Invasive aspergillosis in ICU

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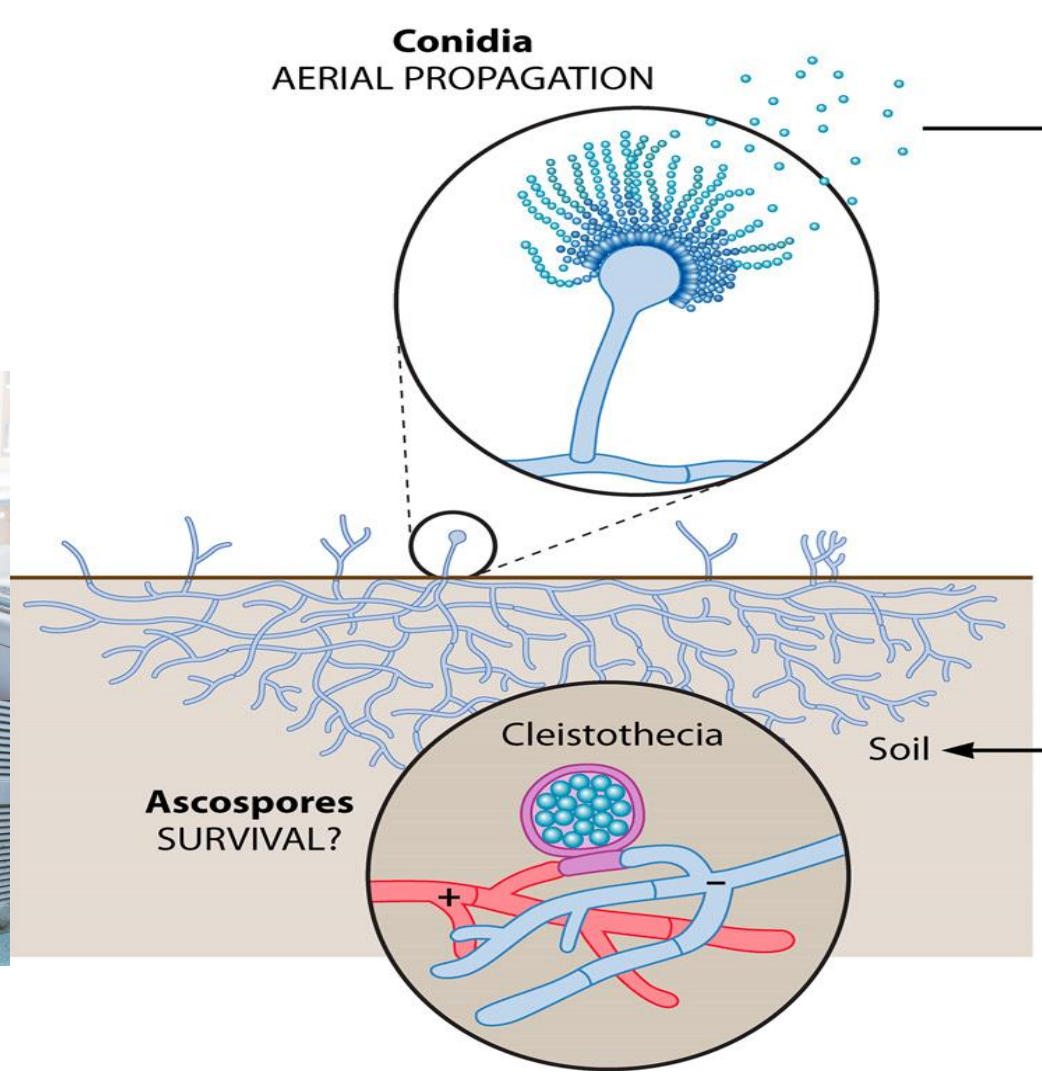
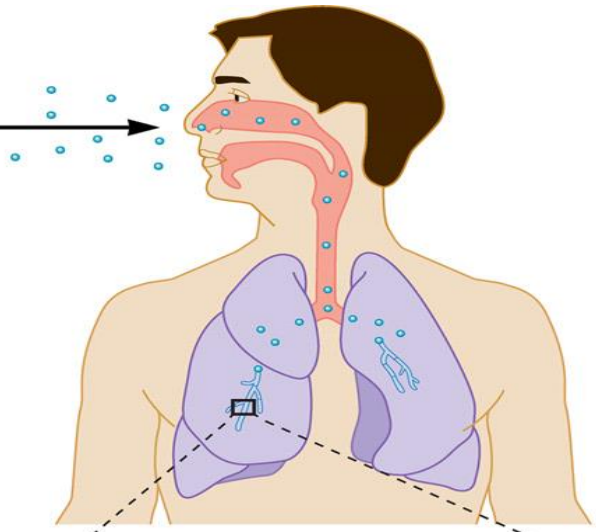
VGHTPE CHEST
INFECTION IMMUNOLOGY

Infectious life cycle of Aspergillus



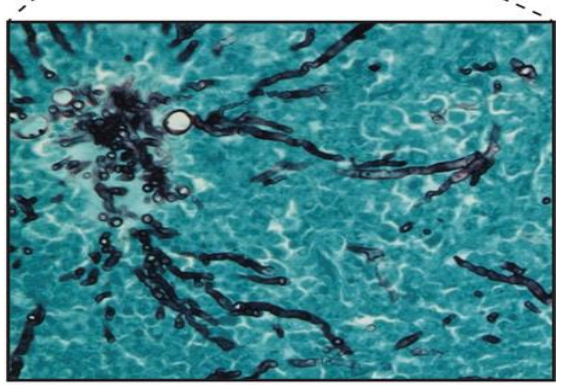
2-3 µm 25-37°C
100-1000/day inhaled



Mycelium
Vegetative GROWTH

Lung

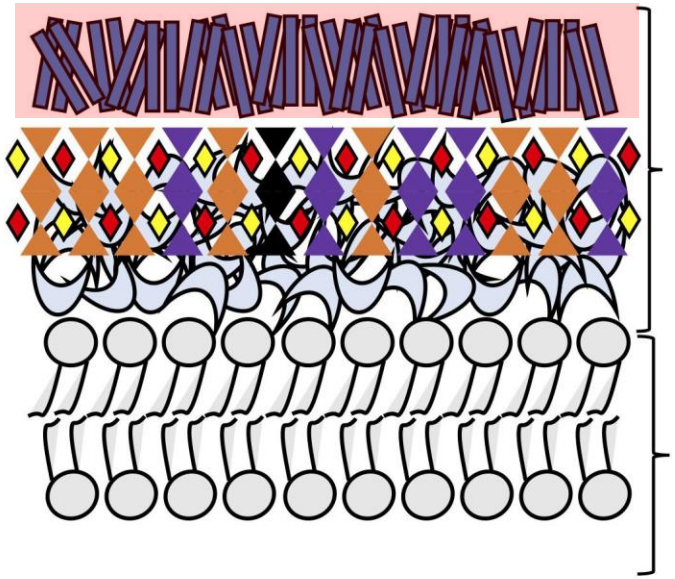
4-6 hours

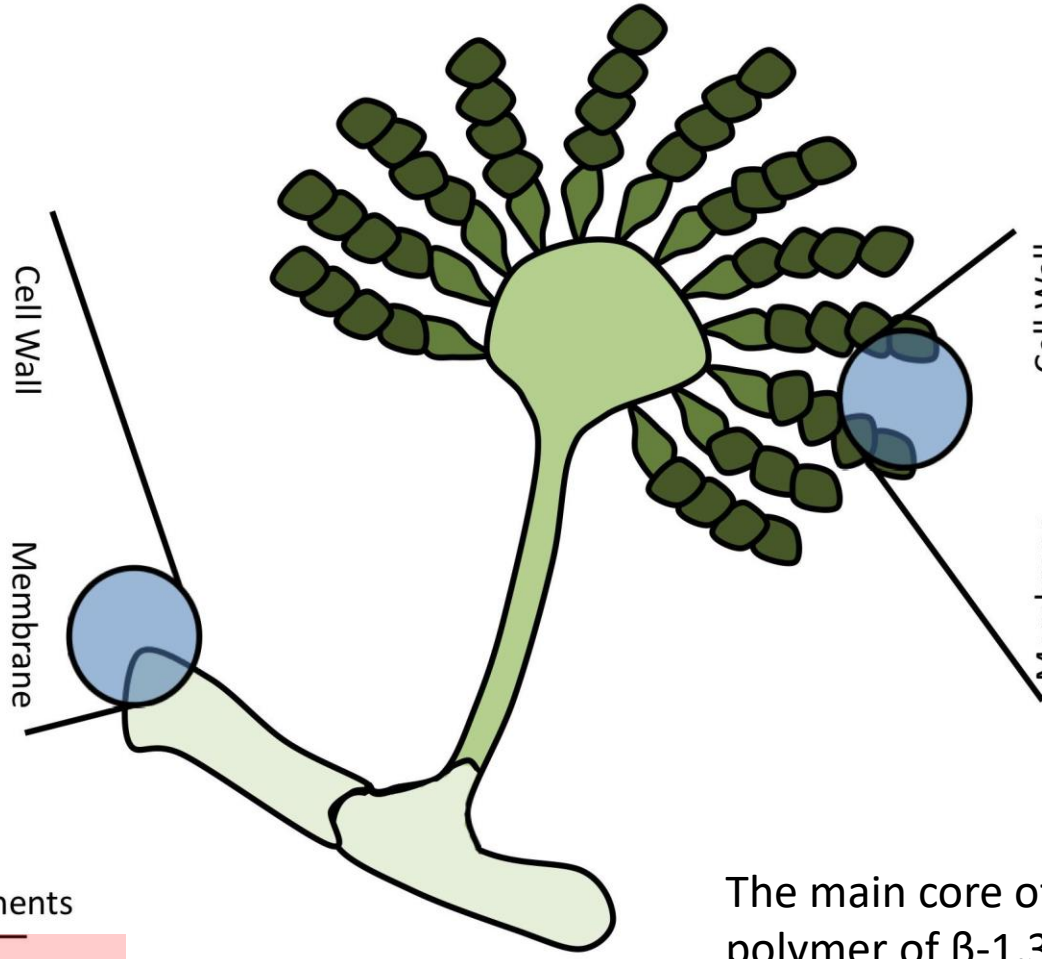


Finger-like branch
Acute angle

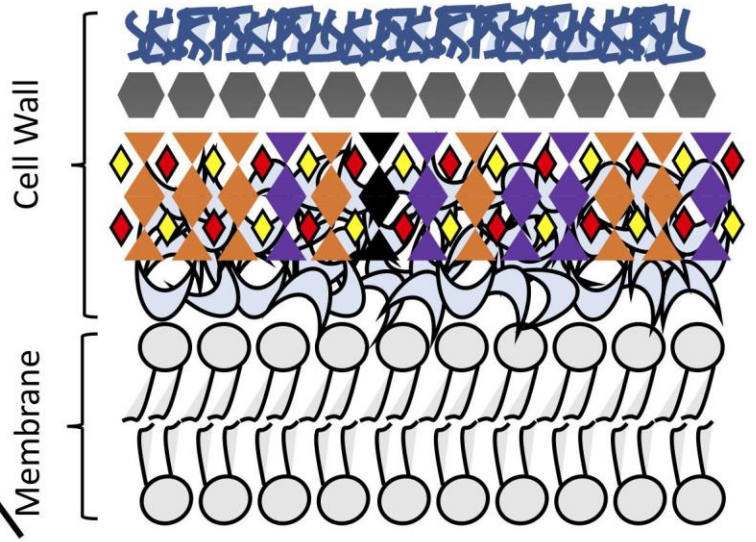
The *Aspergillus fumigatus* cell wall

Hyphae





Conidia



Cell Wall components

Galactosaminogalactan

β -1,3-glucan

β -1,3-1,4-glucan

β-1,6-glucan

α-1,3-glucan

Galactomannan

Melanin

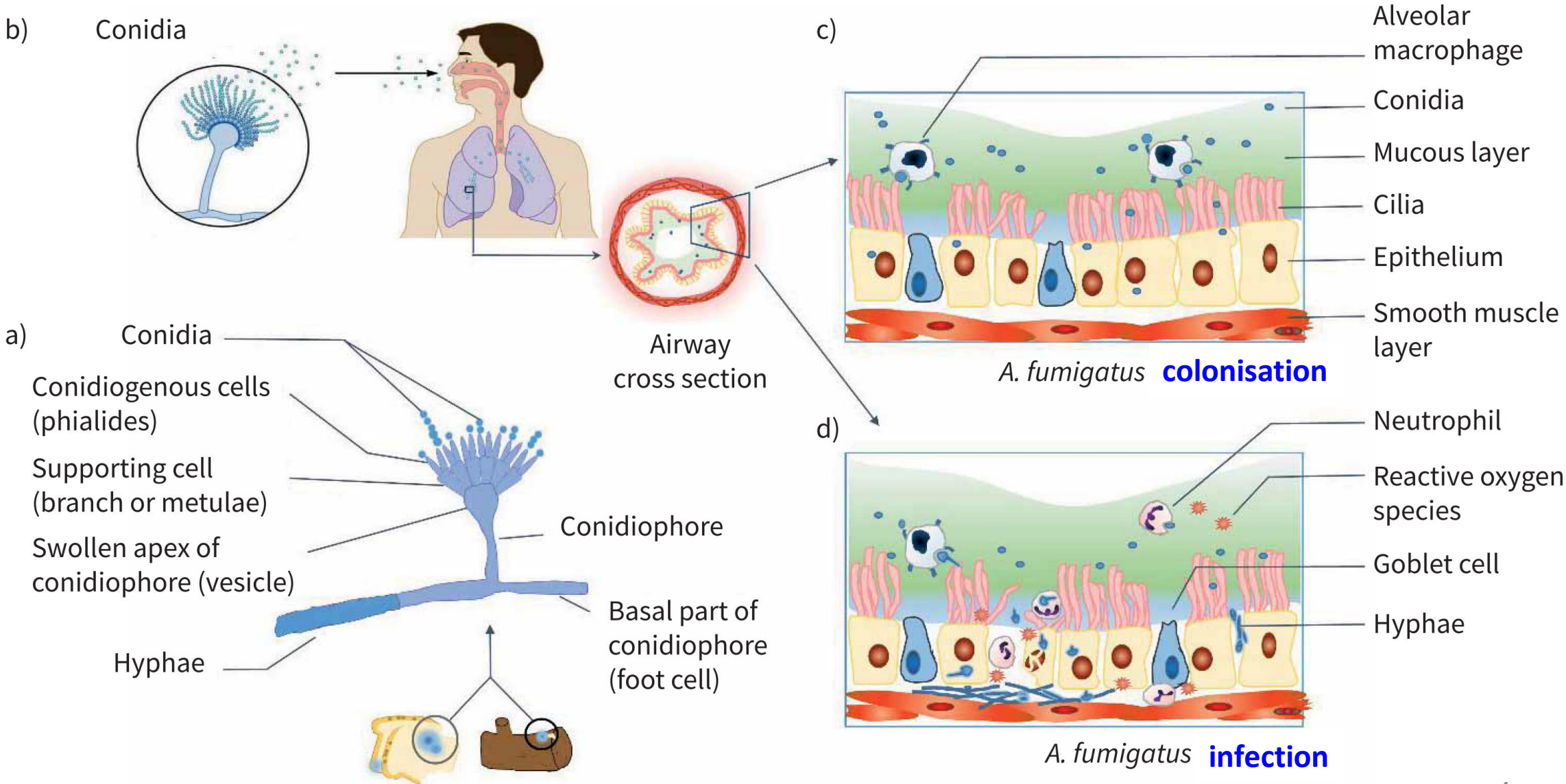
Rodlet

Chitin

The main core of A. fumigatus cell wall consists of a polymer of β-1,3-glucan and chitin which is responsible for the rigidity of this structure. β-1,3-glucan is cross-linked to α-1,3-glucan, galactomannan, galactosaminogalactan…, all of them covalently bound one to the other

