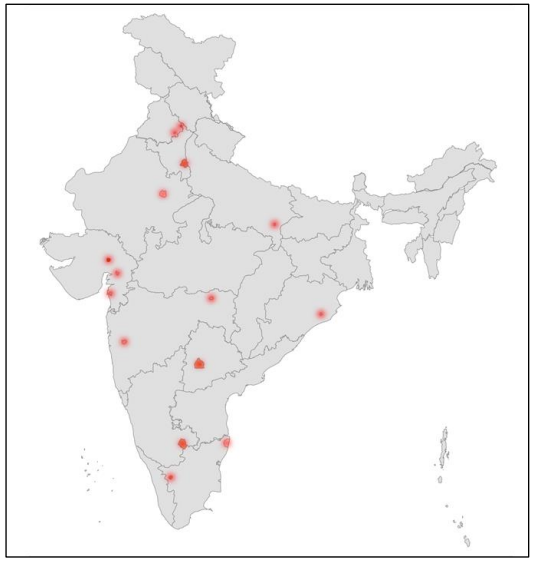
Steroid protocol.

Day	C-Reactive Protein (CRP)	Steroid	Dose	Duration
Day 1 Hypoxia Saturation< 93% or PaO_2/FiO_2 Ratio <300		Methyl Prednisolone	1 mg/kg not more than 40 mg twice daily	3 days
Day 4	If CRP> 50 mg/L	Continue	Continue	For 2 days more (total of 5 days)
Day 4	If CRP< 50 mg/L	Continue	40 mg Daily	For 2 days
Day 6		Prednisolone	30 mg/day	Wean over 5 days

- **a nurse driven strict glycemic control regime** (blood glucose level maintained between 140 & 180 mg/dl) through the admission in ICU & was achieved consistently in 842 (82%) patient
- **No case of mucormycosis was reported during the stay in the hospital & during immediate outpatient department follow up.**

Mucov2 study

25 centers; 1733 CAM cases, 3911 controls



Parameter	Adjusted odds ratio (95% CI)	P-value
Female sex	0.92 (0.74-1.14)	0.46
Rural residence	**2.88 (2.12-3.79)**	**0.0001**
Risk factor		
No risk factor	Reference category	
Diabetes mellitus	**6.72 (5.45-8.28)**	**0.0001**
Renal transplantation	**7.58 (3.31-17.40)**	**0.0001**
Others*	1.20 (0.67-2.18)	0.54
Presence of any comorbid illness	**0.50 (0.39-0.63)**	**0.0001**
Diabetic ketoacidosis during COVID-19	**4.41 (2.03-9.60)**	**0.0001**
Cumulative glucocorticoid dose for COVID-19†	**1.006 (1.004-1.007)**	**0.0001**
Zinc supplementation during COVID-19	**2.76 (2.24-3.40)**	**0.0001**
C-reactive protein at admission	**1.004 (1.002-1.006)**	**0.0001**
Serum ferritin, µg/L	1.00 (1.00-1.00)	0.21
Neutrophil-to-lymphocyte ratio	1.0 (0.99-1.01)	0.92

Muthu V,…….Chakrabarti A. Emerg Infect Dis 2023; 29: 8-19

Other case control studies from India (>100 patients)

