

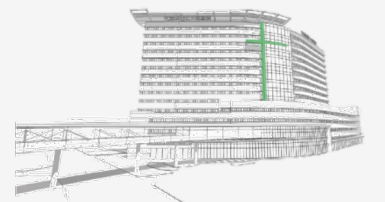


The Evolution of Invasive Mold Infections in Asia What We Had Learned in the Period of COVID-19 Pandemic

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Disclosures

Speaker for Pfizer, Gilead, AstraZeneca, and GlaxoSmithKline

Advisory board for Pfizer, Gilead

Research grand from Pfizer, Merck Sharp & Dohme

Presented at MMTN August 4–6 2023.
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Disclaimer

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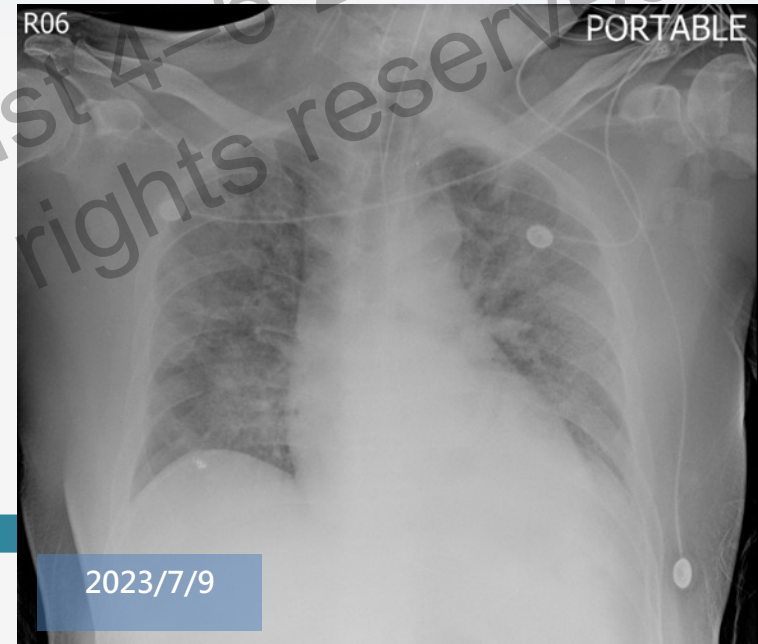
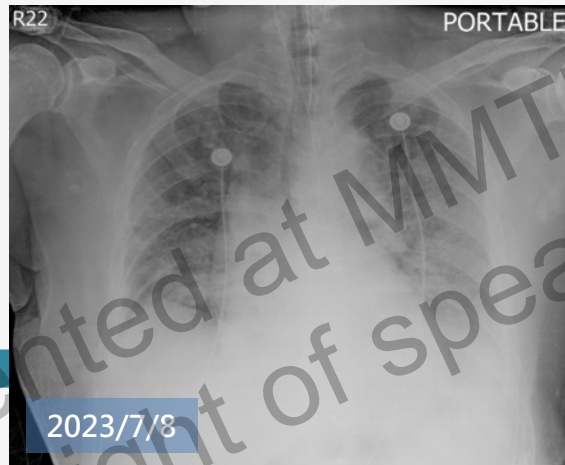
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Patient scenario

57 y/o man

- HTN, gout, hyperlipidemia
- Cough, shortness of breath for 3 days
- COVID-19 rapid screen test: Positive

Progressive dyspnea
Low grade fever



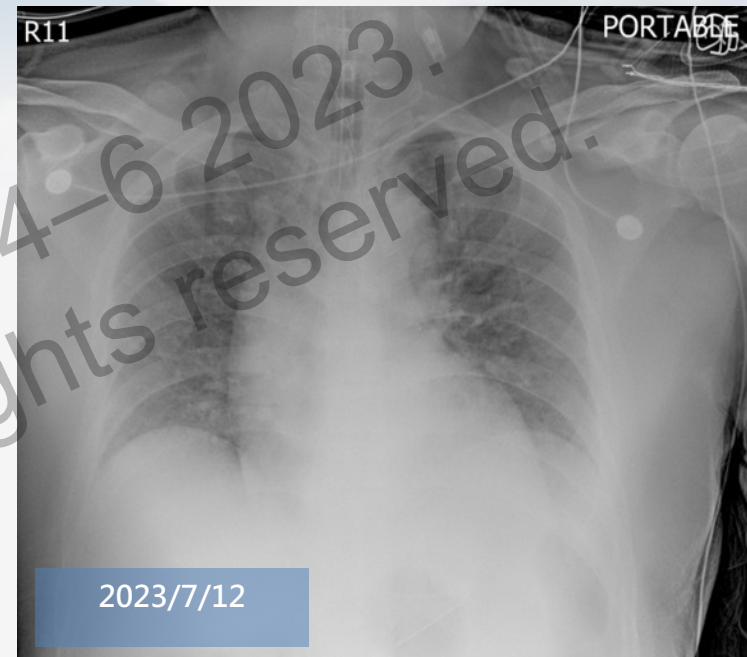
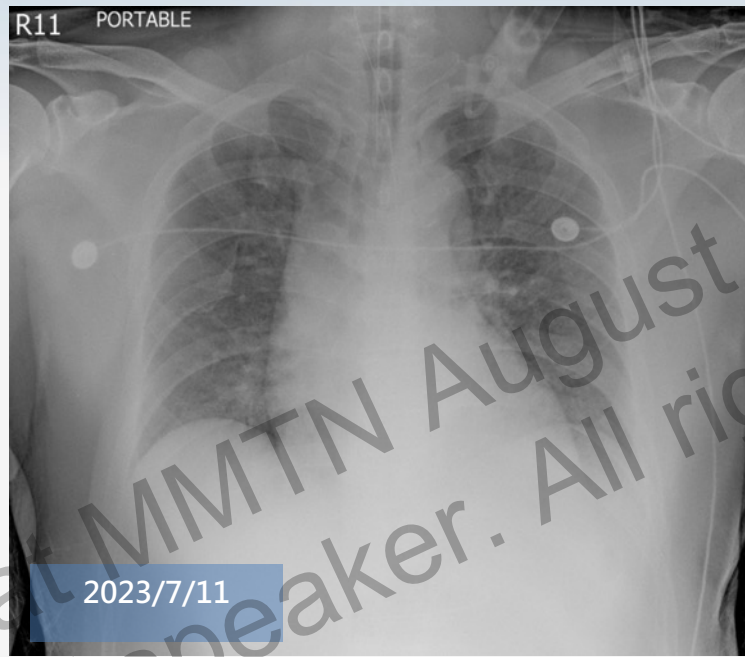
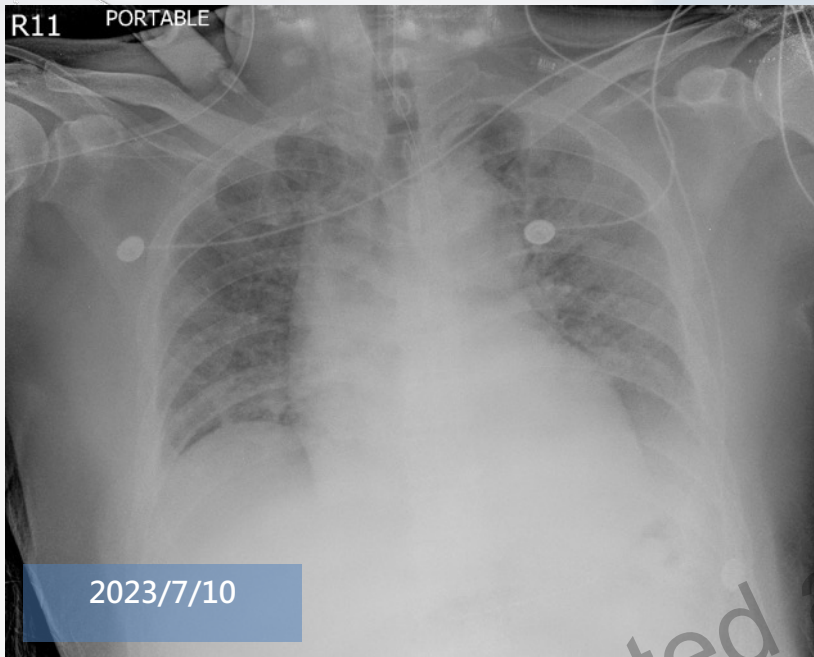
ER

ICU

- Desaturation under ambient air (SpO₂: 73%)
- **COVID-19 PCR: Positive (Ct 18.16)**