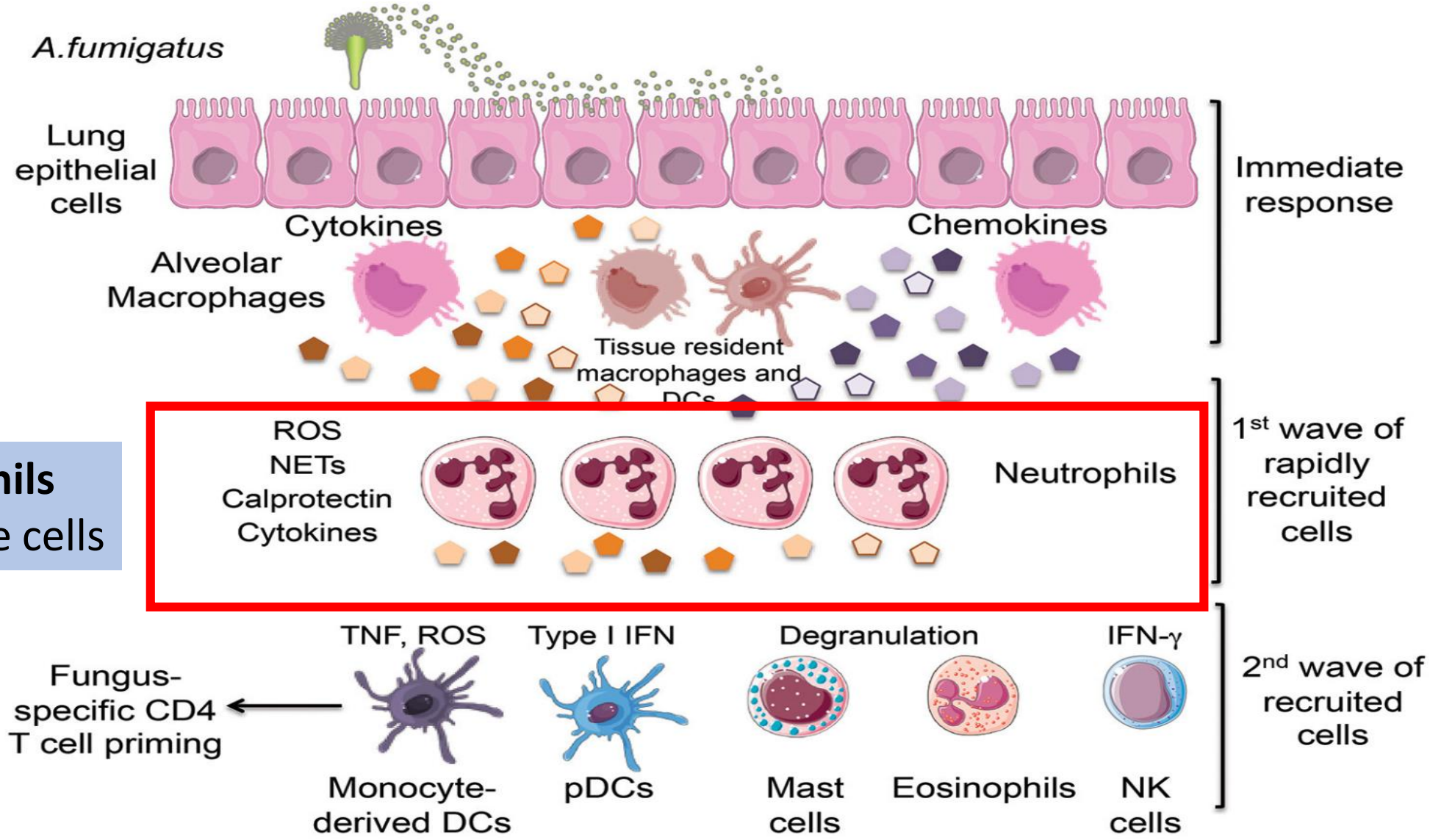
Front Microbiol. 2020 Jan 9;10:2993.

Colonization vs. Infection

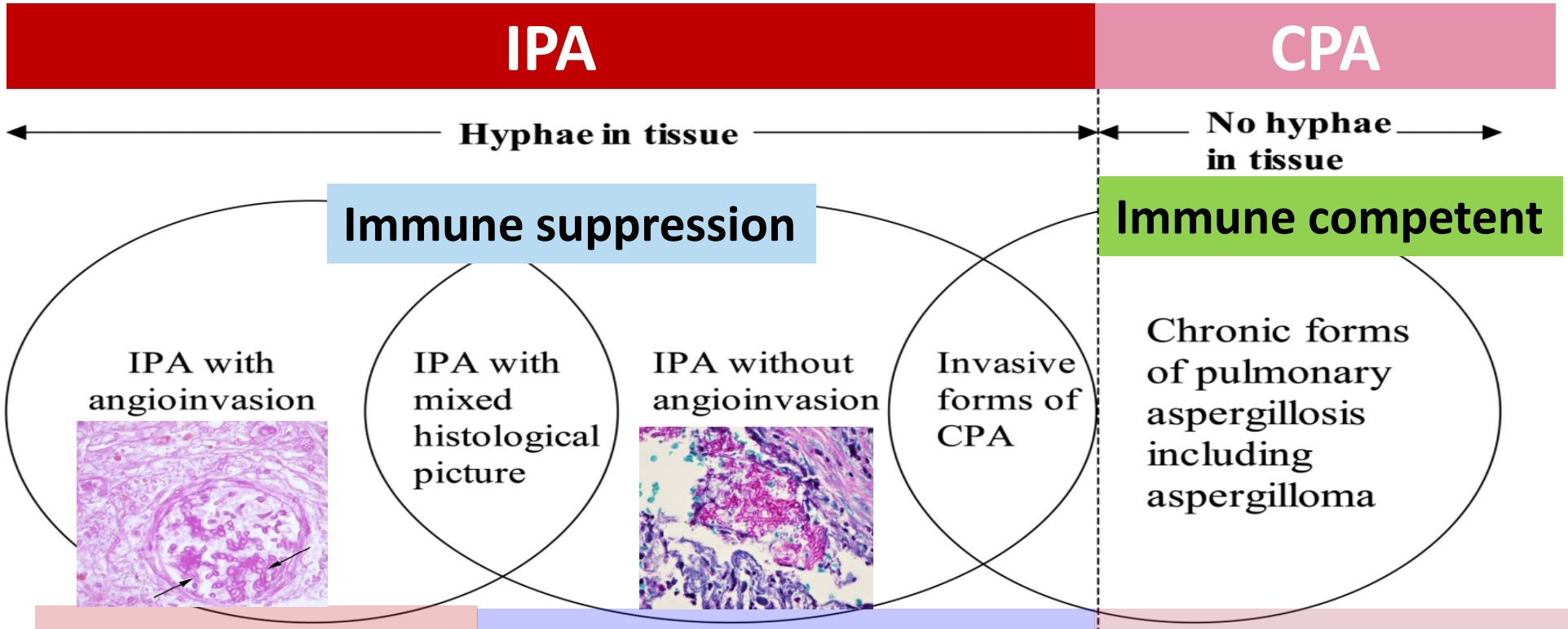


Lv Q, et al. Eur Respir Rev 2021

Neutrophils
Key immune cells



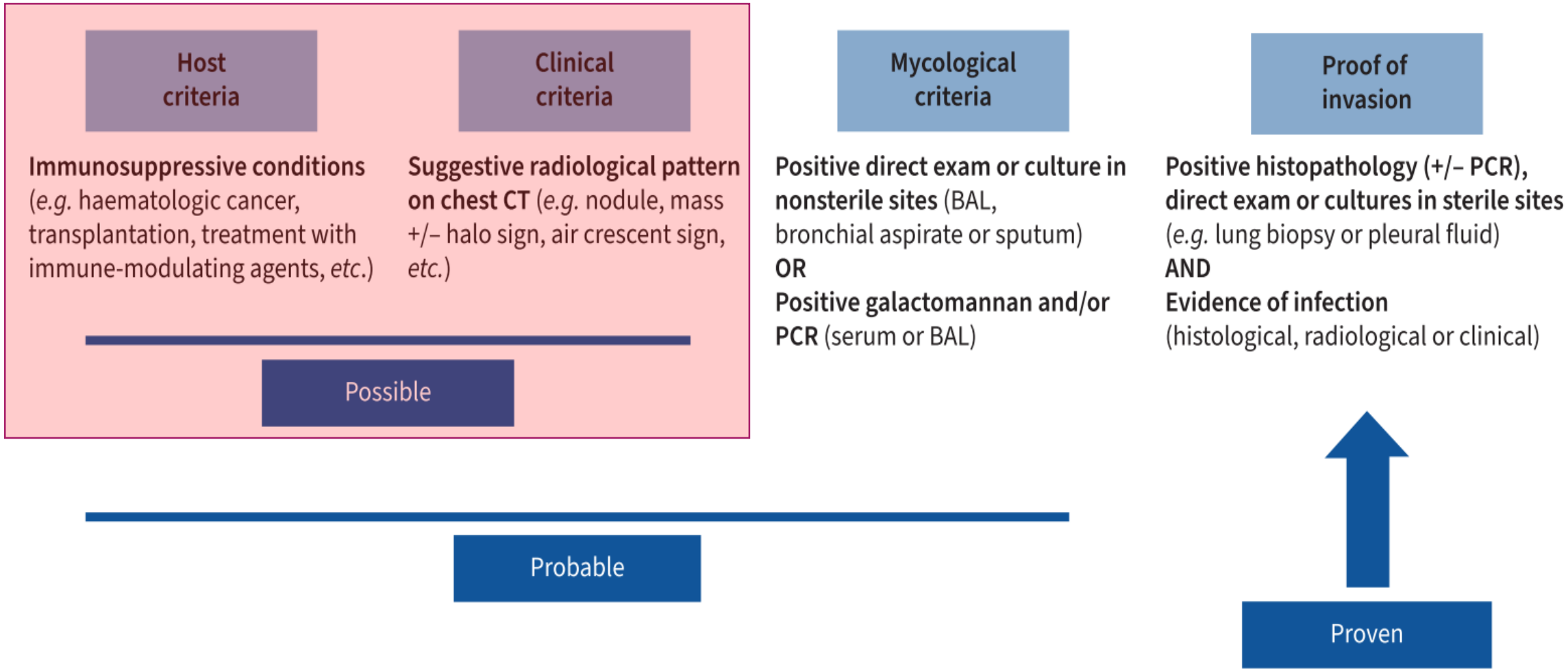
Espinosa V, et al. Front Micro 2016



Pathology	Angioinvasion, coagulative necrosis, haemorrhagic infarction	No angioinvasion, pyogranulomatous inflammation, inflammatory necrosis	No angioinvasion, hyphae confined to pre-existing lung cavity
Host	Prolonged and profound neutropenia	Non-neutropenic with CGD, corticosteroid therapy, HIV/AIDS, non-neutropenic HSCT recipients, GVHD	Pre-existing structural lung disease, minor immunological defects
Time-course	Days-weeks	Weeks-months	Months-years