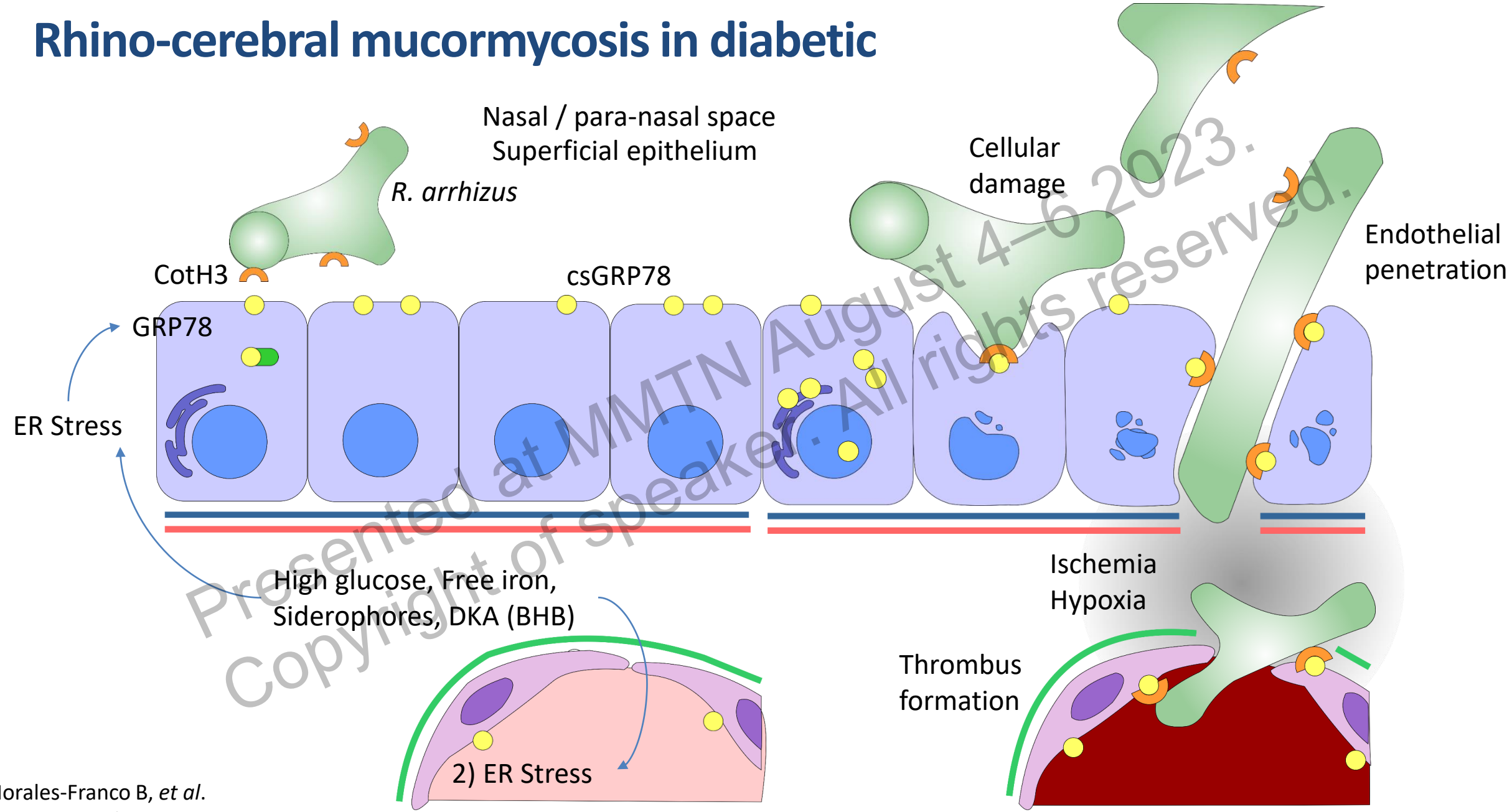
Author/year	Centre	CAM (n)	COVID-19 control (n)	Key findings
Arora/2022	Single, Delhi	152	200	**DM, steroid, hyperglycemia, cloth mask** (multivariate)
Karat/2022	Bengaluru	69	138	**Elevated Glycated Hb & CRP** (multivariate)
Kumar/2022	Single, Wardha	55	50	**Zinc use** (univariate)
Pandit/2022	Single, Delhi	61	60	**Serum creatinine & d-dimer** (multivariate)
Patel/2022	Single, Ahmedabad	64	205	**DM, steroid, home isolation** (multivariate)
Ponniah/2022	Multicenter	383	487	**DM, steroid, frequent nasal wash** (hospitalized) **DM, steroid, cloth mask** (non-hospitalized) (multivariate)
Vasanthapuram/2022	Multicenter	179	361	**Male, DM, steroid, hypoxemia** (multivariate)

Arora U, *et al*. J Infect 2022; 84: 383-90; Karat S, Karat S, *et al*. Indian J Ophthalmol 2022; 70: 3096-101; Kumar S, *et al*. Cureus 2022; Pandit AK, *et al*. Microorganisms 2022; 10; Patel Ak, *et al*. Med Mycol 2022; 60: Ponnaiah M, *et al*. PLoS One 2022; 17: e0272042; Vasanthapuram VH, *et al*. Orbit 2022; 1-12