- **SARS-CoV-2 infectious pneumonia with acute respiratory failure**
- Elevated CRP (23.87 mg/dL), D-dimer: 960.8 (ng/mL)
- Procalcitonin: 0.24 (ng/mL)

Patient scenario



MICU

ICU day 3

Under MV support

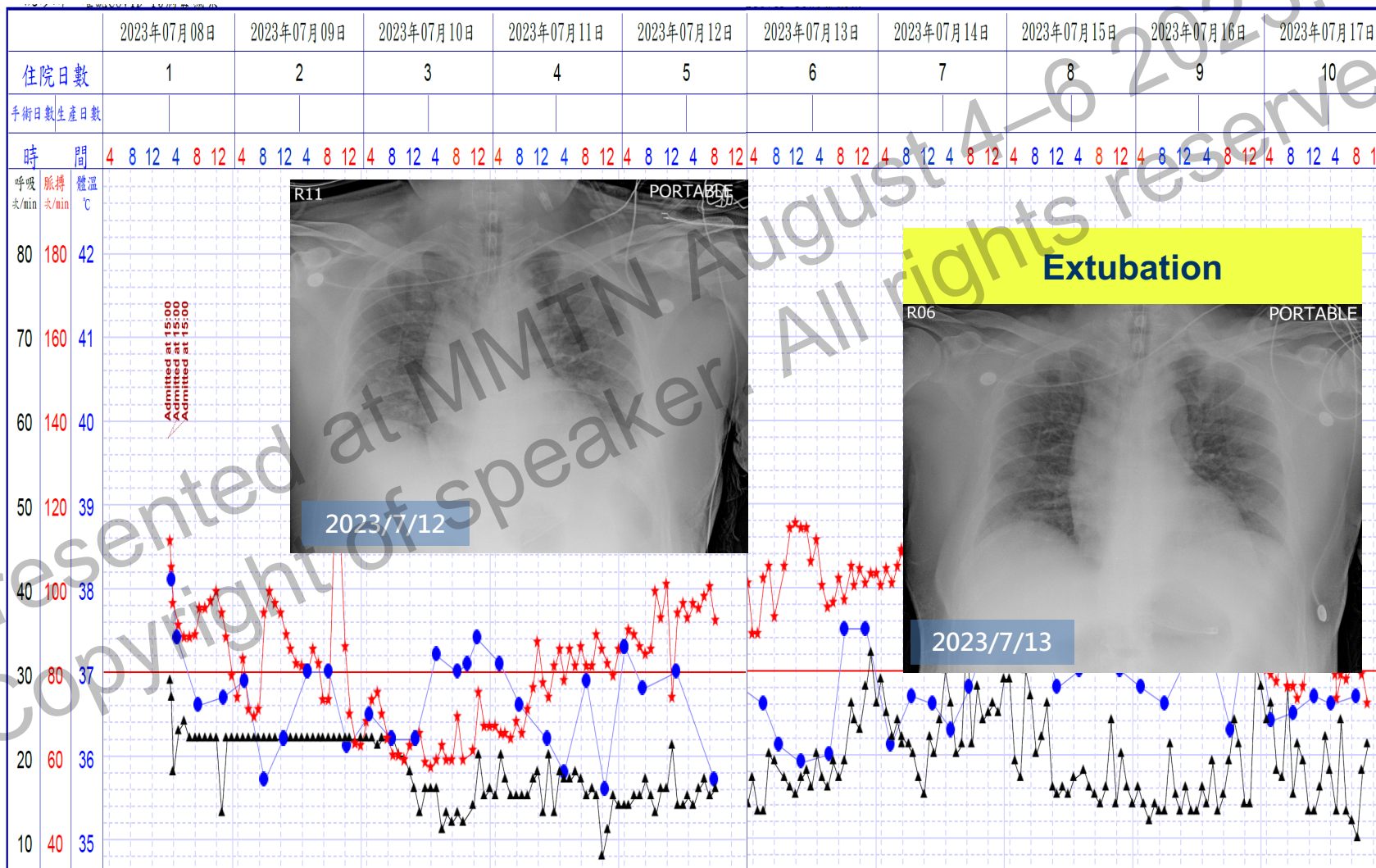
Remdesivir
Dexamethasone
Tocilizumab
Empirical Abx Ceftaroline

Endotracheal aspirate (ETA):
Aspergillus Ag (GM): 0.147
Aspergillus LFA: 0.000
Aspergillus PCR: Negative
Serum *Aspergillus* Ag(GM): 0.095

ICU day 5

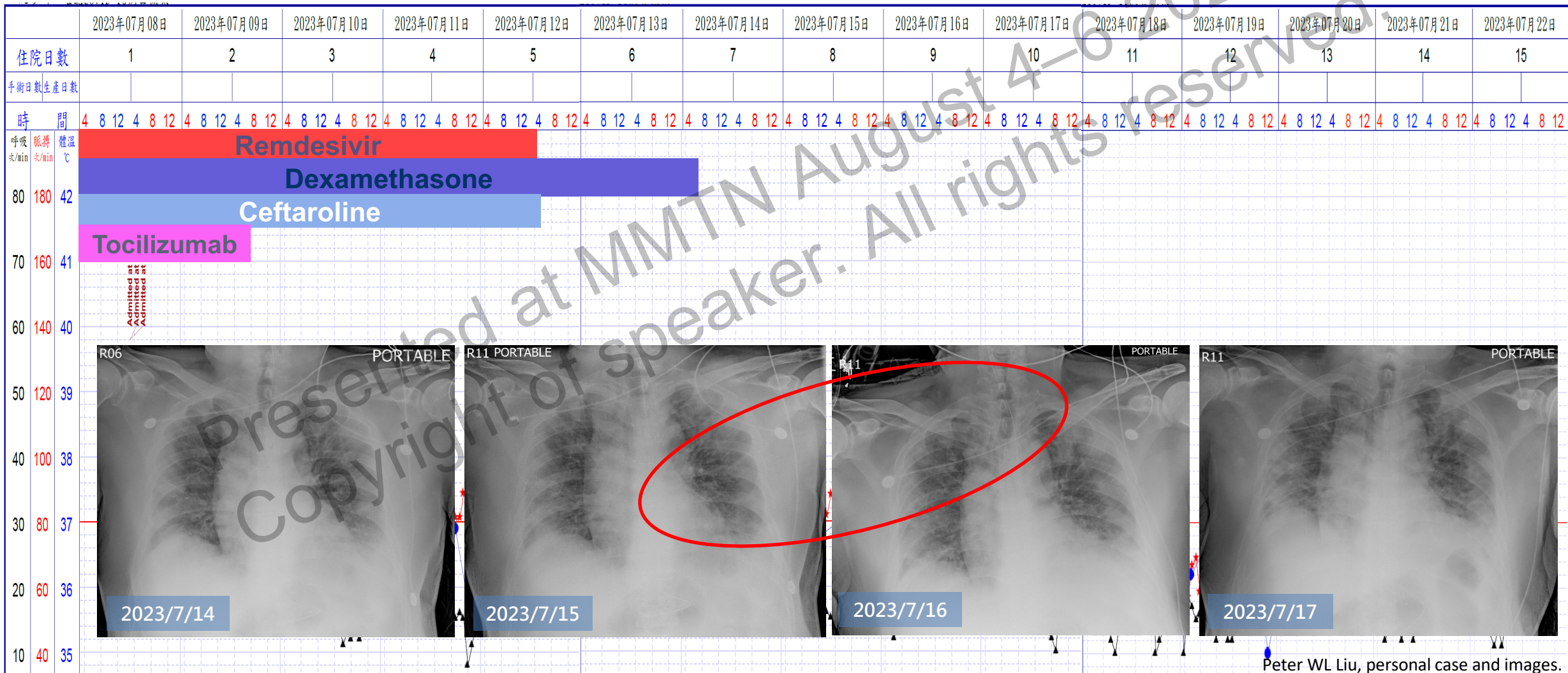
Peter WL Liu, personal case and images.