Kosmidis C, et al. Thorax 2015

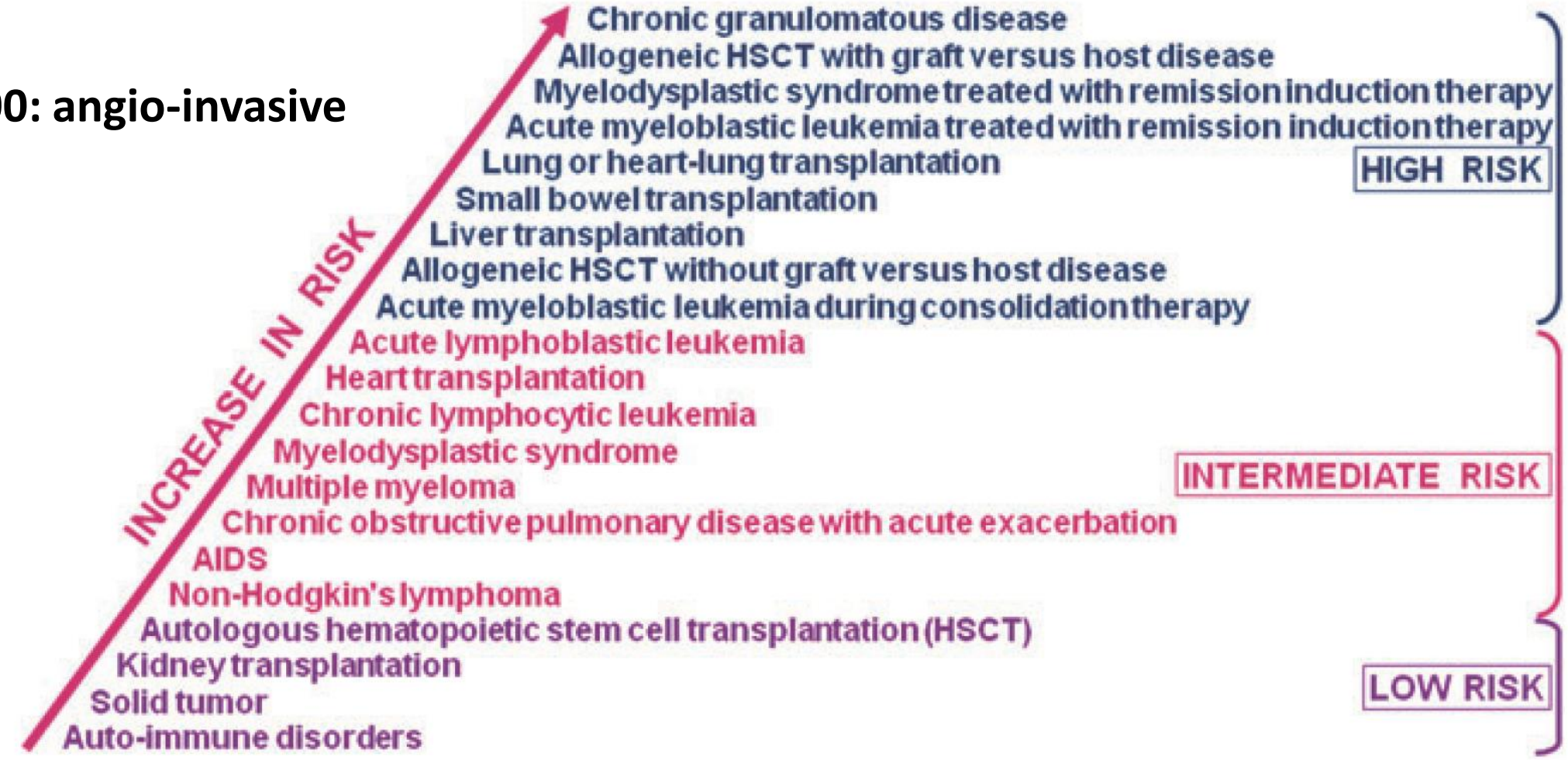
When to consider IPA



Lamoth F,e t al. Eur Respir Rev. 2022

Classical Risk factors for IPA

ANC<500: angio-invasive



Herbrecht R. Ann N Y Acad Sci. 2012

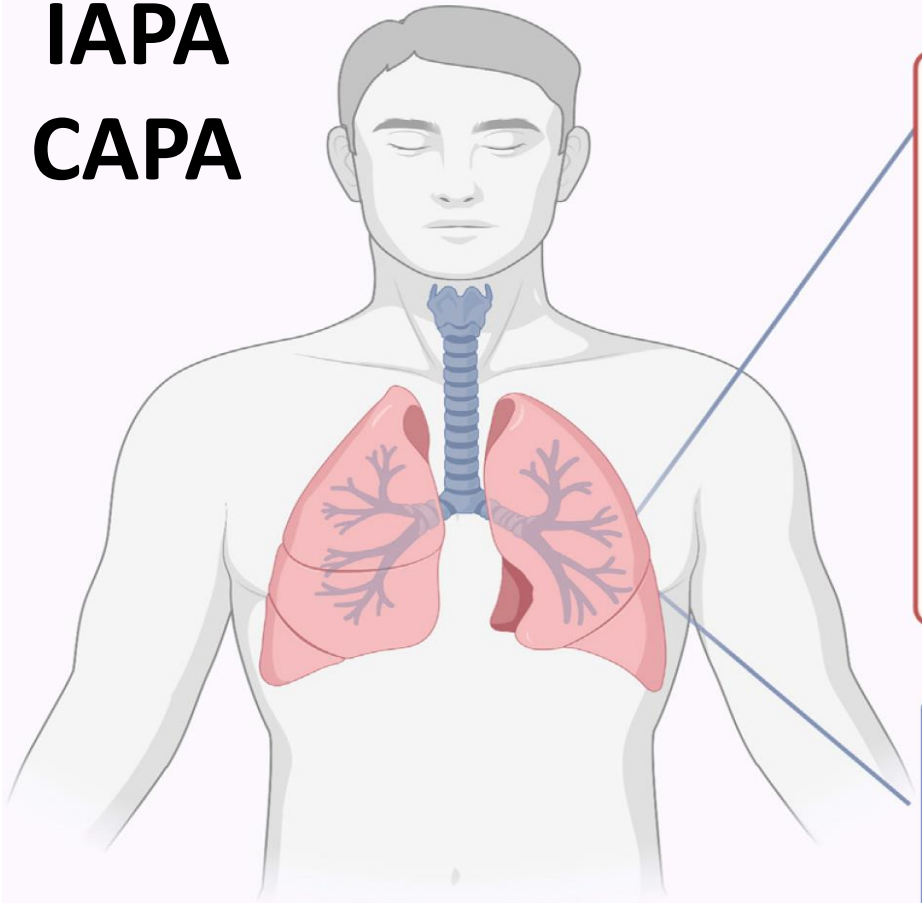
New- ICU patients at risk for IPA

Table 1. Risk factors for IA in non-neutropenic ICU patients.

Risk factor
•Prolonged corticosteroid treatment
•Chronic obstructive pulmonary disease (COPD)
•Advanced (decompensated) liver cirrhosis with a duration of stay in the ICU longer than 7 days
•Solid tumors requiring admission to the ICU
•HIV infection
•Solid organ (esp. lung) transplantation
•Systemic diseases requiring immunosuppressive therapy
Underlying conditions causing an immunocompromized status or immunosuppression
• Influenza IAPA
• COVID-19 CAPA
• Sepsis
• Concentration of *Aspergillus* spores in the air
• Diabetes
• Alcoholism
• Malnutrition
• Lifestyle: Smoking tobacco or marijuana, body piercing, tattooing, intravenous drugs use

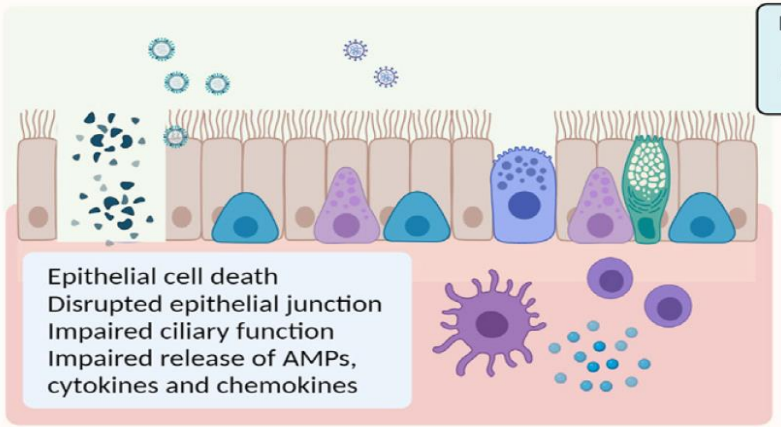
Kluge S, et al. Medical Mycology 2022

IAPA
CAPA



Virus-induced airway damage in severe influenza and COVID-19

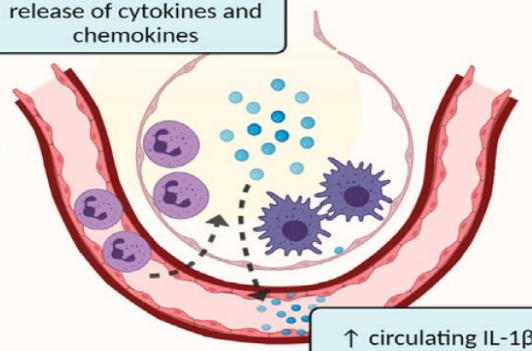
Airway epithelial damage



Epithelial cell death
Disrupted epithelial junction
Impaired ciliary function
Impaired release of AMPs, cytokines and chemokines

Hyperinflammation

Immune cell activation in the lungs triggers the release of cytokines and chemokines

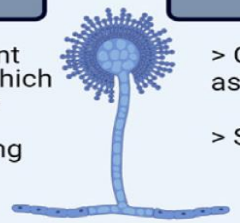


↑ circulating IL-1β, IL-1α, TNF-α, IL-6

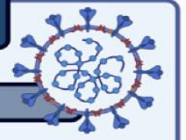
Specific factors in severe influenza/COVID-19 predisposing to IAPA or CAPA

IAPA

> Suppression of NADPH oxidase-dependent ROS production in alveolar macrophages, which is important for *Aspergillus* clearance in the lungs
> Corticosteroid administration before/during admission
> Use of neuraminidase inhibitors as an additional risk factor