Covid associated mucormycosis

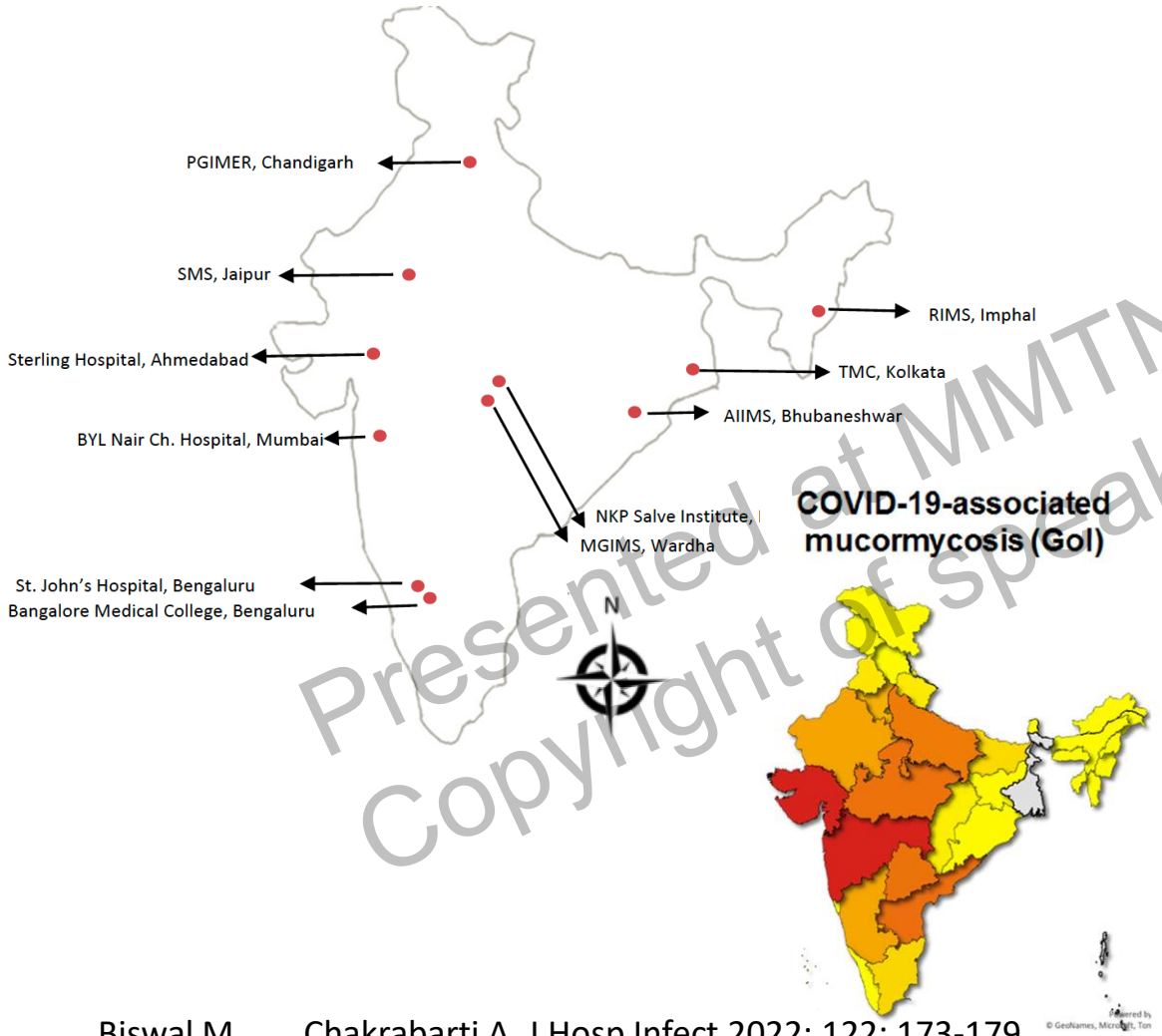
- **Hyperglycemia** - **Diabetes, COVID-19** infects & impairs pancreatic β cells, **steroid, stress** (Wu CT, *et al.* Cell Metab 2021 May 18; Tan X, et al. Cell Metab 2021 May 19)
- **Hyperglycemia** - causes **inflammatory state**, & antiviral immunity to COVID19 also potentiates this **inflammation** (Morales-Franco B, *et al*. Curr Trop Med Rep 2021; 1-12)
- **Alteration of iron metabolism -** in severe COVID-19 (IL6 stimulate ferritin synthesis & down regulates iron export) – 'Hyper ferritinemic syndrome' ➡ excess intracellular iron in cells ➡ reactive oxygen species resulting tissue damage ➡ free iron in circulation (Perricone C, *et al*. Immunol Res 2020; 68: 213; Edeas M, *et al*. Int J Infect Dis 2020; 97: 303)
- **'Endothelialitis'** – autopsies indicated widespread severe vascular endothelial injury in COVID-19 than patients died of influenza A, H1N1 (Ackermannn M, *et al*. N Eng J Med 2020; 383: 120; Verga Z, *et al*. Lancet 2020; 395: 1417*)*
- Hyperglycemia & academic state induce the endothelial receptor glucose regulated protein **(GRP 78)** + Mucorales receptor protein homologs **(CotH)** ➡ 'perfect storm' for **increased adhesion & penetration** of Mucorales (Ibrahim AS, *et al*. Clin Infect Dis 2012; 54, Suppl 1: S16-S22)