Clinical course





Clinical course



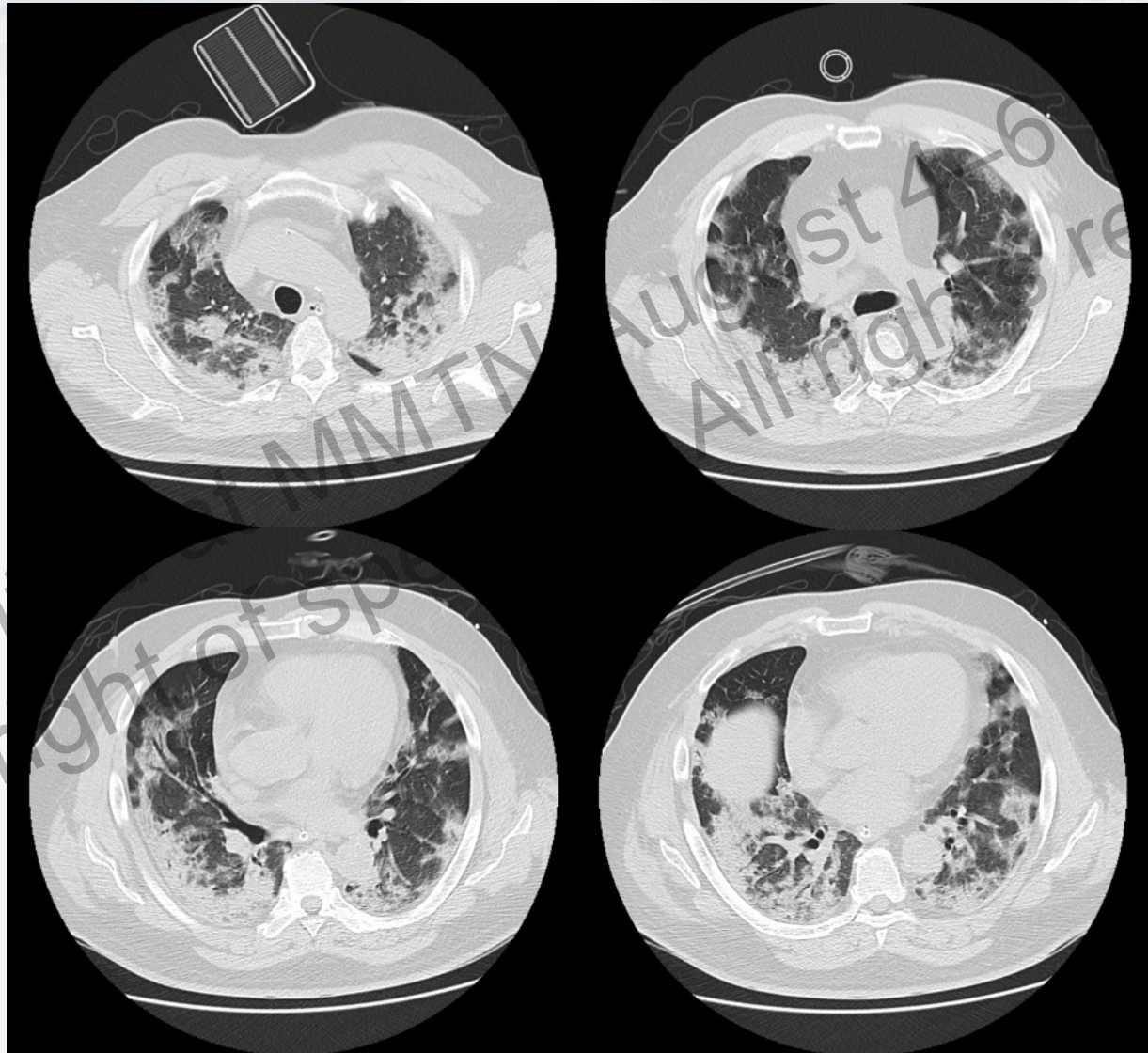
藍●表示體溫

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黑△表示呼吸



Chest CT



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Question

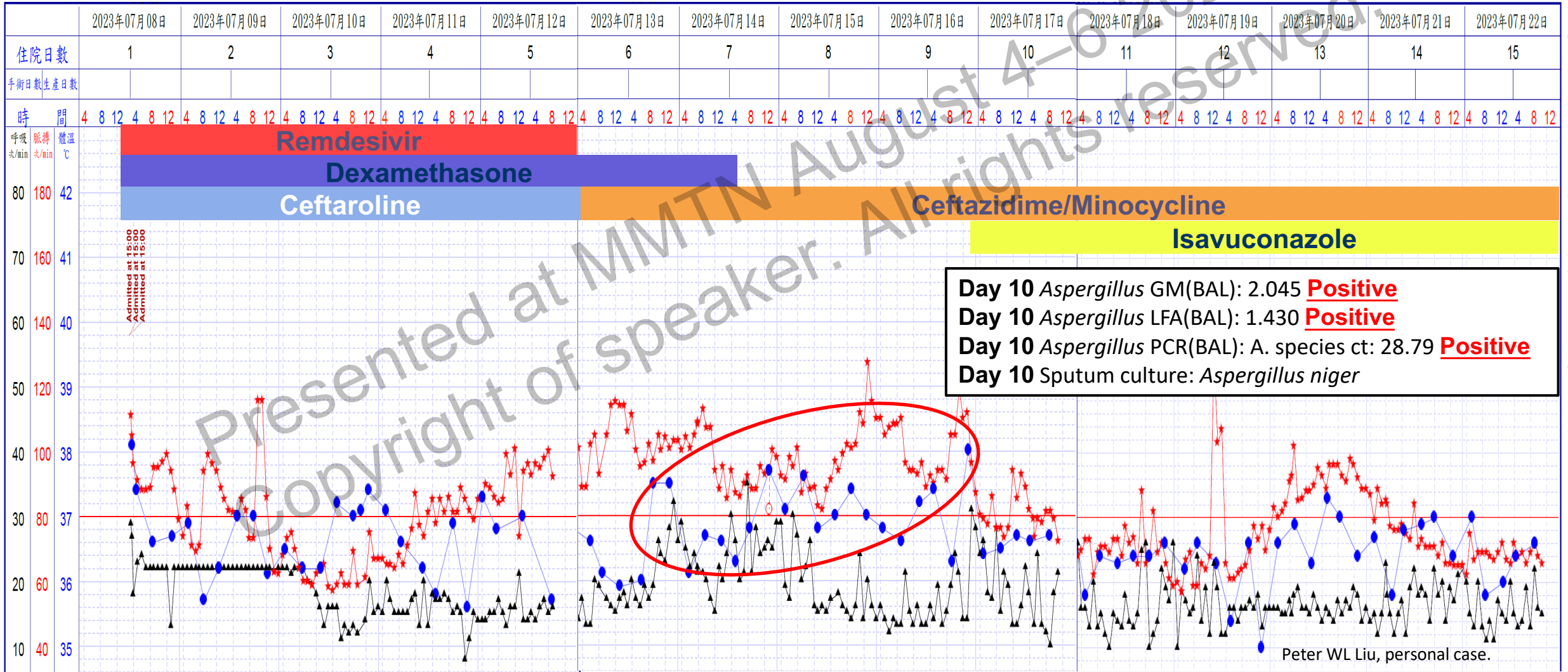
What is your treatment plan?

- (1) Escalate anti-bacterial agent
- (2) Restart remdesivir
- (3) Restart dexamethasone
- (4) Start anti-fungal agent
- (5) Others?