CAPA

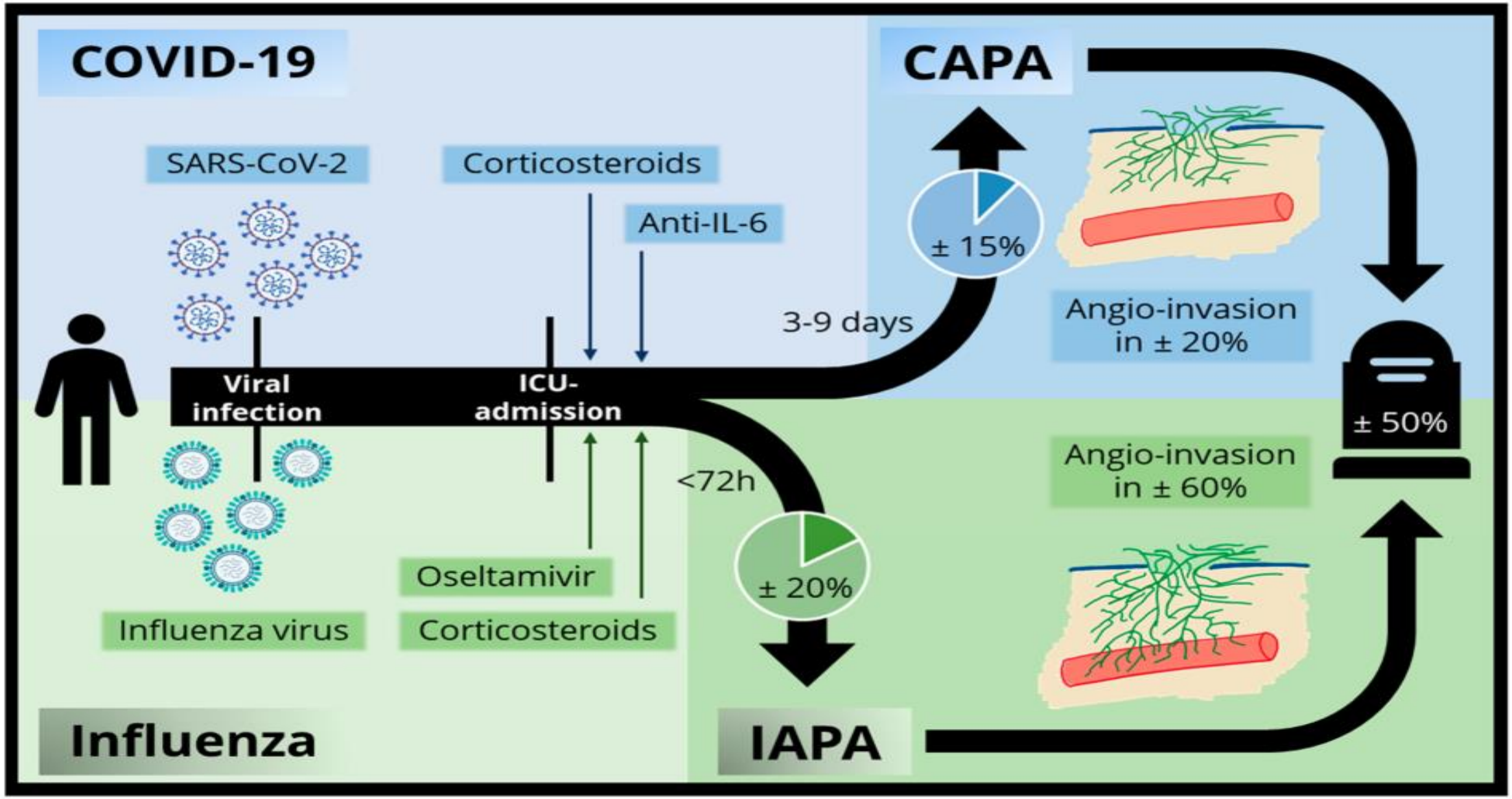


> Conflicting data on corticosteroids as a risk factor for CAPA

> Suppression of Type I and III IFNs

Current potential host-directed therapies

Dewi IM, Cur Opin Micro 2021



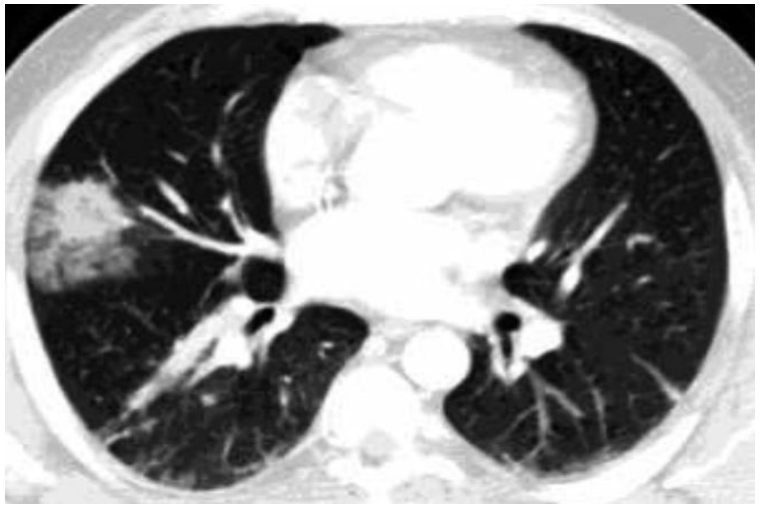
Feys S, et al. J Fungi 2021

Risk Factor of CAPA

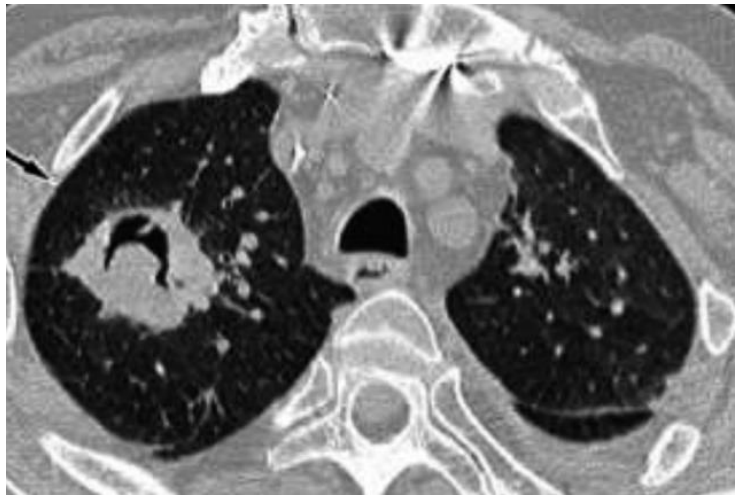
Country	Number of Cases	Comorbidities
Italy	108	Obesity, AH, DM, coronary disease, COPD, CRF, hemodialysis, cerebrovascular disease, malignancies, solid organ transplant, chronic steroid treatment, and atrial fibrillation.
France	615	AH, obesity, DM, BA, cardiac disease, gout, thyroid cancer, MDS, Hashimoto disease, hyperlipidemia, cancer, hemopathy, CRF, kidney transplant recipient, HIV, steroid treatment, COPD, dialysis, stroke, CHF (NYHA classification 3–4), arrhythmias, CRF.
Belgium	20	AH, DM, hypercholesterolemia, CRF, obesity, AML, HIV.
China	152	DM, AH, heart disease, COPD, CRF.
Germany	21	AH, COPD, DM, obesity, OSA, pulmonary fibrosis.
Netherlands	74	Cardiomyopathy, COPD, BA, DM, AH, chronic steroid treatment, neutropenia, stem cell transplant, immunodeficiency, DM, CRF.
Austria	1	COPD, OSA, Obesity, DM, AH, and cardiac disease.
Netherland	74	Reflux, polyarthrosis.
Ireland	1	DM, AH, hyperlipidemia, obesity.
Brazil	1	AH, DM, CRF.
Pakistan	23	DM, AH, atrial myxoma, recent stroke.
Switzerland	118	AH, DM, obesity, pulmonary fibrosis, BA.
Spain	239	MDS, HIV, DM, COPD, ankylosing spondylitis, acquired hemophilia A, hypothyroidism, CLL, cardiac disease, AH, BA, obesity, CRF, non-alcoholic fatty liver disease, and CNS disease.
Denmark	8	AH, BA.
UK	916	DM, AH, CRF, obesity, cancer, CRF malignancy, hyperlipidemia, cardiac and vascular disease, and autoimmune disorders.
USA	46	Atrial fibrillation, COPD, AH, OSA, DM, CRF, coronary disease, CHD, ESRD, nephrectomy, vasculitis, junctional tachycardia, bipolar disorder, hypercholesterolemia, obesity, hypothyroidism, gastric ulcer, atherosclerosis, and sarcopenia.

Castro-Fuentes CA, et al. Pathogens 2022

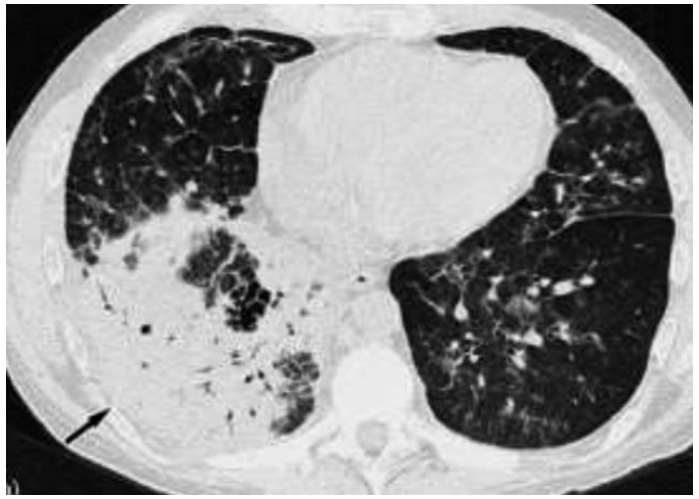
Radiological features of IPA/CAPA- Non-specific



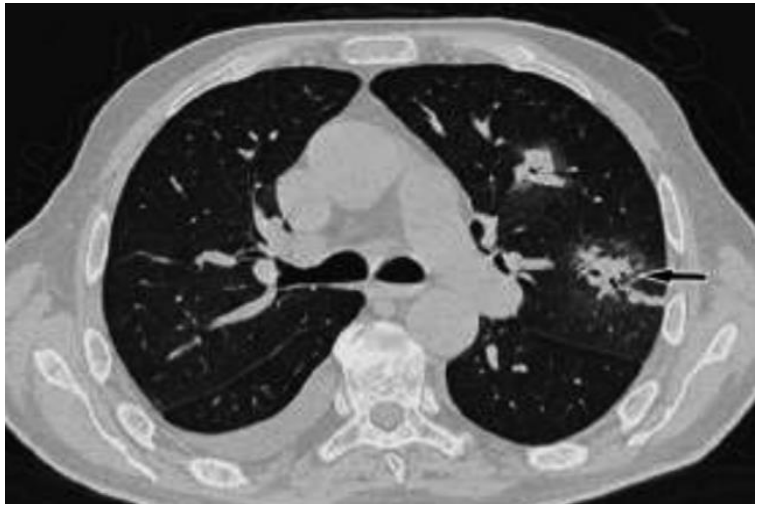
Nodules with halo sign



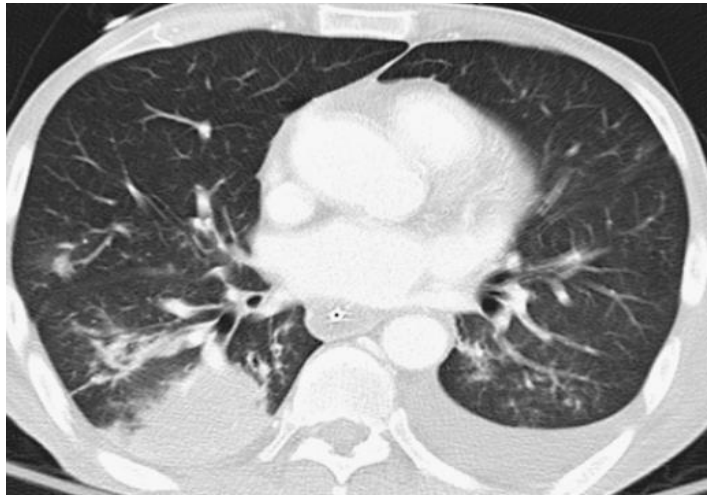
Cavity with air-crescent



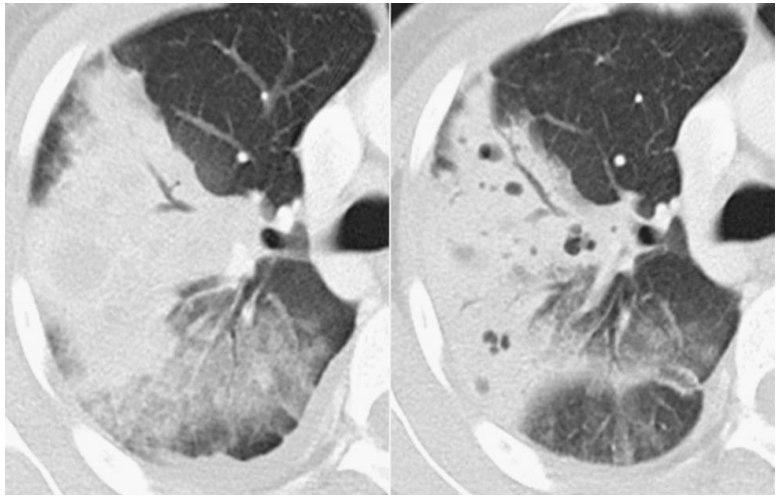
Extensive consolidation



Small consolidation with halo sign



Wedge-shape consolidation



Necrotic consolidation

Analysis of initial and follow-up CT findings in patients with invasive pulmonary aspergillosis after solid organ transplantation

46 adult patients with SOT and meet 2008 EORTC/MSG criteria

21 survivors and 15 died of IPA

Incidence and extent of CT findings on initial CT and comparison between survival and IPA-related death group.

	All patients ($n = 46$)		Survival group ($n = 21$)		IPA-related death ($n = 15$)	
	Incidence		Incidence		Incidence	
Large nodule	27	(59%)	12	(57%)	10	(67%)
Consolidation or mass	33	(72%)	13	(62%)	14	(93%)
Infarcted consolidation	22	(48%)	10	(48%)	9	(60%)
Halo sign	13	(28%)	4	(19%)	7	(47%)
Cavity	13	(28%)	9	(43%)	2	(13%)
Air-crescent sign	1	(2%)	0	(0%)	0	(0%)
GGO (lobe)	23	(50%)	8	(38%)	9	(60%)
Internal low attenuation	14	(30%)	6	(29%)	6	(40%)

Lim C, et al. Clin Radiol. 2012

TABLE 1 Characteristics of nonculture commercialised diagnostic tests for invasive pulmonary aspergillosis

Target	Type of test (manufacturer)	Technique	Spectrum of detection	Type of sample	Cut-off
Galactomannan	Platelia™ *Aspergillus* EIA (Bio-Rad)	Immunoenzymatic sandwich assay	All *Aspergillus* species (specific)[#]	Serum, BAL	0.5–1.0 ODI[¶]
	Soña *Aspergillus* galactomannan LFA (IMMY)	Immunochromatographic assay (LFA)			Visual reading or cube reader: 0.5–1.0[¶] (index values)
	Aspergillus galactomannan VirClia™ (Vircell)	Chemoluminescent assay			1.0 (index value)
(1→3)-β-D-Glucan	Fungitell™ (Associates of Cape Cod)	Colorimetric assay (microplate)	All *Aspergillus* species (not specific)[+]	Serum	60–80 pg·mL^{-1}[§]
	Fungitell STAT™ (Associates of Cape Cod)	Colorimetric assay (single tube)			0.75–1.2 (index values)[§]
	Wako β-glucan test (Fujifilm Wako Chemicals)	Turbidimetric assay (single tube)			7.0 pg·mL^{-1}
	Dynamiker Fungus (1–3)-β-D-glucan (Dynamiker Biotechnology)	Colorimetric assay (microplate)			70–95 pg·mL^{-1}[§]
***Aspergillus* DNA**	MycAssay *Aspergillus*™ (Myconostica Ltd., now Microgen Bioproducts Ltd.)	Real-time PCR (18S rDNA)	Most relevant *Aspergillus* species	BAL, other respiratory samples, serum	NA
	AsperGenius™ (PathoNostics)	Multiplex real-time PCR (28S rDNA and *Cyp51A*)	Most relevant *Aspergillus* species, *Cyp51A* mutations (L98H, TR34, T289A, Y121F)		NA
	MycoGenie™ (AdemTech)	Real-time PCR (28S rDNA and *Cyp51A*)	*Aspergillus fumigatus*, *Cyp51A* mutations (L98H, TR34)		NA
	Fungiplex *Aspergillus* azole-R™ (Bruker Daltonics GmbH)	Multiplex real-time PCR	*Aspergillus* species, *Cyp51A* (TR34, TR46)		NA

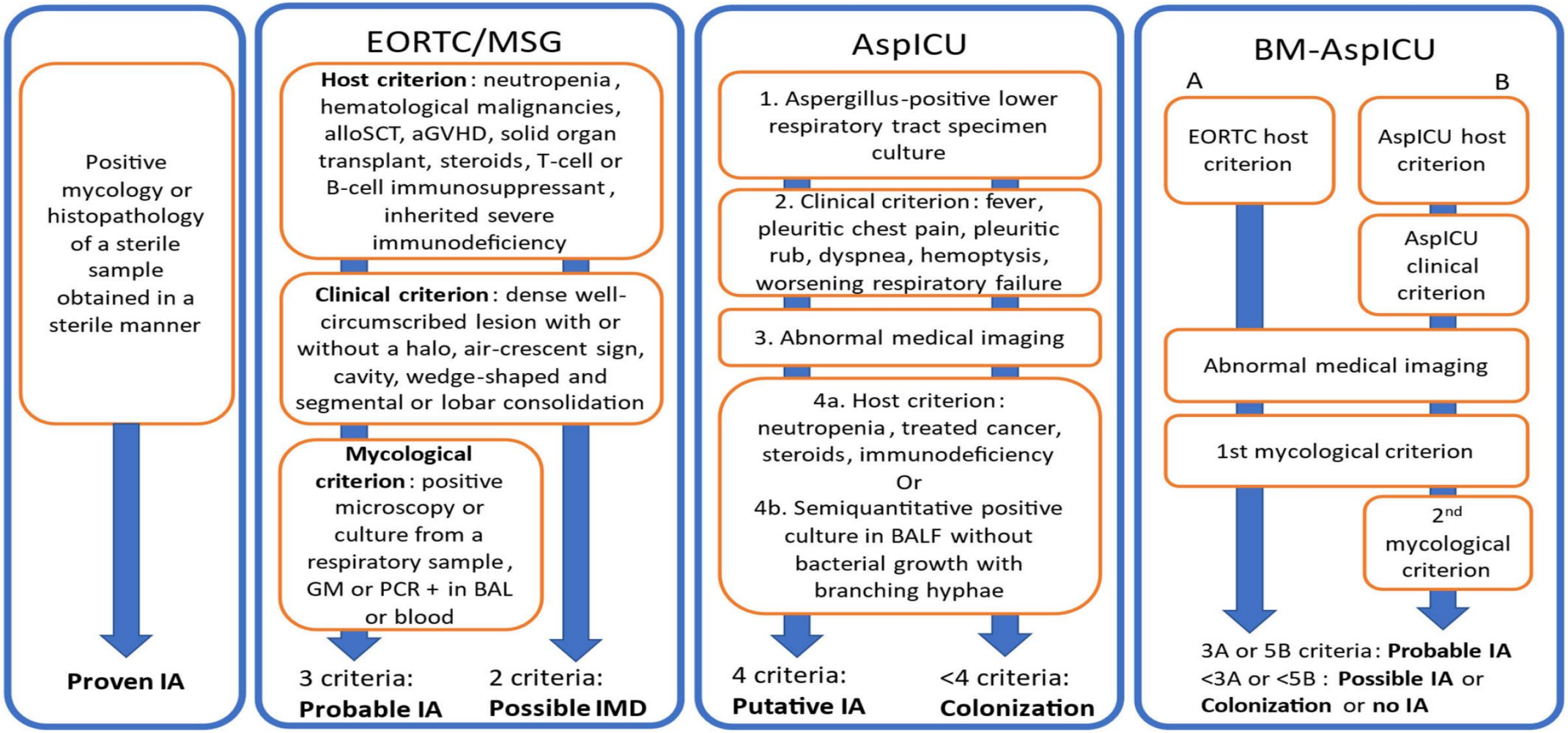
Lamoth F,e t al. Eur Respir Rev. 2022

TABLE 2 Performance of galactomannan (GM) and *Aspergillus* PCR in serum and bronchoalveolar lavage fluid (BAL) for the diagnosis of invasive pulmonary aspergillosis (IPA) in haematologic cancer patients: results of the most relevant meta-analyses