Rhino-cerebral mucormycosis in diabetic



Morales-Franco B, *et al*.
Curr Trop Med Rep 2021; 1-12

Hospital environment study
- 11 centers

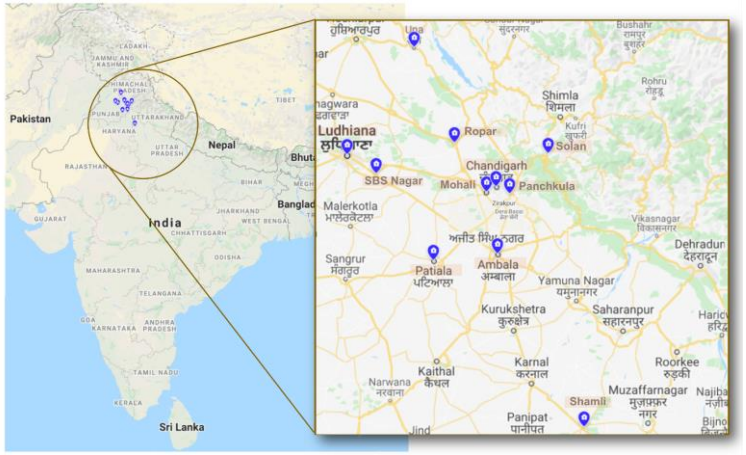


Biswal M,…….Chakrabarti A. J Hosp Infect 2022; 122: 173-179

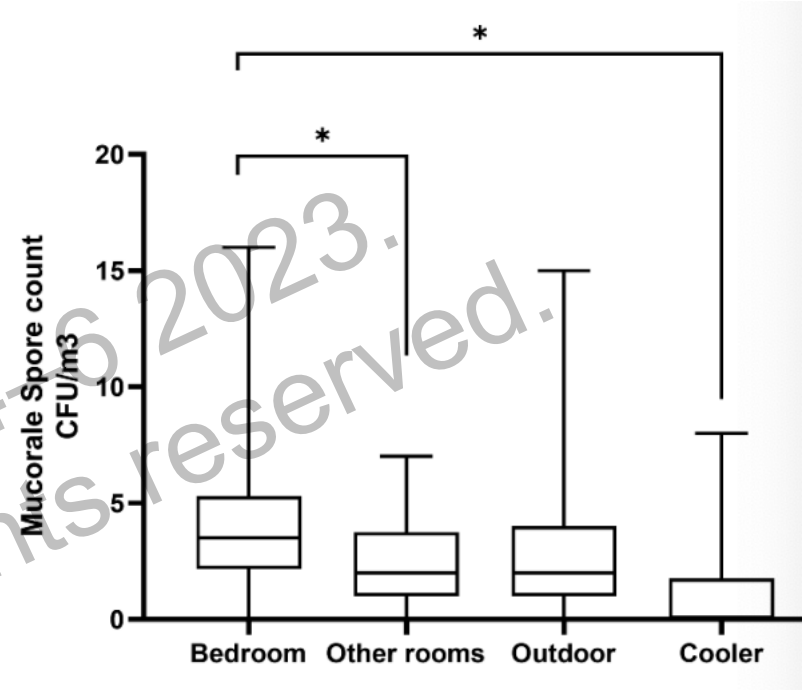
- **Neither** the **oxygen port or oxygen cylinder or humidifier** water had Mucorales contamination
- **11.1% AC vents had Mucorales** – requires regular cleaning
- Only **1.7% of 172 repeated used cloth masks contained Mucoraceous fungi** – Masks cannot be major source for the outbreak
- **High Mucorales spores in air** of both indoor & outdoor vicinity of the hospital is serious issue
- **Overall spore count in air positively correlated with the number of CAM patients treated at respective hospitals** (Pearson correlation coefficient 0.728)
- **But, considerable number of COVID-19 patients acquired mucormycosis in home environment**