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Clinical course

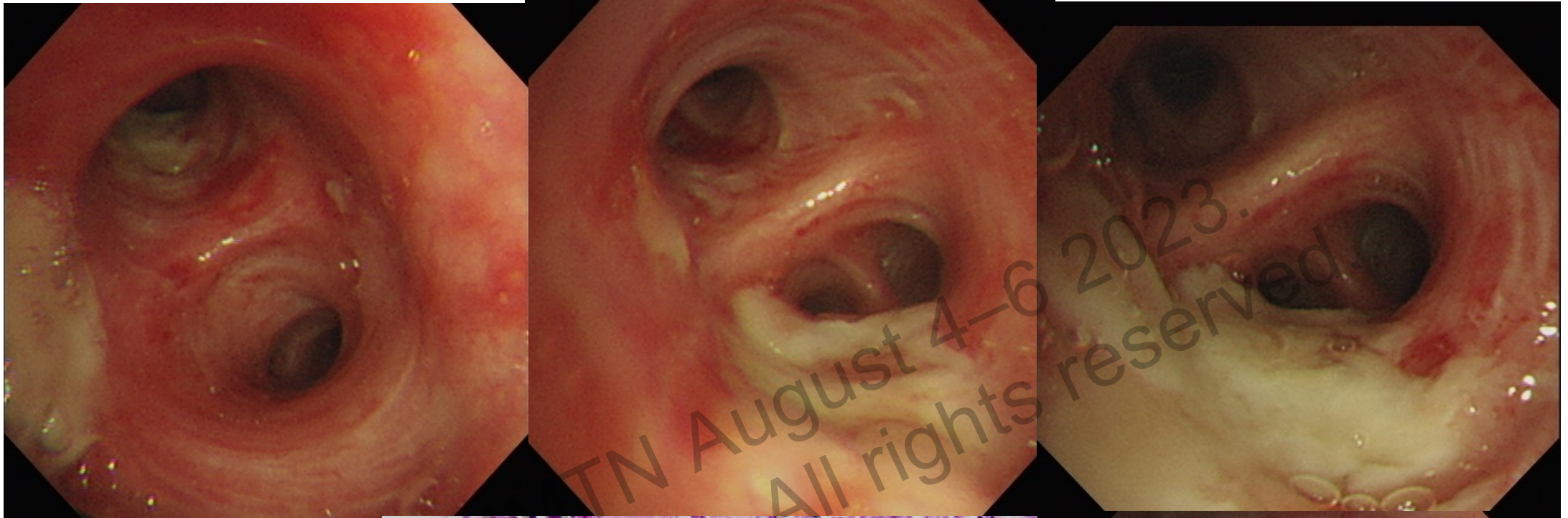
Day 06 S/C: Burkholderia cepacia



藍●表示體溫

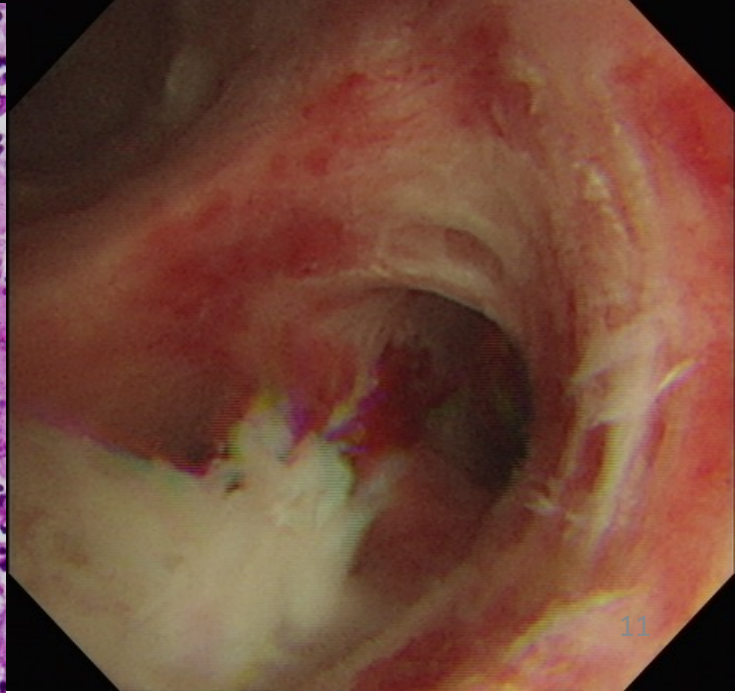
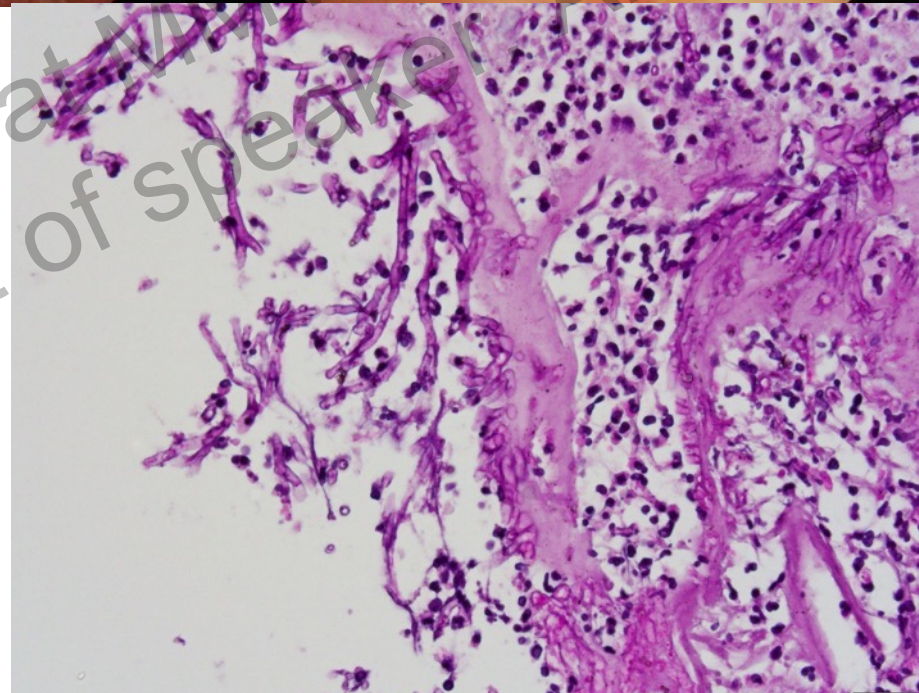
紅★表示脈搏

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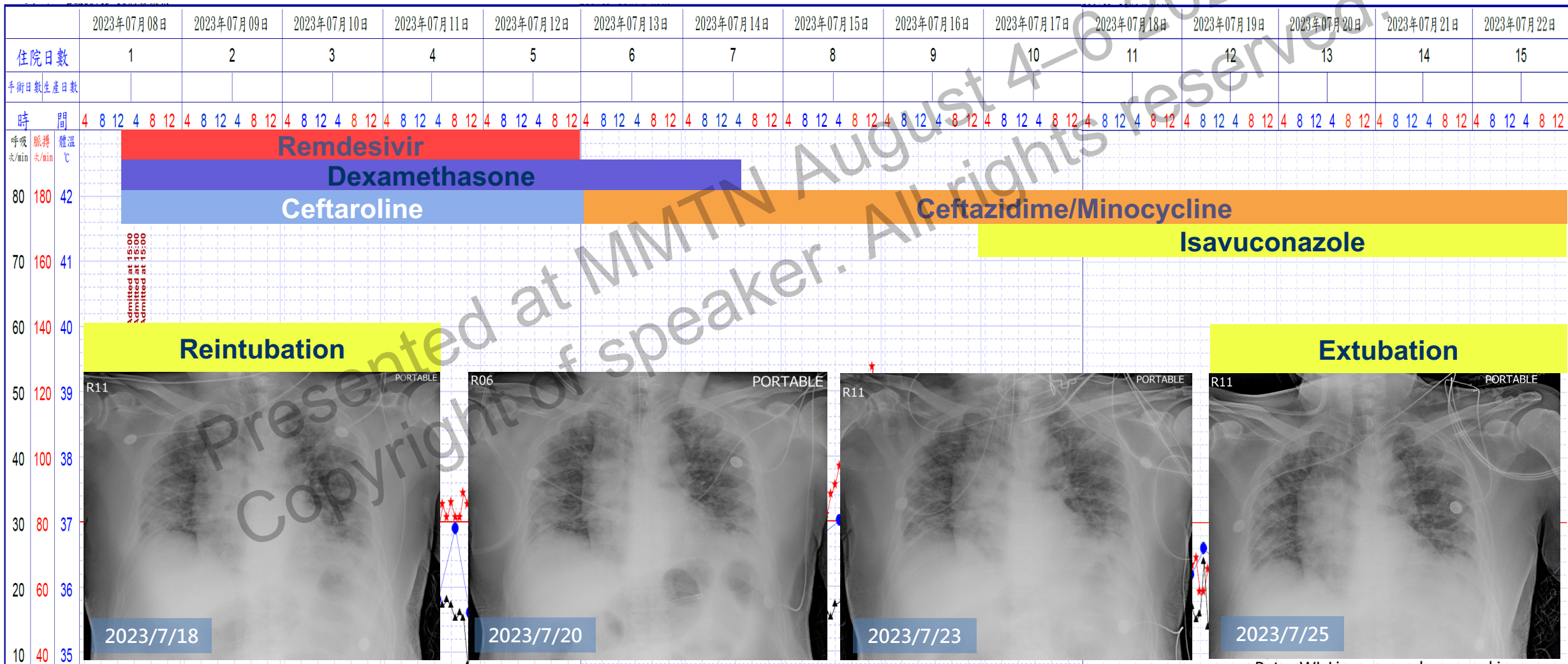
Bronchial biopsy

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



Clinical course

Day 06 S/C: Burkholderia cepacia



藍●表示體溫

紅★表示脈搏

黑△表示呼吸

Evolving risk factors for invasive mold infections

Time → 2005 2010 2015 2020

Risk factors for invasive aspergillosis

Invasive aspergillosis in the ICU:

- Haematological malignancy¹
- Neutropenia¹
- Allogeneic haematopoietic stem-cell transplantation¹
- Solid organ (lung) transplantation¹

Invasive aspergillosis in the ICU:

- Prolonged treatment with corticosteroids before admission to the ICU¹
- Chronic obstructive pulmonary disease¹
- Liver cirrhosis¹

Critically ill with viral pneumonitis

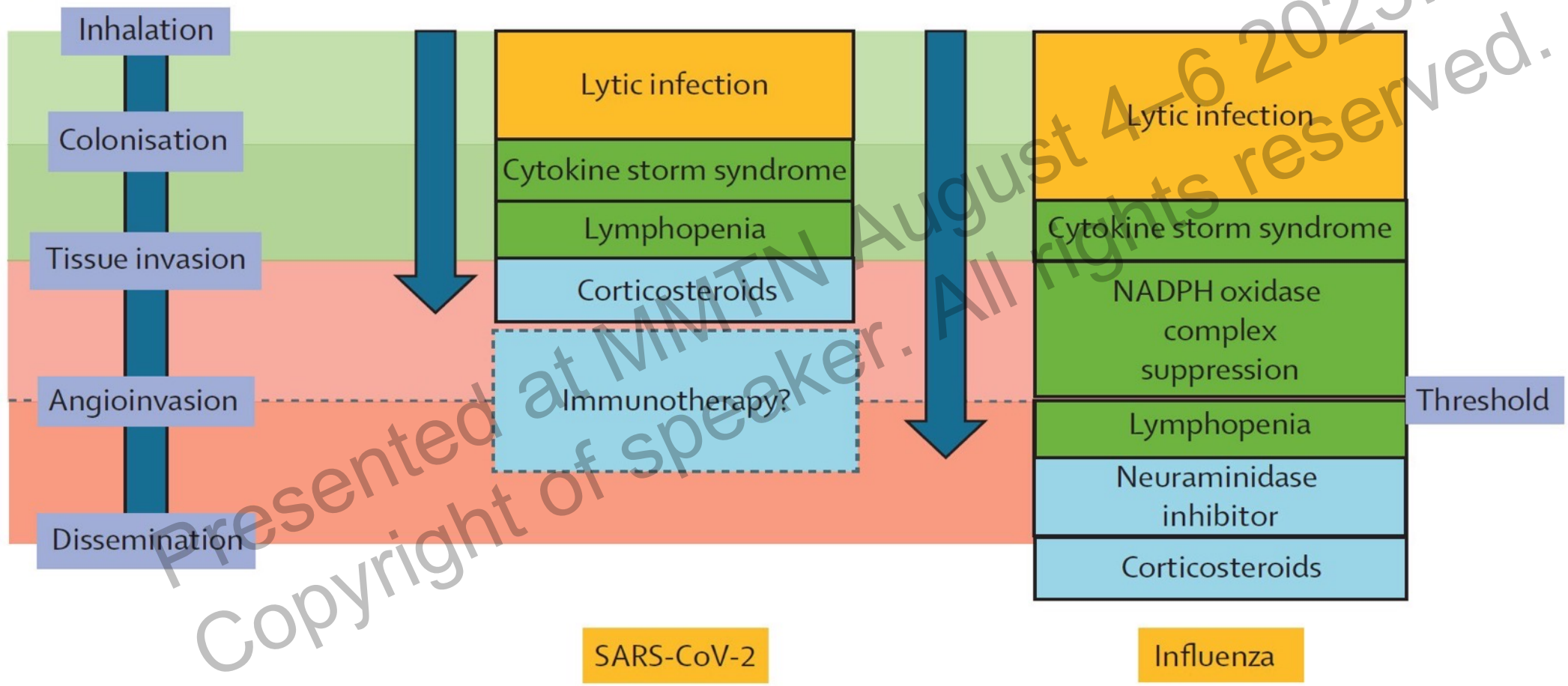
Influenza²

COVID-19³

Genetic polymorphisms?
 European Organisation for Research and Treatment of Cancer and
 Mycoses Study Group Education and Research Consortium factors

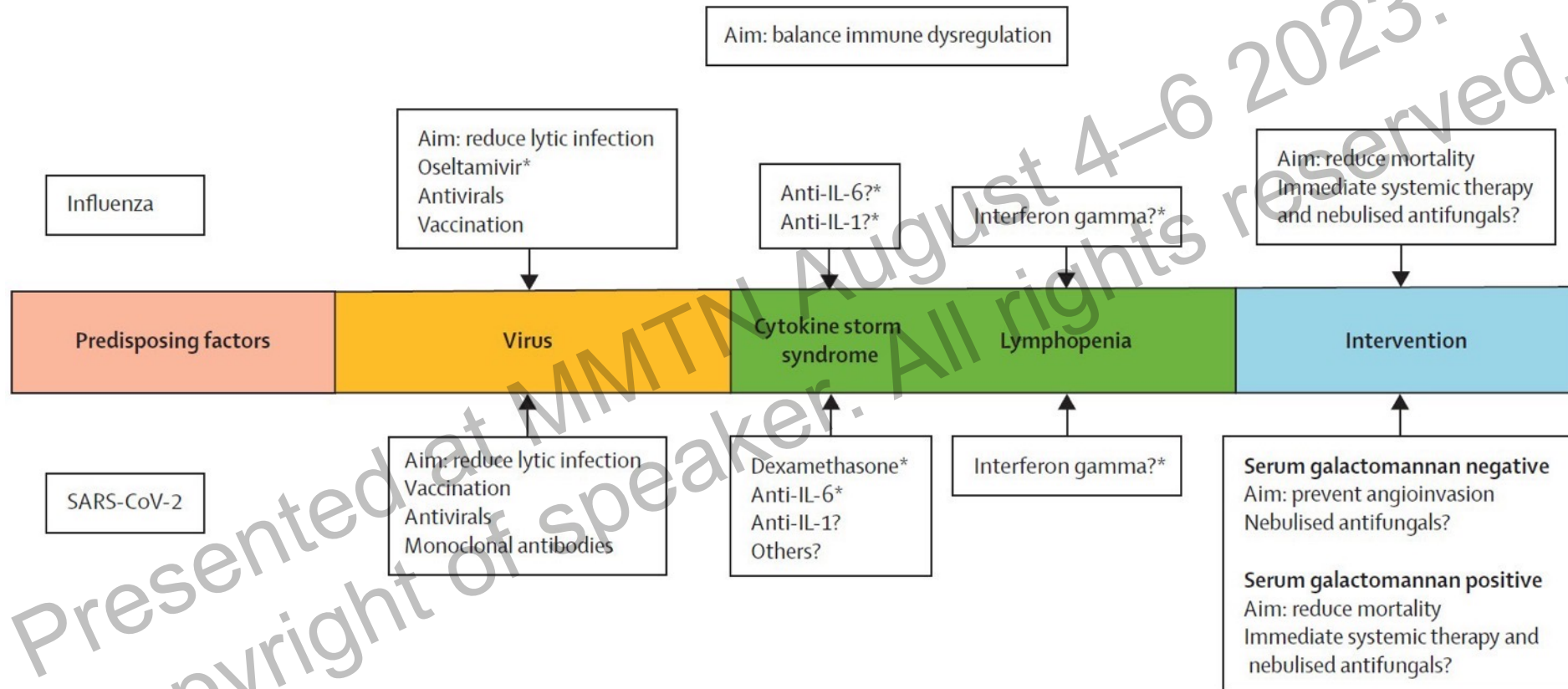
- Predisposing factors
- Virus
- Host
- Intervention

Aspergillus infection



NADPH, nicotinamide adenine dinucleotide phosphate hydrogen..

Interventions: *Aspergillus* tracheobronchitis



IL, interleukin; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2.

*Can have both beneficial and harmful effects on reaching threshold.