Fungal biomarker	Study	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
Serum			
GM 0.5	Pfeiffer *et al.* [38]	58 (52–64)	95 (94–96)
Spec > Sens	Leeflang *et al.* [98]¶	78 (70–85)	85 (78–91)
	Arvanitis *et al.* [28]	92 (83–96)	90 (81–95)
PCR	Mengoli *et al.* [99]	88 (75–94)	75 (63–84)
	Arvanitis *et al.* [28]	84 (71–92)	76 (64–85)
GM and PCR#	Arvanitis *et al.* [28]	99 (96–100)	98 (94–100)
BAL			
GM 1.0	Guo *et al.* [100]¶	85 (72–93)	94 (89–97)
Spec > Sens	Avni *et al.* [29]¶	85 (62–95)	100 (97–100)
	Zou *et al.* [101]¶	86 (76–92)	95 (91–97)
	Heng *et al.* [30]	75 (55–88)	95 (87–98)
	De Heer *et al.* [102]¶	78 (61–95)	93 (87–98)
PCR	Sun *et al.* [103]¶	91 (79–96)	92 (87–96)
Spec > Sens	Avni *et al.* [29]¶	93 (70–98)	98 (93–99)
	Zou *et al.* [101]¶	82 (61–93)	98 (85–100)
	Heng *et al.* [30]	57 (31–80)	99 (60–100)
GM and PCR#	Avni *et al.* [29]¶	97 (83–99)	97 (93–99)
	Heng *et al.* [30]	84 (79–88)	94 (91–97)

General comparable performance in GM and PCR; BAL better than serum; suggest combine

Lamoth F,e t al. Eur Respir Rev. 2022


2008
2020
2012
2018 (IAPA)
2021
IAPA
(2020)
CAPA
(2021)
Positive mycology or histopathology of a sterile sample obtained in a sterile manner
Proven IA
EORTC/MSG
Host criterion: neutropenia, hematological malignancies, alloSCT, aGVHD, solid organ transplant, steroids, T-cell or B-cell immunosuppressant, inherited severe immunodeficiency
Clinical criterion: dense well-circumscribed lesion with or without a halo, air-crescent sign, cavity, wedge-shaped and segmental or lobar consolidation
Mycological criterion: positive microscopy or culture from a respiratory sample, GM or PCR + in BAL or blood
3 criteria: Probable IA
2 criteria: Possible IMD
AspICU
1. Aspergillus-positive lower respiratory tract specimen culture
2. Clinical criterion: fever, pleuritic chest pain, pleuritic rub, dyspnea, hemoptysis, worsening respiratory failure
3. Abnormal medical imaging
4a. Host criterion: neutropenia, treated cancer, steroids, immunodeficiency
Or
4b. Semiquantitative positive culture in BALF without bacterial growth with branching hyphae
4 criteria: Putative IA
<4 criteria: Colonization
BM-AspICU
A
B
EORTC host criterion
AspICU host criterion
AspICU clinical criterion
Abnormal medical imaging
1st mycological criterion
2nd mycological criterion
3A or 5B criteria: Probable IA
<3A or <5B : Possible IA or Colonization or no IA

Criteria for IPA		Clinical	Radiological	Mycological
EORTC/MSGERC Donnelly JP, CID 2020	Proven IPA	-	-	Lung biopsy, at least 1: • Histo/cytopathologic, or direct microscopic exam (Hyphae + tissue damage) • Culture from sterile material or blood with compatible clinical process
	Probable IPA	Host factors: • Neutropenia(<500,>10d) • Receipt of allo-SCT(+SOT) • **CS(0.3mg/kg/d*3wk in 60d)** • T-cell(+B-cell, e.g., BTKi) immunosuppressant in 90d • Hematologic malignancy • Acute GvHD(gut, lung, liver, refractory to steroid)	At least 1 CT pattern • dense, well-circumscribed lesion • air-cresent • cavity • wedge-shape consolidation	At least 1: • Culture or microscopic(+) in respiratory specimens • BAL GM ≥ 1 • Serum GM≥ 1 • BAL GM ≥ 0.8 + serum GM ≥ 0.7 • **2X** positive Aspergillus **PCR** (**serum or BAL**)
	Possible IPA	As above	As above	-

<table>
<tr><th colspan="2">Criteria for IPA</th><th>Host factor</th><th>Clinical</th><th>Mycological</th></tr>
<tr><td rowspan="3">AspICU algorithm

Blot SI, AJRCCM 2012</td><td>Proven IPA</td><td>-</td><td>-</td><td>Lung biopsy, at least 1:
• Histo/cytopathologic, or direct microscopic exam (Hyphae + tissue damage)
• Culture from sterile material or blood with compatible clinical process</td></tr>
<tr><td>Putative IPA</td><td colspan="3">1. Entry criterion: aspergillus in LRT culture</td></tr>
<tr><td></td><td>4a. Host risk factors
• ANC<500
• Hema/Onco s/p CT
• Prolonged steroid
• Immunosuppresants</td><td>2. CXR or CT scan
• Abnormal imaging (any infiltrate)
3. Compatible s/s
• Fever, pleuritic chest pain, dyspnea, hemoptysis, respiratory insufficiency</td><td>4b. BAL
• Culture (+ or ++) in BAL fluids
• Without bacteria
• Cyto: branching hyphae</td></tr>
<tr><td></td><td>Aspergillus colonization</td><td colspan="3">≥ 1 criterion to putative IPA not meet</td></tr>
</table>

Criteria for IPA		Host factor	Clinical	Mycological
Modified *Asp*ICU algotithm (IAPA) Schauwvlieghe. Lancet Resp Med 2018	Proven IPA	-	-	Identical to EORTC/MSGERC
	Putative IPA	-	Clinical Criteria • Refractory fever • Dyspnea • Hemoptysis • Worsening resp. distress Radiological criteria • **Abnormal infiltrate**	At least 1: • Positive culture in BALF • **GM in BAL ≥ 1** • **GM in serum ≥ 0.5**
IAPA Verweij PE, et al. ICM 2020	Proven IAPA	-		• Histo/cytopathologic, or direct microscopic • Culture or **PCR +** from tissue
	Probable IAPA	-	CXR or CT image • Pulmonary infiltrates	At least 1: **Serum GM > 0.5 or BAL GM ≥ 1.0** BAL culture(+)
			• Cavitating infiltrates (without other causes)	Positive culture in tracheal aspirate or sputum
	Aspergillus tracheobronchitis	-	Bronchoscopic examination - Airway plaque, - pseudomembrane, ulcer	At least 1: **Serum GM > 0.5 or BAL GM ≥ 1.0** Culture + in BAL, tracheal aspirate or sputum Positive direct microscopic

Criteria for IPA		Host factor	Clinical	Mycological
Modified *Asp*ICU algotithm (IAPA) Schauwvlieghe. Lancet Resp Med 2018	Proven IPA	-	-	Identical to EORTC/MSGERC
	Putative IPA	-	Clinical Criteria • Refractory fever • Dyspnea • Hemoptysis • Worsening resp. distress Radiological criteria • **Abnormal infiltrate**	At least 1: • Positive culture in BALF • **GM in BAL ≥ 1** • **GM in serum ≥ 0.5**
BM-*Asp*ICU Hamam, et al. AIC 2021 (Entry: Cul + or Clinical + or Radio +)	Proven IAPA	-		Identical to EORTC/MSGERC
	Probable IPA	≥ 1 EORTC host factor (strong)	≥ 1 Abnormal image (any infiltrate)	≥ 1 Mycological • BAL GM ≥ 1 • Serum GM≥ 1 • BAL GM ≥ 0.8 + serum GM ≥ 0.7 • **2X positive Aspergillus PCR (serum or BAL)**
	Probable IPA	≥ 1 Other host factor (weak)	≥ 1 Abnormal image (any infiltrate) ≥ 1 Clinical sign	≥ 2 Mycological
	Colonization, possible IPA, no IPA	≥ 1 criterion to putative IPA not meet		

Criteria for CAPA		Clinical	Radiological	Mycological
ECMM/ISHAM Koehler P, et al. Lancet Inf Dis 2021 **COVID-19 ICU ARDS**	Proven CAPA	-	-	• Histo/cytopathologic, or direct microscopic in tissue • Culture or **PCR +** from tissue
	Probable CAPA (pulmonary)	• Refractory fever • Pleural rub • Chest pain • Haemoptysis	CXR or CT • Pulmonary infiltrates • Cavity	At least 1 • Microscopic(+) in BALF (hyphae) • Positive culture in BALF • **Serum GM > 0.5 or BAL GM ≥ 1** • Positive **PCR** in **serum x2 or BAL x1** or Serum & BAL x1 (CT <36)
	Probable CAPA (**tracheobro)**	Bronchoscopic exam Airway plaque, pseudomembrane, ulceration, nodule		At least 1 • Microscopic(+) in BALF (hyphae) • Positive culture in BALF • **Serum GM > 0.5 or BAL GM ≥ 1** • Positive **PCR** in **BAL x1**
	Possible CAPA	Identical to probable CAPA	Identical to probable CAPA	At least 1 • Microscopic(+) in **NBL** (hyphae) • Positive culture in NBL • **NBL** GM > 4.5 x1 or >1.2 x2 • **NBL** GM > 1.2 + PCR+ in NBL

Mycological Evidence of IPA

Mycology	EORTC/MSG (2020)	Modified *Asp*ICU	IAPA	CAPA
Direct microscopy	+ (all resp. specimens)	+ (with +ve culture)	+ (for tracheobronchitis)	+ (for tracheobronchitis)
Culture	+ (all resp. specimens)	+ (BAL)	+ [2]	+ (BAL)
GM_{serum} [1]	**≥ 1.0[1]**	**≥ 0.5**	**≥ 0.5**	**≥ 0.5**
GM_{BAL} [1]	≥ 1.0[1]	≥ 1.0	≥ 1.0	≥ 1.0
PCR	1. $PCR_{serum/plasma/WB}$ Positive ≥ 2 consecutive tests; or 2. PCR_{BAL} Positive ≥ 2 duplicate tests; or 3. $PCR_{serum/plasma/WB}$ Positive for 1 test & PCR_{BAL} Positive for 1 test.	NA	NA	1. $PCR_{serum/plasma/WB}$ Positive ≥ 2 consecutive tests[3]; or 2. PCR_{BAL} Positive ≥ 1 test[3]; or 3. $PCR_{serum/plasma/WB}$ Positive for 1 test & PCR_{BAL} Positive for 1 test[4].

[1] GM_{serum} ≥ 0.7 + GM_{BAL} ≥ 0.8; [2] all resp. specimens for tracheobronchitis; BAL in any pulmonary infiltrates or sputum or tracheal aspirate in cavitating infiltrates; [3] < 36 cycles; [4] any threshold cycle permitted.

Epidemiology of IA in critically ill patients

- IA in general ICU
  - **0.3~5.8%** of general ICU population

Meersseman W, et al. AJRCCM 2004
Taccone FS, et al. Crit Care 2015
Garnacho-Montero J, et al. Crit Care 2005

- Influenza associated invasive aspergillosis (IAPA)
  - **16-23%** of critically ill influenza

Am. J. Respir. Crit. Care Med.2017, 196, 524–527.
Intensive Care Med. 2012, 38, 1761–1768.
J. Formos. Med. Assoc. 2017, 116, 660–670

- COVID-19 associated invasive aspergillosis (CAPA)
  - **5~25%** of ICU-admitted COVID-19 patients
  - **15.3%** (11/72) in ICU-admitted COVID-19 in VGHTPE in 2021

Delliere S, et al. CMI, 2021
Gangneux JP, et al. , Lancet Resp Med, 2021
Huang JR et al. JCMA 2022

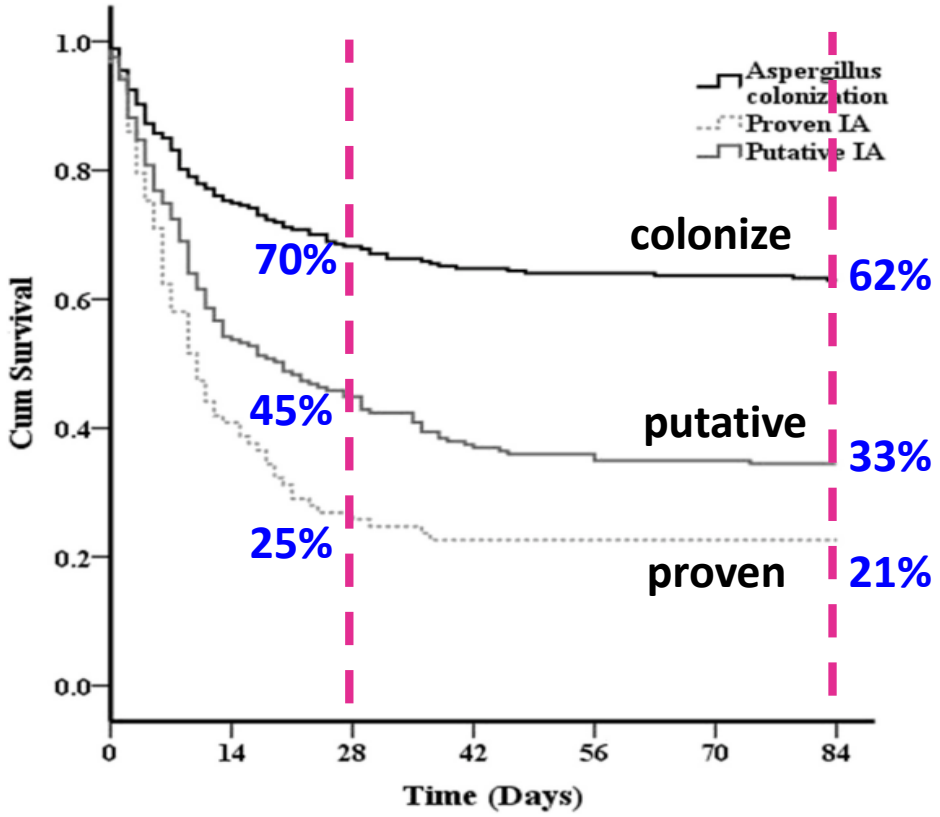
Epidemiology of invasive aspergillosis in critically ill patients: clinical presentation, underlying conditions, and outcomes