Sen M, *et al.* Indian J Opthalmol 2021; 69: 1670-92

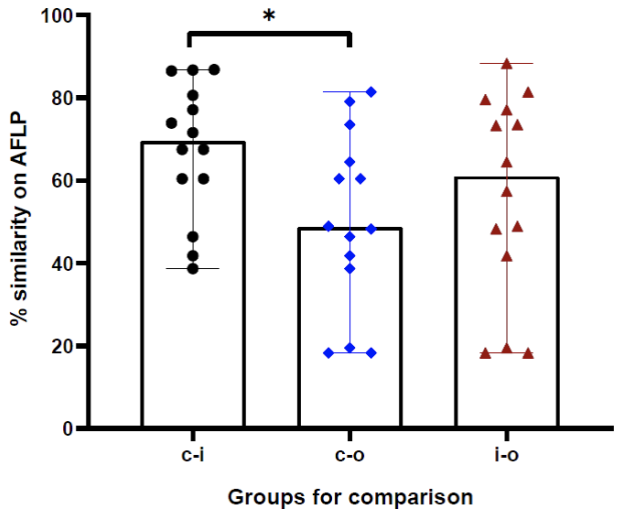
Home environment study



- 25 patients' residence
- Treated for COVID-19 at home
- Acquired mucormycosis at home



State (no. of patients)	Mucorales spore counts (values in cfu/m^3) (mean ± SD)	Organisms isolated from environment	Clinical isolates
Haryana (N = 4)	Air: 3.5 ± 0.9 to 9.5 ± 5.1	*Rhizopus arrhizus* (n = 4) *Rhizopus delemar* (n = 1) *Rhizopus microsporus* (n = 2) *Cunninghamella bertholletiae* (n = 2)	*R. arrhizus* (n = 3) *R. delemar* (n = 1)
Punjab (N = 13)	Air: 0.8 ± 1.5 to 3.6 ± 3.7	*R. arrhizus* (n = 13) *R. delemar* (n = 3) *R. microsporus* (n = 2) *C. bertholletiae* (n = 6) *Lichtheimia corymbifera* (n = 1) *Mucor racemosus* (n = 1) *Syncephalastrum racemosum* (n = 1)	*R. arrhizus* (n = 7) *R. delemar* (n = 1) *R. microsporus* (n = 2) *Rhizopus homothallicus* (n = 3)
Uttar Pradesh (N = 3)	Air: 2 ± 1 to 5.6 ± 0.5	*R. arrhizus* (n = 3) *R. delemar* (n = 2) *C. bertholletiae* (n = 2)	*R. arrhizus* (n = 2) *R. delemar* (n = 1)
Himachal Pradesh (N = 3)	Air: 0.8 ± 0.8 to 3.6 ± 3.1	*R. arrhizus* (n = 3) *R. microsporus* (n = 1) *C. bertholletiae* (n = 2)	*R. arrhizus* (n = 2) *Saksenaea vasiformis* (n = 1)
Chandigarh (N = 2)	Air: 1 ± 0 to 1.8 ± 0.2	*R. arrhizus* (n = 2) *R. microsporus* (n = 1) *C. bertholletiae* (n = 2)	*R. arrhizus* (n = 2)



- C-I - clinical & indoor isolates
- C-O – clinical & outdoor isolates
- I-O – Indoor & outdoor isolates