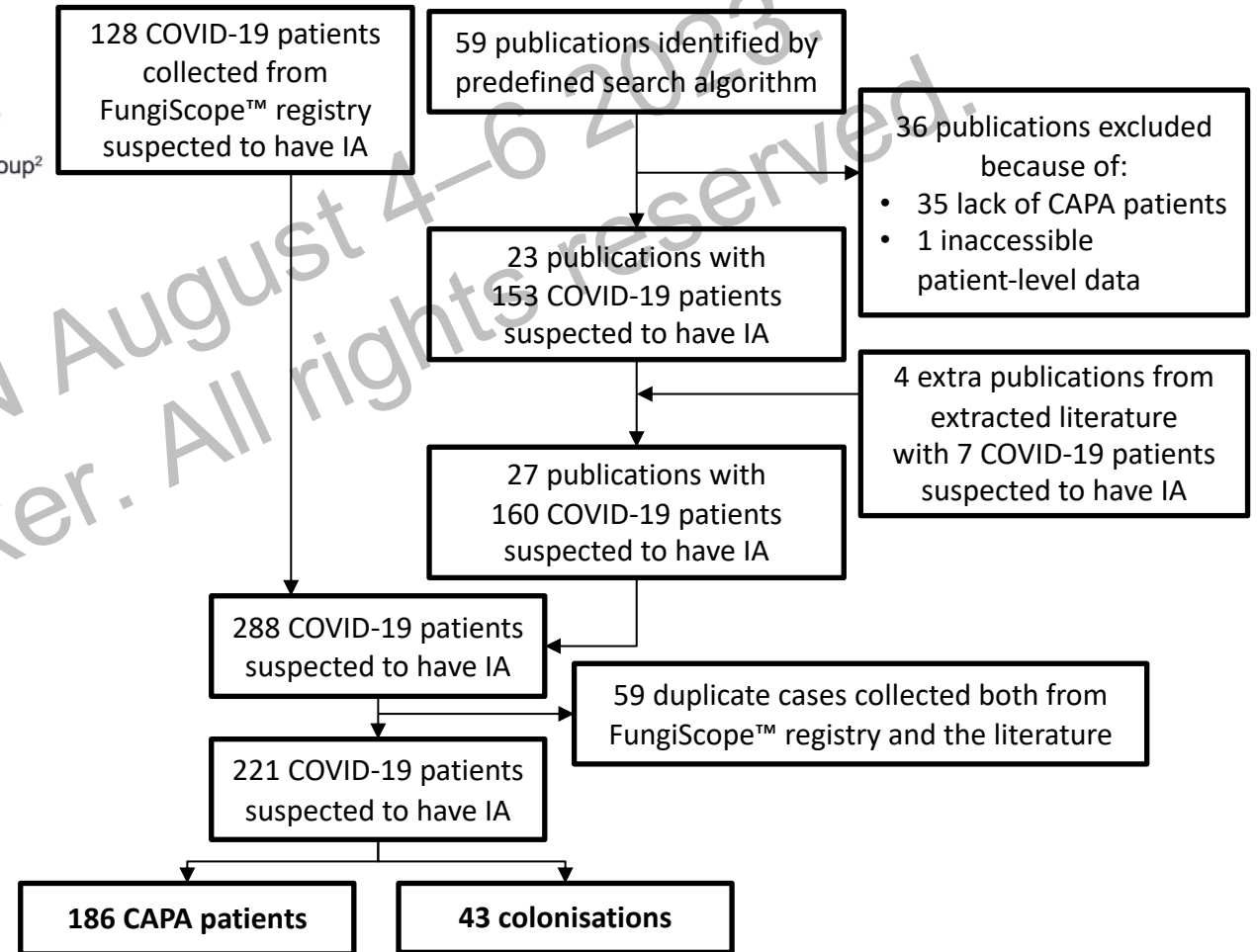
COVID-19–Associated Pulmonary Aspergillosis, March–August 2020

Jon Salmanton-García, Rosanne Sprute, Jannik Stemler, Michele Bartoletti, Damien Dupont, Maricela Valerio, Carolina Garcia-Vidal, Iker Falces-Romero, Marina Machado, Sofia 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 Group²

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

221 suspected cases

n=186 CAPA
n=43 colonisation

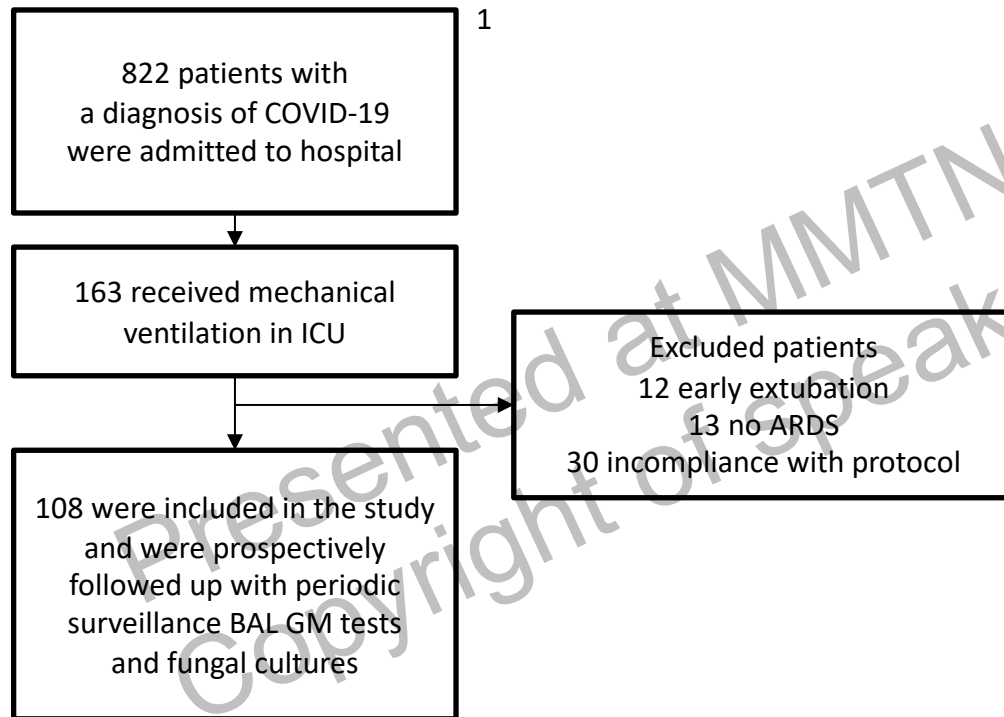


Epidemiology of CAPA

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

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

Michele Bartoletti,^{1,9} 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 Viale¹; for the PREDICO Study Group⁸



BAL at admission 0–2 days¹

BAL at 1 week ±2 days of MV¹

BAL upon clinical worsening¹

Definition IAPA (CAPA):¹

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

Definition AspICU (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*. 2021 Dec 6;73(11):e3606-e3614.
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	20 (18)	19 (63)	19 (100)	1 (1)
<i>A. fumigatus</i>	16 (15)	15 (50)	15 (79)	1 (1)
<i>A. niger</i>	3 (3)	3 (10)	3 (16)	0 (0)
<i>A. flavus</i>	1 (1)	1 (3)	1 (5)	0 (0)
BAL-positive GM (index >1)	30 (28)	30 (100)	18 (95)	0 (0)
Positive BAL GM on first determination (Day 0–2)	14 (13)	14 (47)	11 (58)	0 (0)
Positive BAL GM on second determination (Day 5–9)	9 (8)	9 (30)	4 (21)	0 (0)
Other BAL GM determination	5 (5)	7 (23)	4 (21)	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 <i>Aspergillus</i> PCR ^c	26/67 (38)	20/30 (67)	19/19 (100)	5/36 (14)

6/30 patients with tracheobronchitis

Risk factors for CAPA

Intubated Patients With COVID-19: A Prospective Study

Michele Bartoletti,^{1,6} 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 Viale¹; for the PREDICO Study Group⁸

Underlying diseases	CAPA (n=30)	No CAPA (n=73)	p value
Obesity, n (%)	10 (37)	34 (49)	0.36
BMI, median (IQR), kg/m ²	28 (26–31)	29 (26–31)	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

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. Italy²	822	108	30 (27.8%)	4 days	Steroids >16 mg/day >2 weeks	44% vs 19%
White, et al. Wales¹	257	135	19 (14.1%)	8 days	High-dose corticosteroids; Chronic respiratory disease	58% vs 38%
Dellière, et al. France³	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	