563 *Asp.* culture+ patients from 30 ICUs in 8 countries

Proven IA (17%) vs. putative IA (36%) vs. colonization (47%)

Site affected: lung 548; sinus 11; abdomen 11, brain 10, skin 9, endovascular 8

	Proven IA (*n* = 94)	Putative IA (*n* = 203)	Colonization (*n* = 266)
ICU stay before first positive culture, days	4 (1 to 11)	4 (2 to 10)	4 (2 to 9)
Non-specific chest CT scan findings, *n*	33/62[b]	55/96[b]	57/65
"Typical" chest CT scan findings, *n*	29/62[b]	41/96[b]	4/65
Microbiologic findings			
BAL[a]/ETA, *n* (%)	79 (92)	182 (98)	216 (97)
BAL[a] performed, *n* (%)	56 (60)[b]	112 (55)[b]	57 (21)
Positive GM culture, *n*/mes (%)	44/52 (84)[b]	31/37 (84)[b]	11/62 (18)
PCR, *n*/mes (%)	0	3/3 (100)	1/1 (100)
EORTC host factors, *n* (%)			
EORTC host factor present on diagnosis	65 (70)[b]	143 (70)[b]	41 (15)
Neutropenia	8 (9)[b]	21 (10)[b]	5 (2)
Glucocorticoid treatment	59 (63)[b,c]	156 (78)[b]	42 (15)



Taccone FS, et al. Crit Care 2015

Coronavirus Disease 2019-Associated Pulmonary Aspergillosis in Mechanically Ventilated Patients

396 COVID-19 cases in US, 39 with CAPA

10%

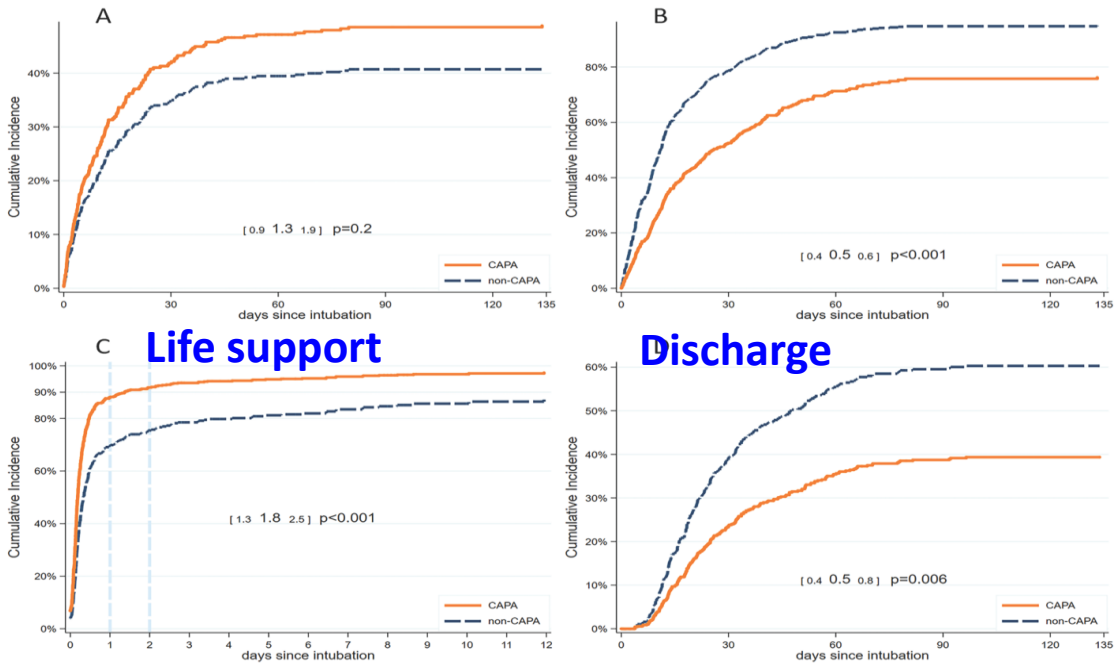
Probable CAPA: Serum GM > 0.5, BAL GM ≥ 1, cul+ in BALF

Possible CAPA: BAL GM:0.5~ 1, BDG >80, cul + in ETA

Therapy During Hospital Admission	Patients, No. (%)[a] Non-CAPA (n = 357)	CAPA (n = 39)	*P* Value
Corticosteroids			
Before intubation	50 (14.0%)	5 (12.8%)	.005[b]
After intubation	102 (28.6)	21 (53.8)	
No corticosteroids use	205 (57.4)	13 (33.3)	
Methylprednisolone	62 (17.4)	10 (25.6)	.20
Total dose, median (IQR), mg	160 (60–420)	245 (60–400)	.8
Duration, median (IQR), d	3 (1–5)	3 (1–7)	.8
Hydrocortisone	43 (12.0)	15 (38.5)	<.001
Total dose, median (IQR), mg	500 (150–1000)	425 (300–900)	.9
Duration, median (IQR), d	4 (1–8)	4 (3–9)	.7
Dexamethasone	75 (21.0)	9 (23.1)	.8
Total dose, median (IQR), mg	50 (20–60)	36 (20–60)	.8
Duration, median, (IQR), d	5 (2–10)	6 (1–10)	>.99
COVID-19–specific therapy			
Tocilizumab	63 (17.6)	9 (23.1)	.39
Remdesivir	83 (23.2)	9 (23.1)	>.99
Hydroxychloroquine	104 (29.1)	9 (23.1)	.58

60D Mortality: 50%

extubation



Life support

Discharge

Permpalung N, et al. Clin Infect Dis. 2022

Defining COVID-19 associated pulmonary aspergillosis: systematic review and meta-analysis

41 studies, 3297 COVID-19 patients in ICU

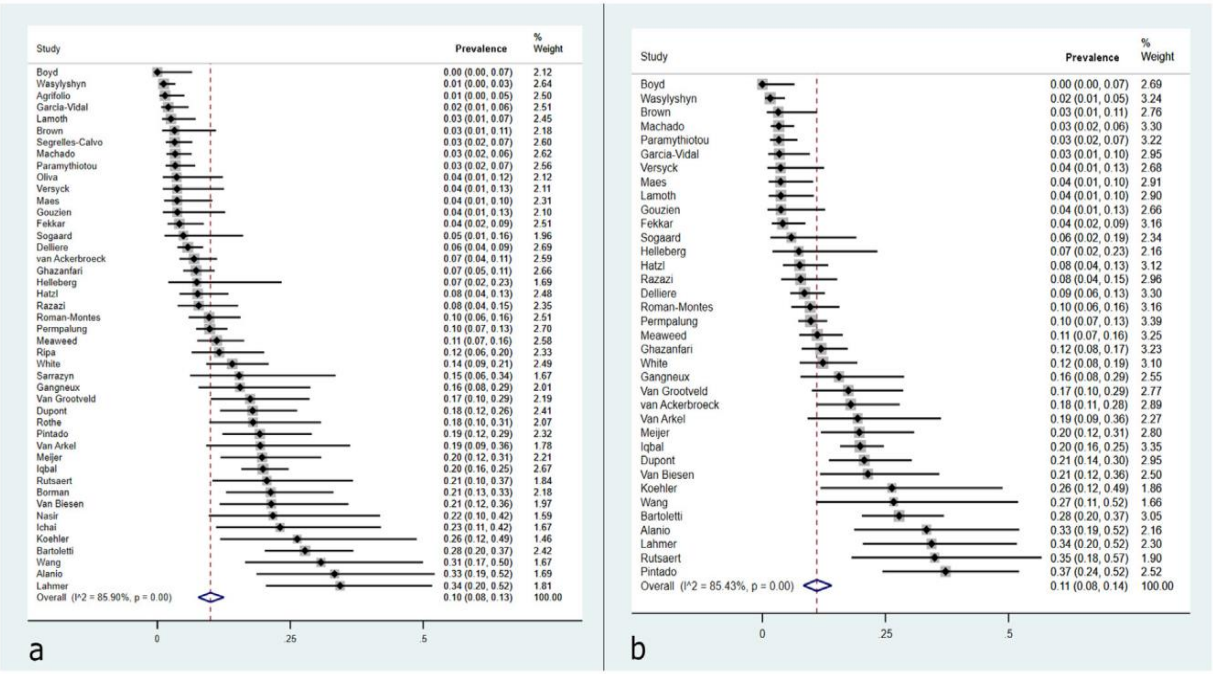
313 (9.5%) diagnosed with CAPA

Mortality rate: **59.2%**

Prevalence

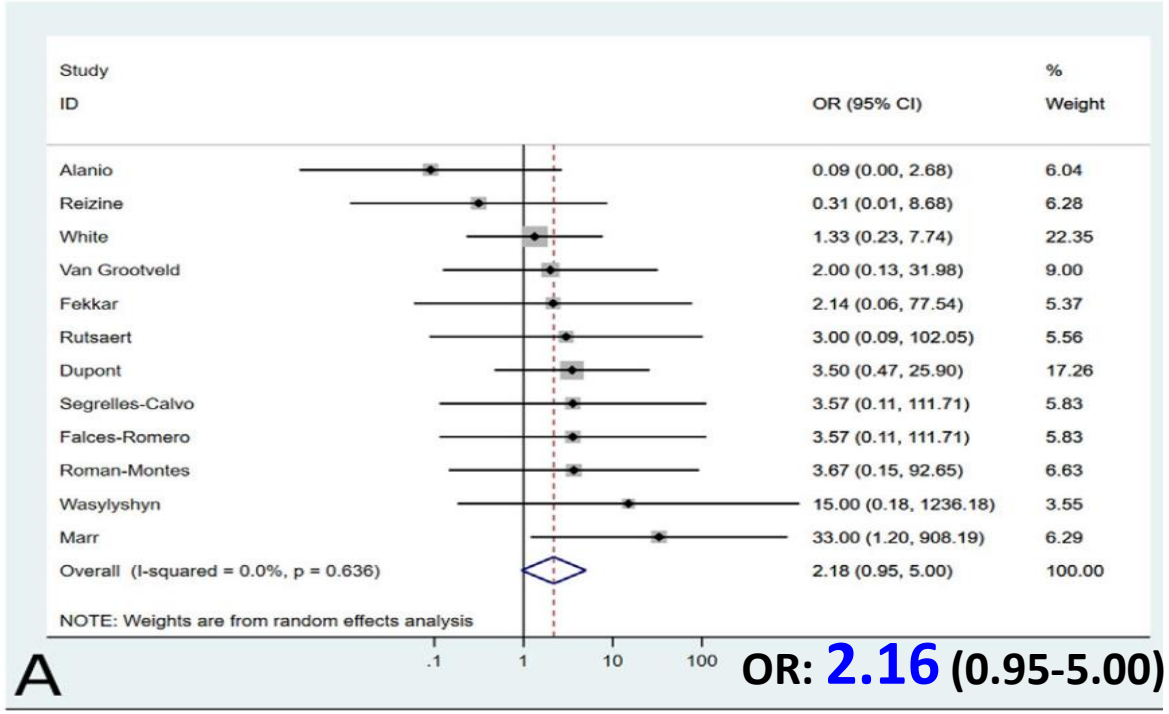
ICU

ICU+IMV



10%

11%



OR: 2.16 (0.95-5.00)

Anti-fungal marginally reduce mortality

Kariyawasam RM, et al. CMI 2022

COVID-19-associated pulmonary aspergillosis is associated with increased in-hospital mortality and prolonged SARS-CoV-2 viral shedding