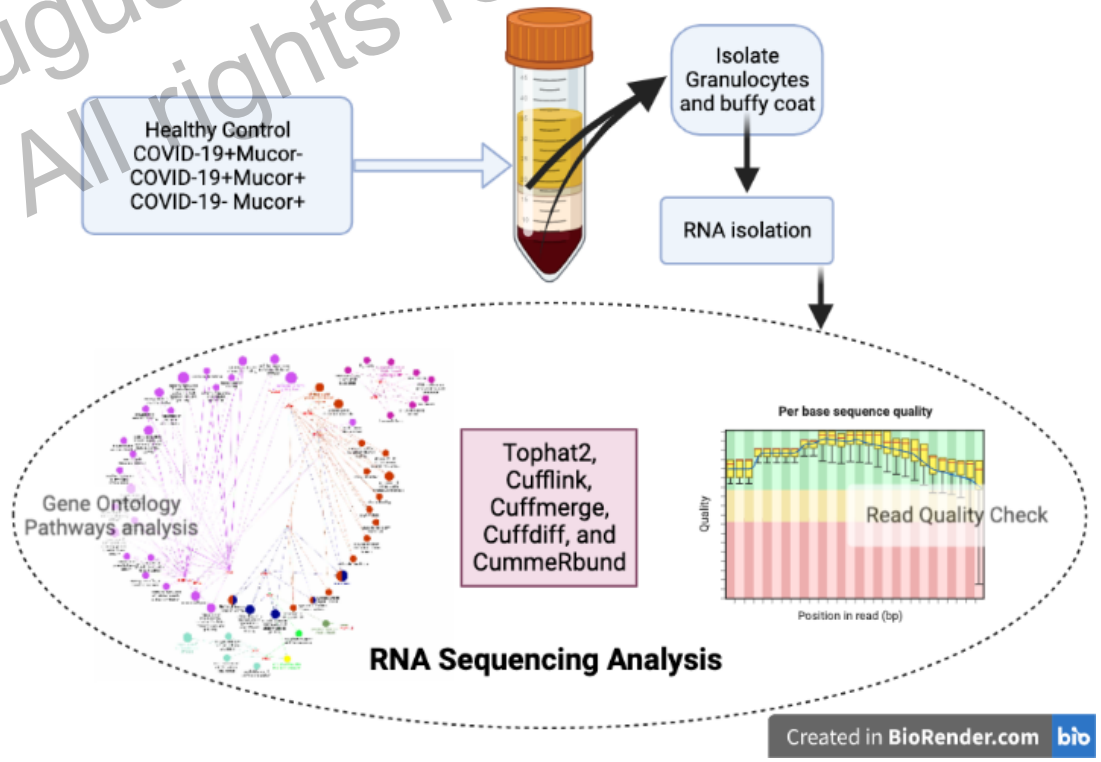
Ghosh A,…….Chakrabarti A. Front Cell Infect Microbiol 2022; 12: 953750

Does COVID-19 virus played role in pathogenesis of mucormycosis

Methodology

- Covid-19 associated mucormycosis (CAM) -5 patients
- Pulmonary mucormycosis (Non-COVID-19) – 5 patients
- COVID-19 without mucormycosis – 6 patients
- Healthy controls – 7 patients

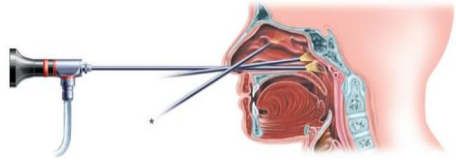
- Monocytes separated using BioLegend MojoSort™ Human CD14+ Monocytes isolation kit.
- Granulocytes separated by Dextran method.
- RNA isolation, Sequencing & Bioinformatics



- **Differential Expression of Genes (DEGs) Analysis in CAM, Mucormycosis, COVID-19, & healthy controls**
- **COVID-19 causes enrichment scores for complement pathway, coagulation cascade (profound intravascular coagulation, thrombotic changes, which may account for associated complications seen in CAM patients)**

Dhaliwal M….Chakrabarti A. (under publication)