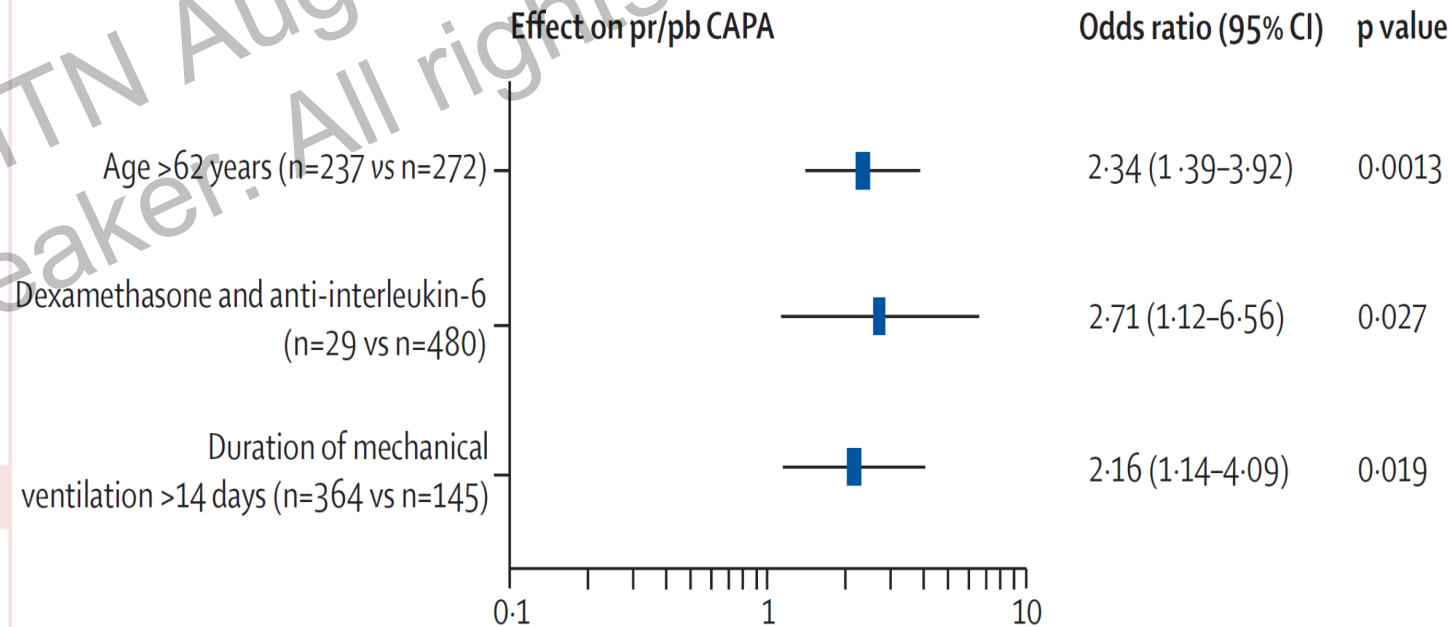
1. P White et al. *Clin Infect Dis*. 2021 Oct 5;73(7):e1634-e1644 2. Bartoletti M, et al. *Clin Infect Dis*. 2021 Dec 6;73(11):e3606-e3614
 3. Dellière S, et al. *Clin Microb Infect*. 2021;27(5):790.e1–790.e5. 4. Permpalung N, et al. 2021. *Clin Infect Dis*. <https://doi.org/10.1093/cid/ciab223>

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

Risk factors for CAPA

- Between Feb 29~July 9, 2020
- 509 COVID-19, MV patients
- 15% CAPA
- 1% CAM

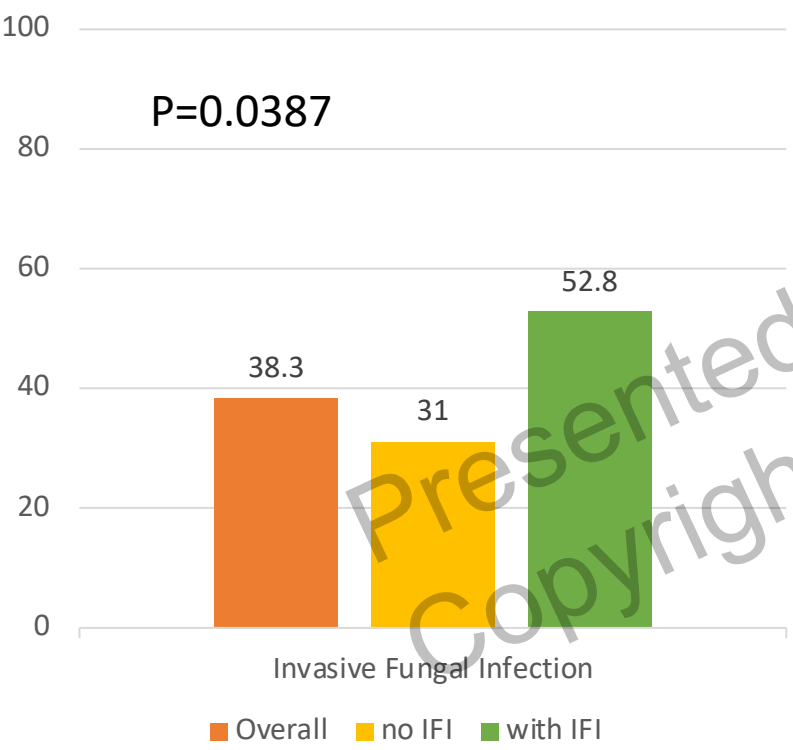
	Prevalence or duration
Prevalence of infections	
CAPA*: pr/pb invasive aspergillosis	76 (15%)
pr/pb invasive fungal infection other than pr/pb CAPA (one or more)	38 (7%)
Candidemia	32 (6%)
Invasive mucormycosis	6 (1%)
Invasive fusariosis	1 (<1%)
Bacterial ventilator-associated pneumonia (n=509)†	374 (73%)
Cytomegalovirus infection (n=491)†	49 (10%)
Herpes simplex virus type 1 infection (n=491)†	76 (15%)
Duration of antifungal treatment, days	
Fluconazole (n=30)‡	19.2 (20.4)
Caspofungin (n=70)‡	7.9 (9.1)
Liposomal amphotericin B (n=34)‡	11.8 (27.5)
Voriconazole (n=73)‡	15.2 (16.1)
Isavuconazole (n=15)‡	12.3 (6.1)



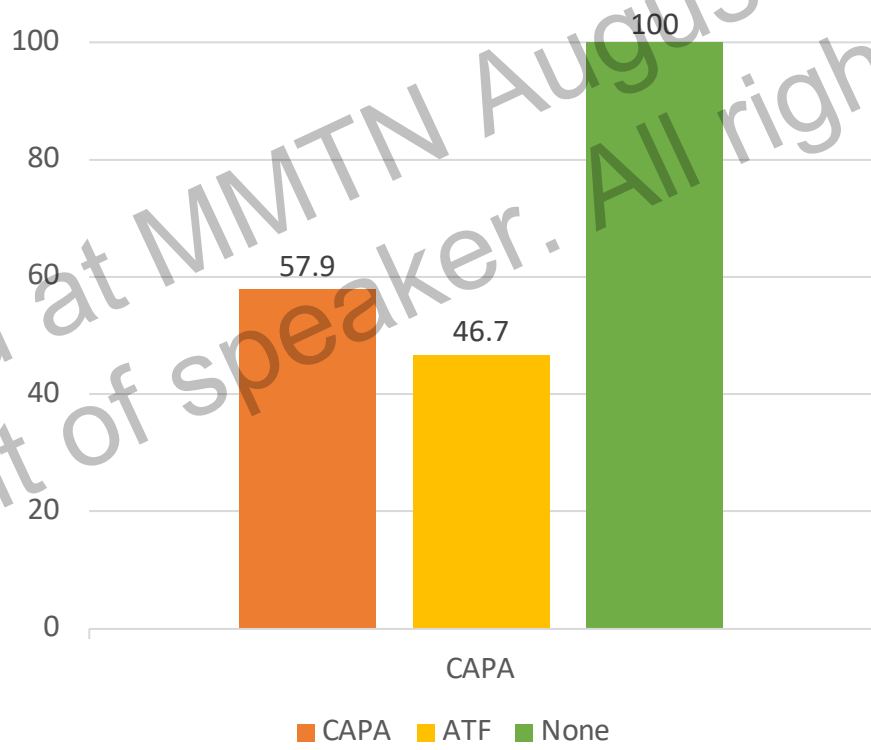
A National Strategy to Diagnose Coronavirus Disease 2019–Associated Invasive Fungal Disease in the Intensive Care Unit