VGHTPE

CAPA

2021/5~2021/8

296 patients admitted to four COVID-19 ICUs from May 14 to Aug 6, 2021

224 patients excluded owing to negative SARS-CoV-2 qPCR results

72 patients with qPCR-confirmed COVID-19 were included in the analysis

Patients with CAPA
15.3% n=11

Patients without CAPA
n=61

Survivors
n=5

Non-survivors
n=6

Survivors
n=53

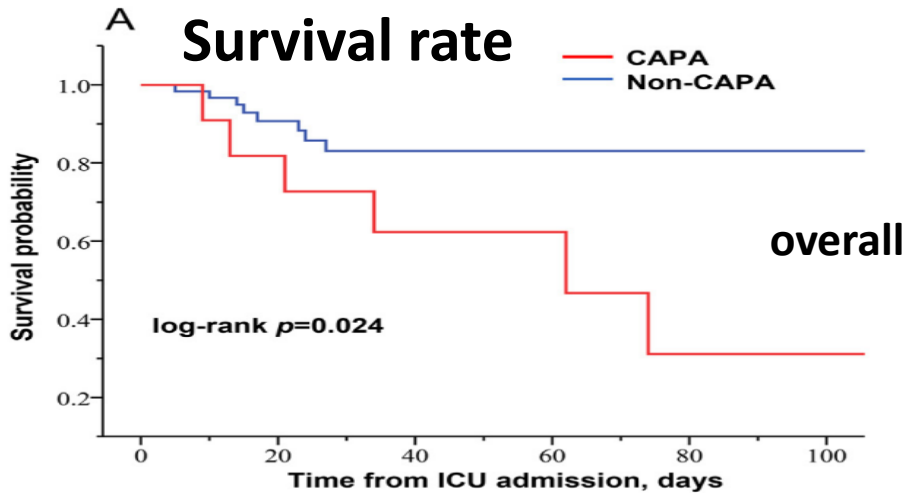
Non-survivors
n=8

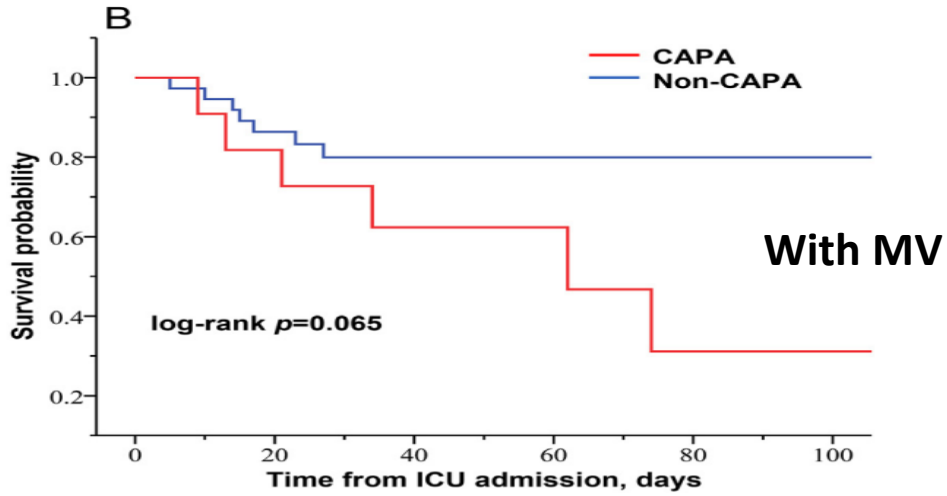
45%

55%

87%

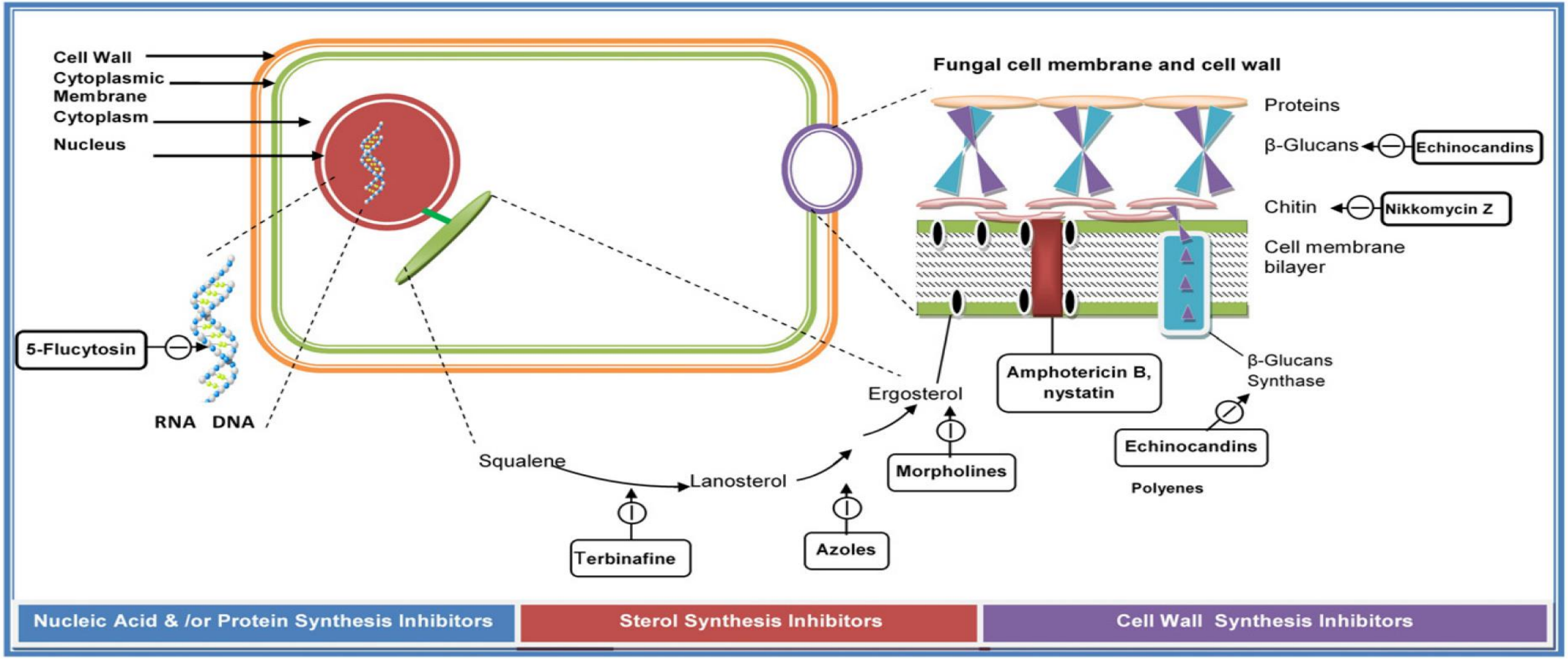
13%





Huang JR, Feng JY, et al. JCMA 2022

MOA of Anti-fungal therapy



Flucytosin | **Azoles** | **Candin, Amp B**

Kathiravan M, et al. Bioorg Med Chem. 2012

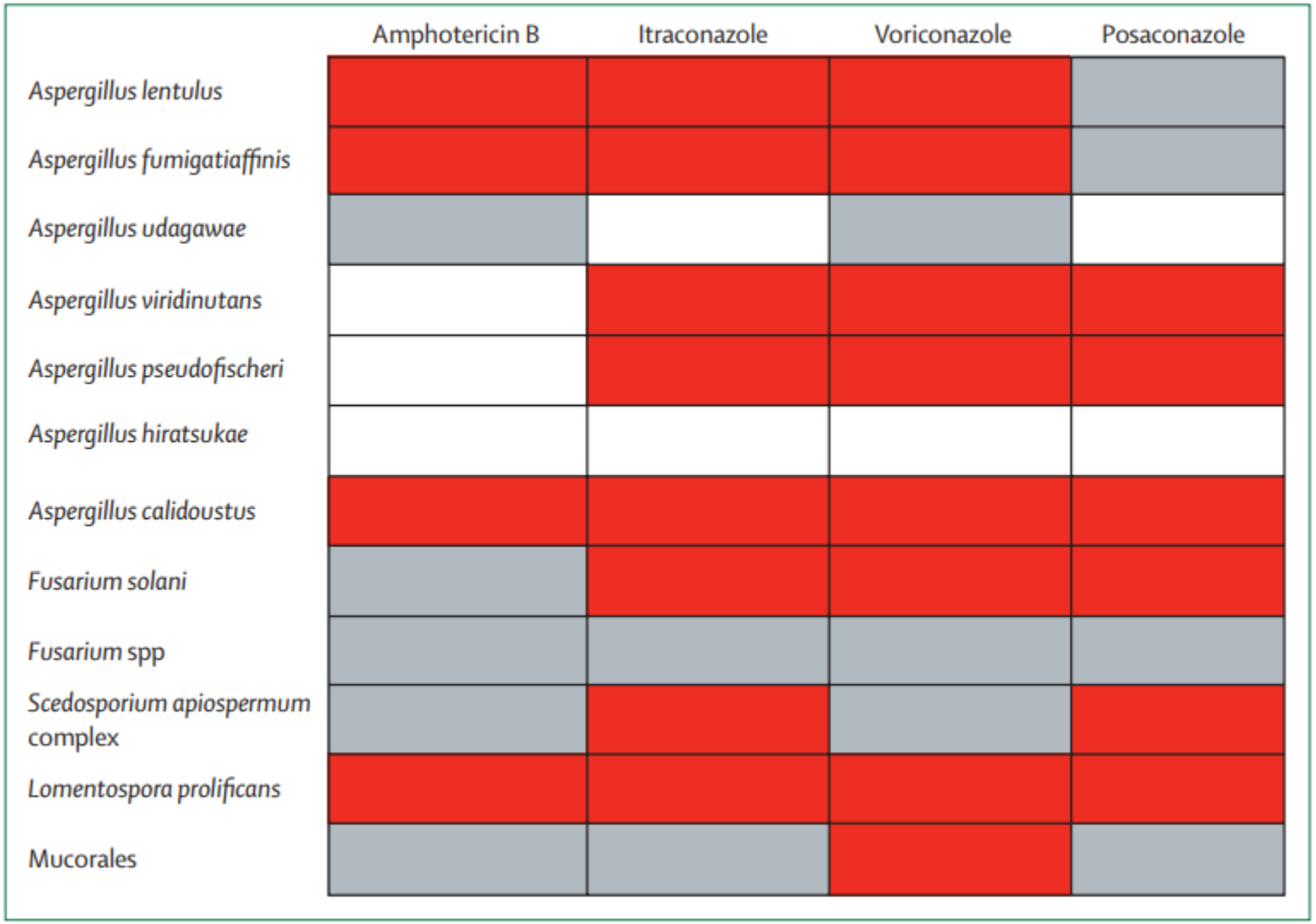
Treatment of IPA- IDSA 2016

Condition	Primary Therapy	Alternative Therapy	Duration
Invasive pulmonary aspergillosis (IPA)	Voriconazole • 6 mg/kg IV Q12h x1d, 4 mg/kg IV Q12h • 200-300mg PO Q12h or weight based	Primary: • Liposomal AmB 3-5 mg/kg/d IV • Isavuconazole 200mg Q8h x6 doses, 200mg daily Salvage: • ABLC 5 mg/kg/d IV • Caspofungin 70 mg/d IV x1d, 50 mg/d IV • Micafungin 100-150mg/d IV • Posaconazole oral suspension 200mg TID; tab 300mg BID x1d then QD; 300mg IV BID x1d then 300 QD • Itraconazole susp 200mg PO Q12h	• Minimum 6-12 weeks, largely dependent on degree and duration of immunosuppression, site of disease, evidence of disease improvement • If require subsequent immunosuppression, secondary prophylaxis should be initiated to prevent recurrence

Evaluate treatment response after 1 week

Patterson TF, et al. CID 2016

Antifungal resistance in less common fungal species



Perlin DS, et al. Lancet Infect Dis. 2017 Dec;17(12):e383-e392.

In Vitro Activity of Antifungal Agents

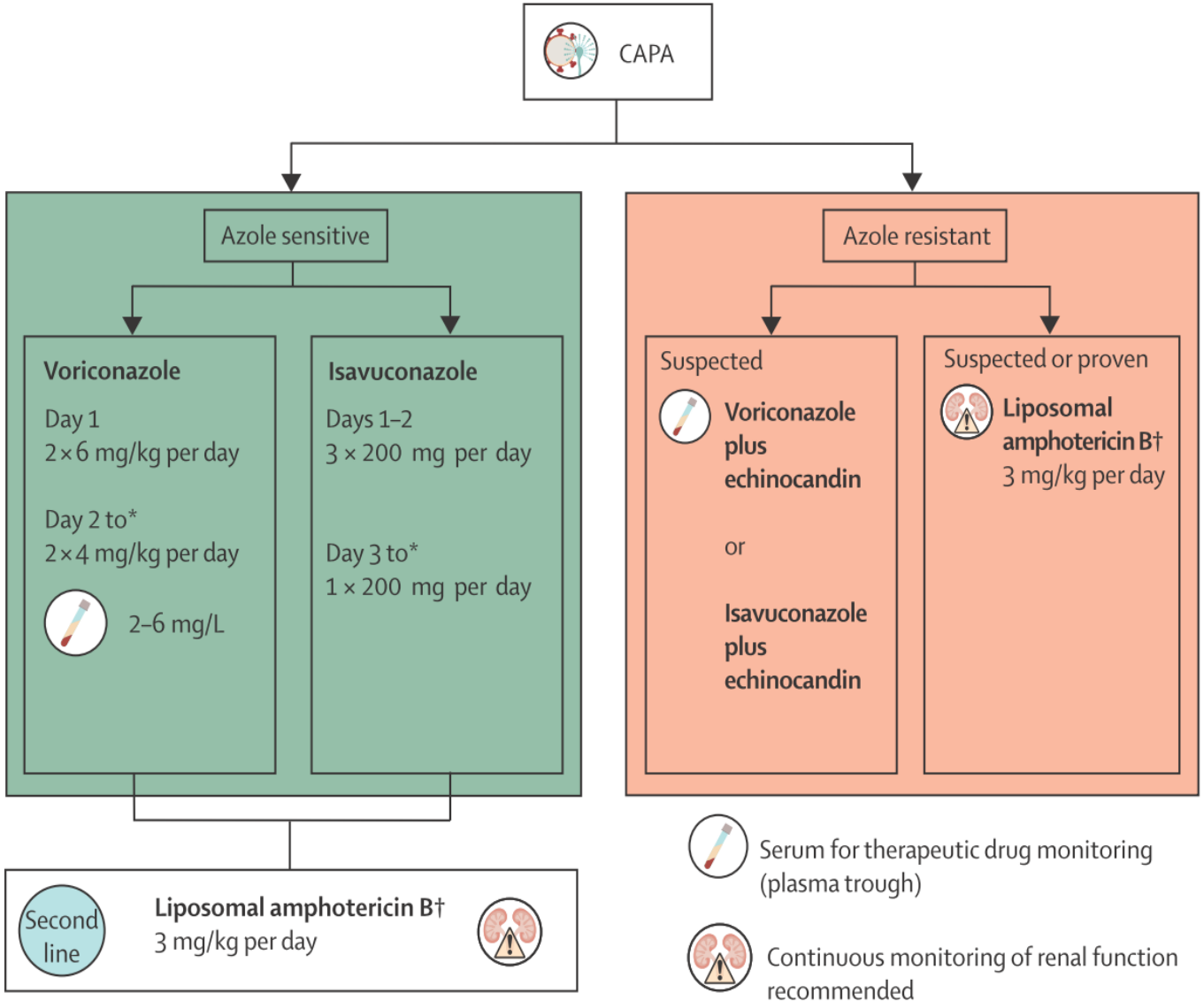
	Candida[a]	*Cryptococcus*[a]	*Aspergillus*[b,c]	*Fusarium*[b,d]	*Mucor*[b,e]
Echinocandins	++++	-	++	-	-
Fluconazole	+++	+++	-	-	-
Itraconazole	+++	++	++	+	-
Voriconazole	++++	+++	+++	+	-
Posaconazole	++++	+++	+++	+	+
Isavuconazole	++++	+++	+++	+	+
Amphotericin B	++++	+++	+++	++	++

a. Pfaller MA, et al. Diagn Microbiol Infect Dis. 2015;82:303-313; b. Sabatelli F, et al. Antimicrob Agents Chemother. 2006;50:2009-2015; c. The European Committee on Antimicrobial Susceptibility Testing. Accessed September 9, 2022. https://www.eucast.org/; d. Al-Hatmi AMS, et al. J Antimicrob Chemother. 2015;70:1068-1071; e. Arendrup MC, et al. Antimicrob Agents Chemother. 2015;59:7735-7742.