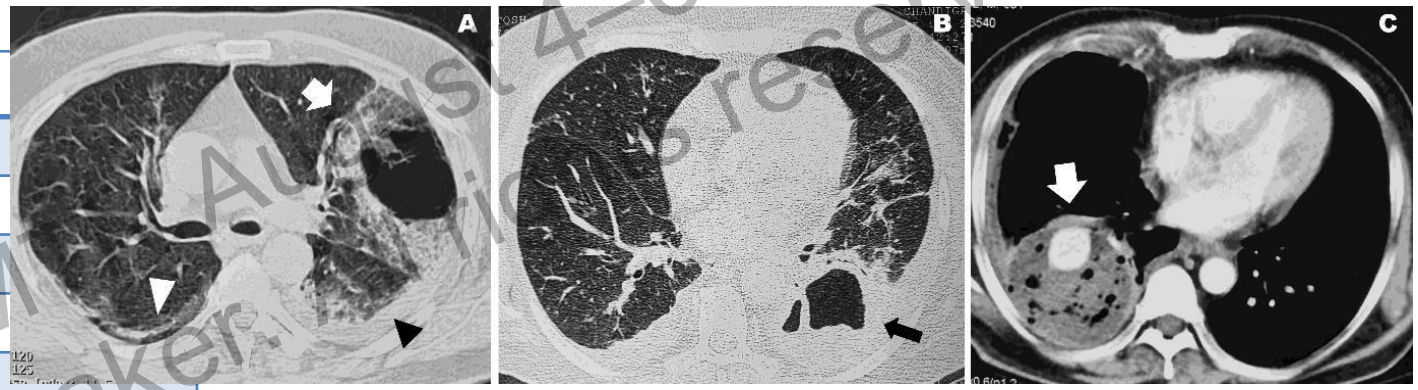
How to diagnose? – Rhino-orbito-cerebral



- **Consult ENT surgeon** for endoscopic collection of debrided tissue/biopsy

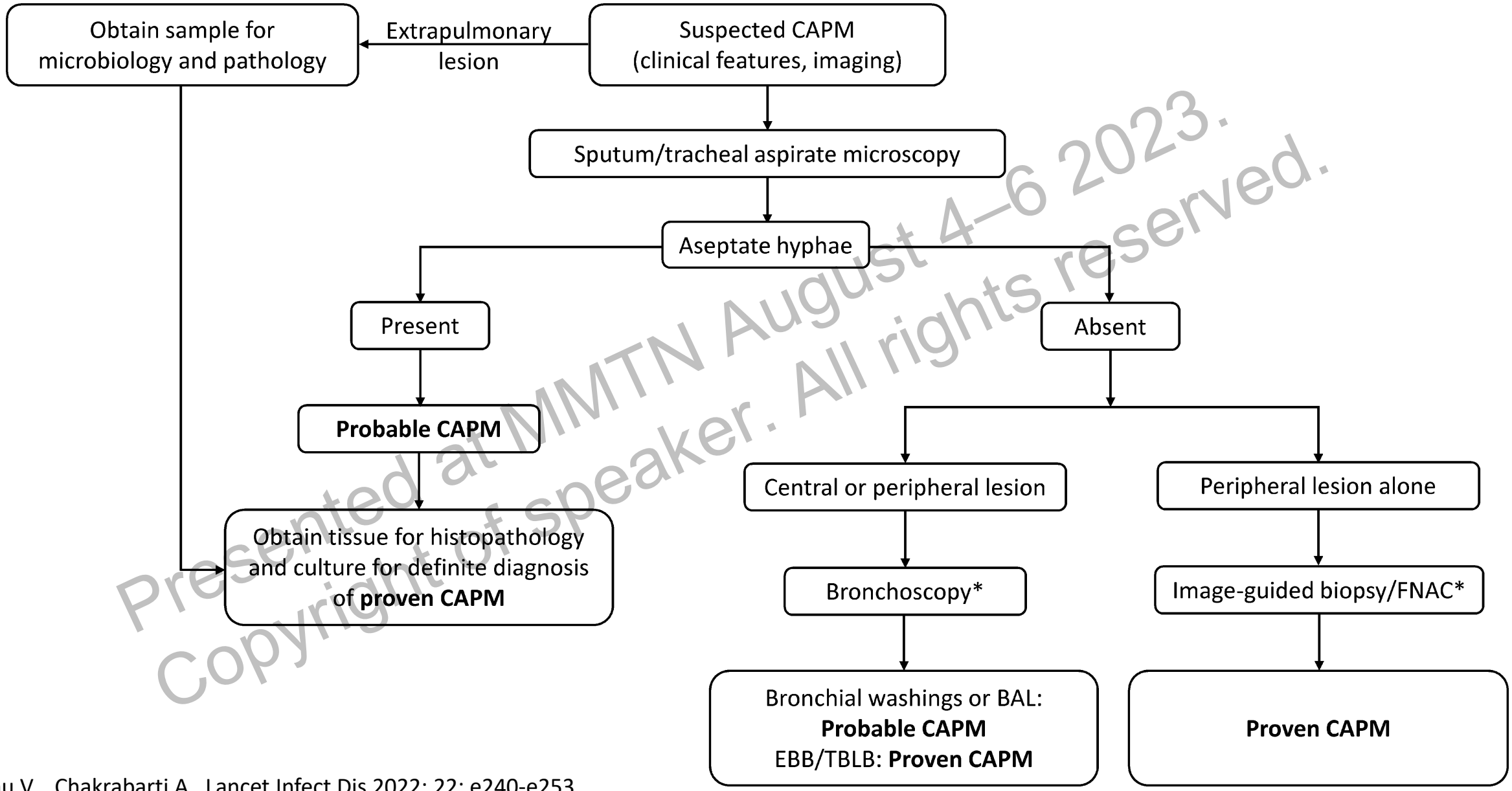
Pulmonary & disseminated mucormycosis

Highly suggestive
Thick-walled cavity
Reversed halo sign
Large consolidation or necrotizing pneumonia
Mycotic aneurysm
Bird's nest sign
Multiple large nodules (nodules >1 cm)
Serial imaging showing cavity with an air-fluid level
Suggestive
Pleural effusion
Non-specific
Pneumothorax
Not suggestive
Enlarged mediastinal lymph nodes
Centrilobular nodules or tree-in-bud appearance



(A) reversed halo sign (white arrow) mild pleural effusion (black arrowhead), intralobular septal thickening (white arrowhead). (B) thick walled cavity (black arrow. (C) mycotic aneurysm (white arrow)

Muthu V,…Chakrabarti A. Lancet Infect Dis 2022; 22: e240-e253



Muthu V,…Chakrabarti A. Lancet Infect Dis 2022; 22: e240-e253

How we controlled CAM?

- As poorly controlled diabetes is the major issue, **good glycemic control** during management of COVID 19 patients is required
- **Systemic steroids should only be used in patients with hypoxemia; blood sugar should be monitored**
- **The dose and duration of steroid therapy should be limited to dexamethasone (0.1mg/kg/day) for 5-10 days**
- **Universal masking** reduce exposure to Mucorales; avoidance of construction sites
- **During discharge of the patients, advice** about the early symptoms (facial pain, nasal blockage & excessive discharge, loosening of teeth etc., chest pain, respiratory insufficiency)

Due to mass campaign in the above line – the outbreak could be contained

	CAPA	CAM	CAC
Prevalence	Prevalence about 10% among invasively ventilated patients with COVID-19[4]	Prevalence of 0.27% among hospitalized patients with COVID-19 in India[15]; limited evidence from Europe suggests prevalence about 1–2% among invasively ventilated patients with COVID-19 (ref. [14])	Unknown; outbreaks reported from 12 countries in the Americas, Europe and Middle East[18,52]
Infectious agents (!, of particular concern)	*A. fumigatus* predominant[4]! Azole-resistant *A. fumigatus*	*Rhizopus* spp. predominant[14,16]	*C. albicans* predominant[53]! *C. auris*
Sites of infection	Lungs[21]	ROM, ROCM[14,16] Pulmonary[14] Gastrointestinal[14] Disseminated[14]	Bloodstream[52] Abdomen
Therapy	Voriconazole or isavuconazole as first-line treatment for possible, probable and proven CAPA[21] Liposomal amphotericin B, posaconazole or echinocandins as second line[21]	Surgical debridement[14] Liposomal amphotericin B[14] If renal compromise, intravenous isavuconazole or intravenous posaconazole[48]	Caspofungin or micafungin as first line[52,53] Liposomal amphotericin B as second line[53]
Challenges	Reluctance to perform aerosol-generating procedures, such as autopsies and bronchoscopies Azole-resistant aspergillosis awareness (not tested if not suspected)	Diagnostics in ICU setting (BAL, gut biopsy)[14] Reluctance to perform aerosol-generating procedures, such as autopsies and bronchoscopies, awareness (not tested if not suspected)	High rate of multidrug resistance for *C. auris*[18] Misleading identifications, ability to form biofilms, reluctance to perform autopsies

Hoenigl M, *et al*. Nature Microbiol 2022; 7: 1127-1140

THANK YOU