Adjunctive Measures for IA

- Reduces doses of **immunosuppressive agents** if feasible
- Colony-stimulating factors may be considered in neutropenic patients
- Granulocyte transfusions can be considered in refractory IA
- Secondary prophylaxis should be considered if immunosuppression is needed in successfully treated IPA
  - **Posaconazole (high quality evidence)**
  - Voriconazole (moderate quality evidence)

Treatment of CAPA-ECMM/ISHAM 2020



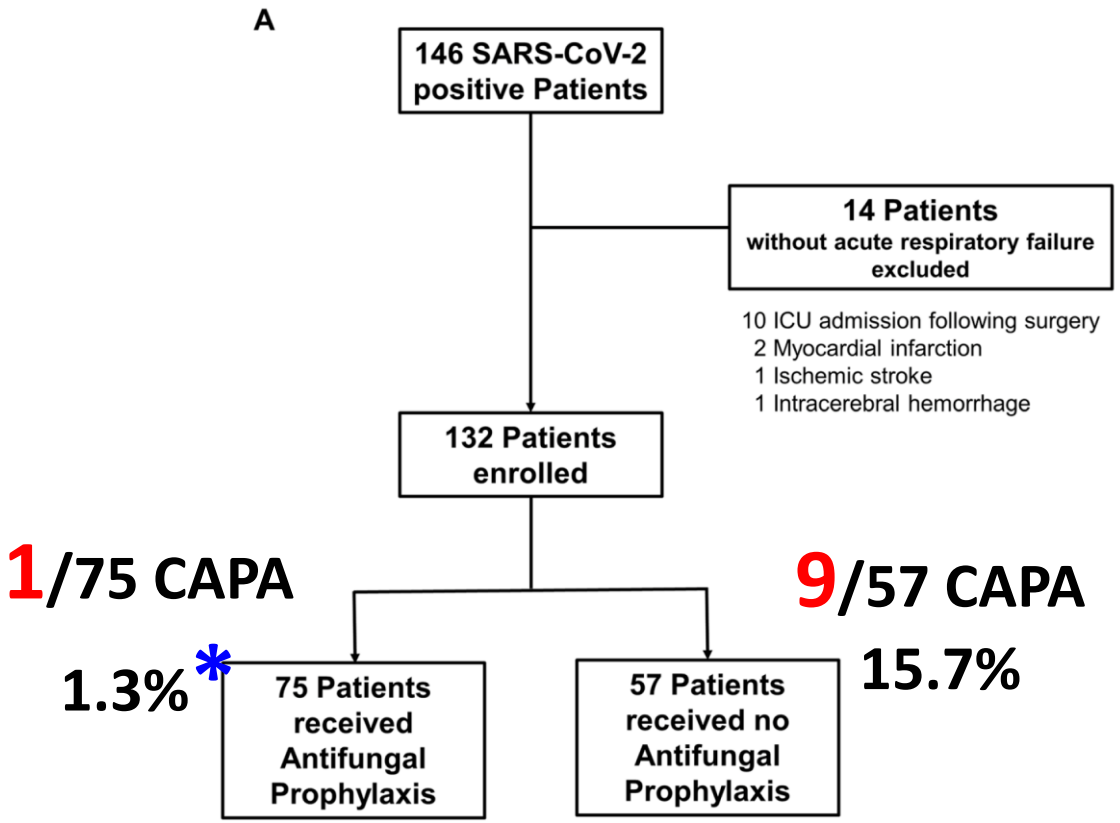
- Voriconazole
  - Narrow therapeutic window
  - Drug-drug interaction
  - Possible interaction with RDV (not fully understood)
- Optimal treatment duration unknown: 6-12 weeks
- No drugs are licensed for prophylaxis

Koehler P, et al. Lancet Inf Dis 2021

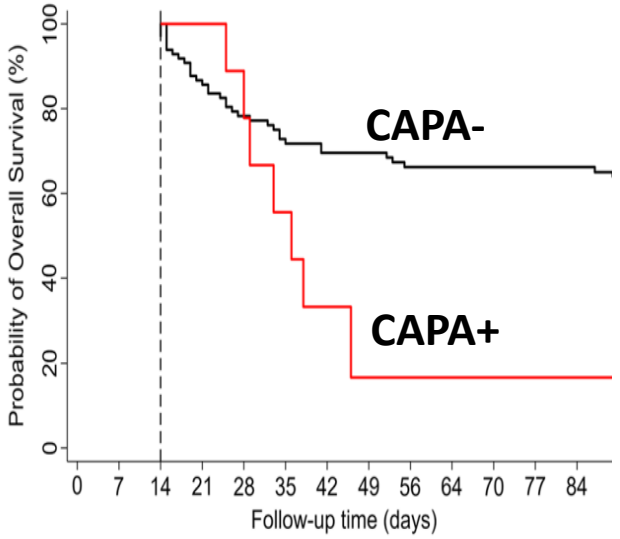
Antifungal prophylaxis for prevention of CAPA in critically ill patients: an observational study

Single center observational study in Austria

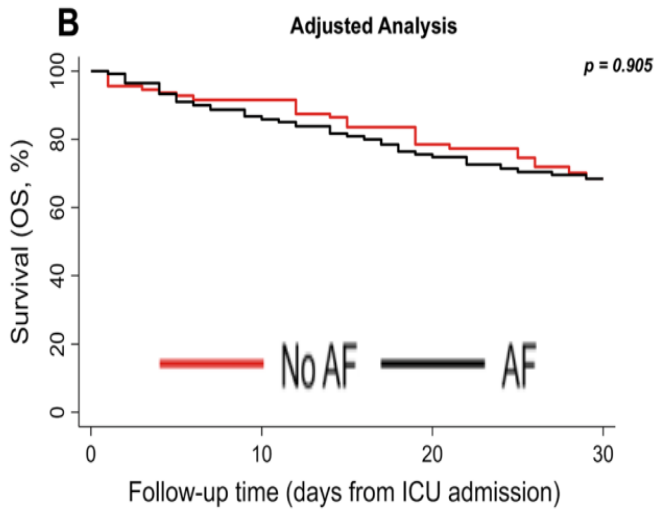
132 COVID-19 in ICU, 57% with posaconazole prophylaxis



Survival vs. CAPA



Survival vs. AF



Inconclusive, RCTs required

Hatzl S, et al. Crit Care 2021

Consideration of PK/PD in anti-fungal

	Voriconazole	Isavuconazole	Posaconazole	Liposomal Amphotericin B
Dosage	IV: 6 mg/kg Q12 × 24 h, 4 mg/kg Q12 starting Day 2 PO: 200 mg Q12 h	IV: 200 mg Q8 h × 48 h, 200 mg daily starting Day 3 PO: 200 mg Q8 h for 48 h, 200 mg daily starting Day 3	IV: 300 mg Q12 × 24 h, 300 mg daily starting Day 2 Delayed-release: 300 mg Q12 ×24 h, 300 mg daily starting Day 2 Oral suspension: 200 mg TID	IV: 3 mg/kg/day
Formulation	PO, IV	PO, IV	PO, IV	IV
Half-Life (h)	6	110–115	27–35	7–10
Bioavailability	Oral, 96%	Oral, 98%	Tablet: 54%Oral suspension: Variable	Oral, 9%
Linear PK	No	High	IV: NoSuspension/Tablet: High	Yes, doses 1–3 mg/kg; No at higher doses
Renal Excretion	2%	<1%	<1%	4.5%
CNS Penetration	High	High (Animal Model)	Low	High (Animal Model)
Metabolism	CYP2C19, CYP2C9, CYP3A4	CYP3A4/5	UGT	Unknown

TDM: twice in the frist week

Jenks JD, et al. J Fungi 2018

TABLE 3
Effect of coadministered drugs on triazoles

	Effect on the triazole			
Coadministered drug	**Voriconazole**	**Posaconazole**	**Itraconazole**	**Fluconazole**
Cimetidine (pH effect and CYP3A4 inhibitor	Not clinically significant	↓ AUC by 39%. Contraindicated	↓ AUC. Acid-reducing agents should be avoided	↓ serum level only with oral administration
Rifabutin (UDP-G and CYP inducer)	↓ serum level Contraindicated	↓ AUC by 50%. Contraindicated	↓ serum level by 90%	–
Phenytoin (UDP-G and CYP inducer)	↓ serum level Increase empirical dosage TDM recommended	↓ AUC by 50%. Contraindicated	↓ serum level by 90%	–
Carbamazapine	↓ serum level Contraindicated	–	↓ serum level Contraindicated	–
HIV protease inhibitors (CYP inhibitor)	↑ serum level TDM recommended	–	↑ serum level Check individual agents. May need to limit itraconazole dose to 200 mg/day	Unlikely. Check individual agents
Ritonavir (CYP inducer) **Paxlovid**	↓ serum level Administration with high-dose ritonavir is contraindicated TDM with low-dose ritonavir	–	↑ serum level Limit itraconazole dose to 200 mg/day	–

Laverdiere M, et al. Can J Infect Dis Med Microbiol 2014

Key Toxicities of Systemic Antifungal Agents

Hepatic

- All azoles
- Amphotericin B
- 5-FC
- Echinocandins

Renal toxicity

- Amphotericin B
- Cyclodextrins possibly toxic (IV voriconazole)

CNS

- Voriconazole

Photopsia

- Voriconazole

Cutaneous

- Rash (all antifungal agents)
- Photosensitivity/ malignancy? (Voriconazole)

GI

- Itraconazole
- Posaconazole
- 5-FC

Cardiac

- Cardiomyopathy (itraconazole)
- QTc prolongation (all azoles, especially with drug interactions)

Infusion reactions

- Amphotericin B
- Echinocandins

Bone marrow suppression

- 5-FC
- Amphotericin B (anemia associated with decreased epoetin production)

CNS, central nervous system; GI, gastrointestinal; QTc, corrected QT interval.

Lewis RE. Mayo Clin Proc. 2011;86:805-817.

IDST recommendation for CAPA- 2023

Disease	Recommendation	Strength of Recommendation/ Quality of Evidence
COVID-19 Associated Pulmonary Aspergillosis (CAPA)	**I. Diagnosis**	
	1. We suggest modified AspICU or ECMM/ISHAM consensus for the diagnosis of CAPA	Weak/Very low (2D)
	3. Considering the feasibility of the diagnostic procedure, non-directed BAL may be an alternative to directed BAL to aid in the diagnosis of CAPA	Weak/Very low (2D)
	II. Prophylaxis and treatment	
	1. We suggest against routine antifungal prophylaxis in COVID-19 patients based on currently available data	Weak/Very low (2D)
	3. We recommend antifungal treatment for proven, probable, possible, and putative CAPA.	Strong/Moderate (1B)
	4. Single or sequential monotherapy with voriconazole (VOR), isavuconazole (ISZ), posaconazole (POS), liposomal-amphotericin B (L-ampB) is recommended	Strong/Low (1C)
	5. Amphotericin-B deoxycholate (AmpB-d)[b] and echinocandins[c] may be considered as an alternative therapy	Strong/Low (1C)

Wu HY, et al. JMII 2023

IDST recommendation for CAPA- 2023

Disease	Recommendation	Strength of Recommendation/ Quality of Evidence
COVID-19 Associated Pulmonary Aspergillosis (CAPA)	7. We suggest reference to the local prevalence rate of resistance or the drug susceptibility test when choosing the drug of choice in antifungal regimens when sequential monotherapy or combination therapy is considered	Weak/Low (2C)
	8. Combination therapy may be considered if drug-resistant fungal infection is a concern[e], such as when coinfections may be due to triazole-resistant *Aspergillus* spp., or when coincidence of triazole-resistant *Candida* spp. Or mucormycosis occurs in CAPA	Weak/Low (2C)
	9. We suggest that the treatment duration of antifungal agents should be determined by the clinical and laboratory evidence of treatment response, such as serum GM testing and chest imaging, and may be discontinued after 6—12 weeks, after a comprehensive evaluation for risk of recurrence	Weak/Very low (2D)

Wu HY, et al. JMII 2023

The Take Away…..

- Invasive pulmonary aspergillosis should be considered in ICU patients with specific risk factors
  - Not only in patients with neutropenia
  - Other host factors: COPD, cirrhosis, prolonged corticosteroid, influenza, COVID-19
- Pathophysiology of CAPA remains uncertain
  - Airway epithelium damage following SARS-CoV-2 infection
  - Corticosteroid, immunotherapy, immune dysfunction further increase the risk
- Diagnosis of IPA is based on host factors/clinical factors/mycology evidences
  - Colonization is possible
  - Keep aspergillus tracheobronchitis in mind
- Galactomannan and Asp. PCR are not perfect diagnostic tools
  - Combination may improve sensitivity and specificity

The Take Away…..

- Treatment of choices is voriconazole for CAPA and IPA
  - Alternative choices: isavuconazole and amphotericin B
  - Treatment duration 6-12 weeks, depends on immune characteristics
  - Consider prophylaxis after IPA treatment if immune suppression required

- Serum level of voriconazole/Posaconazole is highly variable
  - Drug-drug interaction, critical illness, renal/hepatic dysfunction
  - TDM is required in voriconazole and Posaconazole
  - TDM twice in the first week,
  - Further TDM should be considered when
    - Addition of interacting drug
    - Unstable renal/liver function
    - Treatment failure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VGHTPE
CHEST
INFECTION IMMUNOLOGY

Mold susceptibility profile

Species	Antifungal						
	ANF	FC	FLC	ITC	VRC	POS	EQUIN
A. fumigatus	S	R	R	S	S	S	S
Aspergillus flavus	S-I	R	R	S	S	S	S
Aspergillus terreus	I-R	R	R	S	S	S	S
Aspergillus niger	S	R	R	S-I-R**	S	S	S
Fusarium spp.	S-I-R**	R	R	R	S-I-R**	S-I-R**	R
Scedosporium spp.	S-I-R**	R	R	R	S-I-R**	S-I-R**	R
Mucorales	S-I-R**	R	R	R	R	S-I-R**	R