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 Backx¹

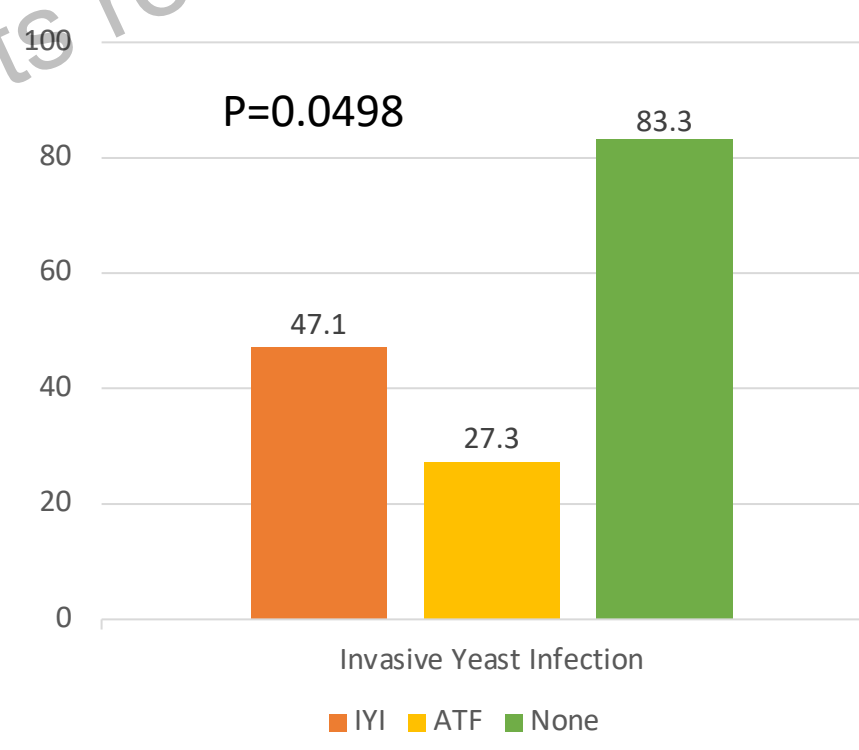
Mortality Rate of Invasive Fungal Infection (IFI) in COVID-19 patients



Mortality Rate in CAPA with and without AFT



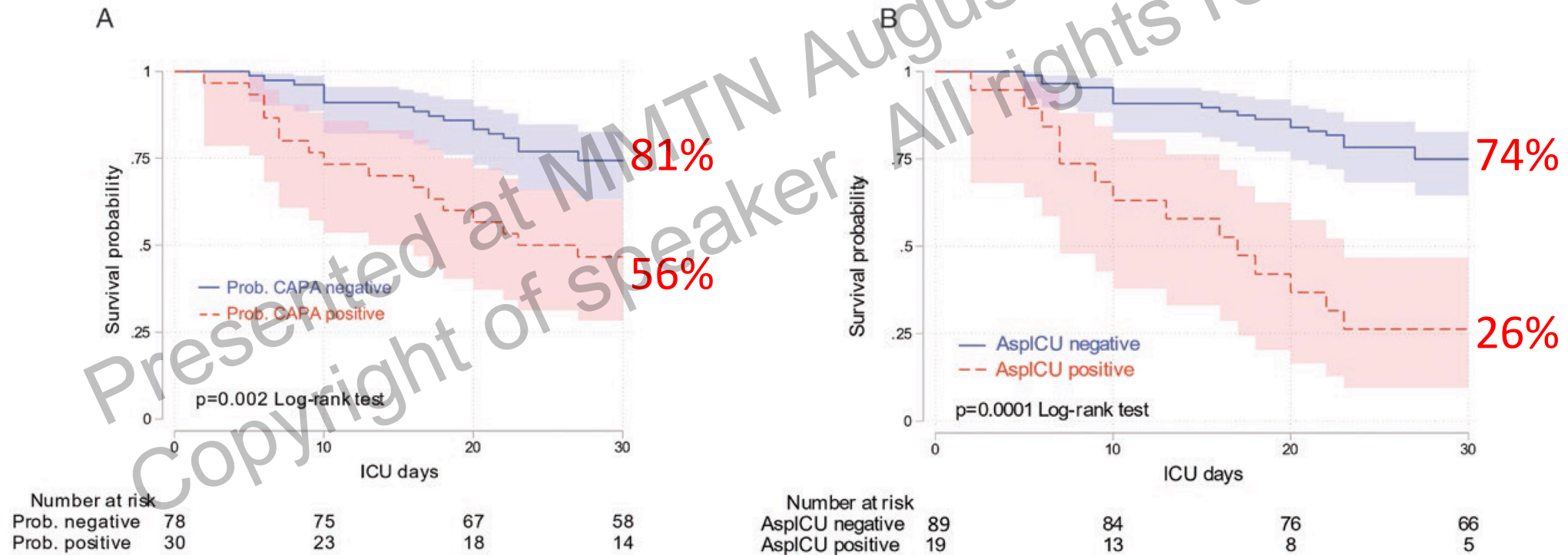
Mortality Rate in IYI with and without AFT



Survival of CAPA

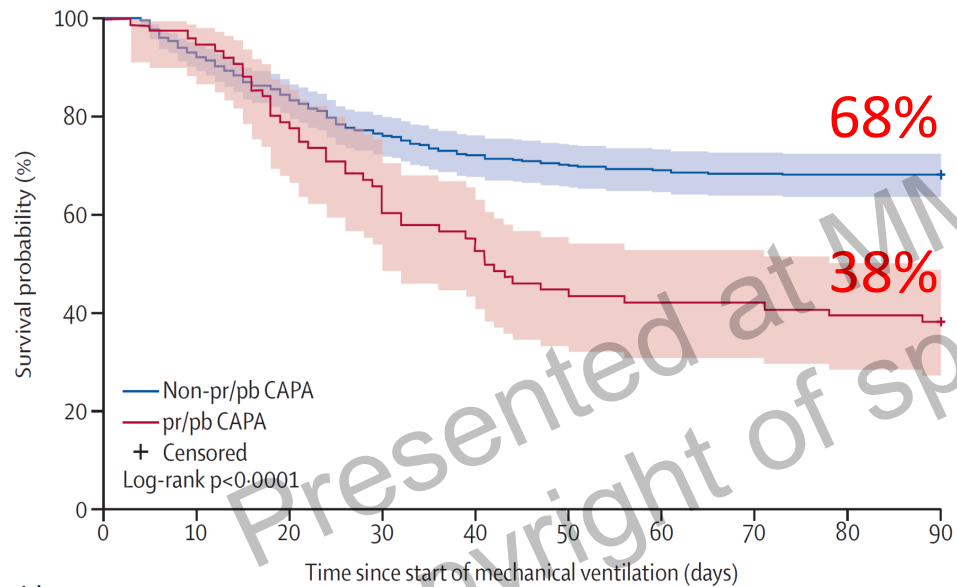
Epidemiology of Invasive Pulmonary Aspergillosis Among Intubated Patients With COVID-19: A Prospective Study

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Survival of CAPA

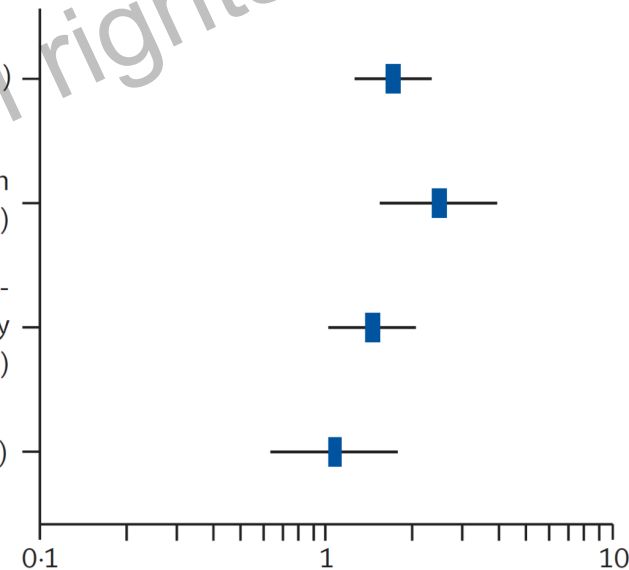
Fungal infections in mechanically ventilated patients with COVID-19 during the first wave: the French multicentre MYCOVID study



Number at risk	0	10	20	30	40	50	60	70	80	90
Non-pr/pb CAPA	432	402	365	331	312	304	299	296	295	295
pr/pb CAPA	76	73	60	50	42	34	32	32	30	29

Effect on mortality

- Age >62 years (n=237 vs n=272)
- Solid organ transplantation (n=35 vs n=474)
- Proven or probable COVID-19-associated pulmonary aspergillosis (n=76 vs n=433)
- Candidaemia (n=32 vs n=477)
































Influenza-associated pulmonary aspergillosis (IAPA)

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

Intensive Care Med

<https://doi.org/10.1007/s00134-020-06091-6>

Paul E. Verweij^{1,2*} , Bart J. A. Rijnders³ , Roger J. M. Brüggemann^{2,4} , Elie Azoulay⁵ , Matteo Bassetti^{6,7} , Stijn Blot^{8,9} , Thierry Calandra¹⁰ , Cornelius J. Clancy^{11,12} , Oliver A. Cornely^{13,14,15} , Tom Chiller¹⁶ , Pieter Depuydt¹⁷ , Daniele Roberto Giacobbe^{6,18} , Nico A. F. Janssen^{2,19} , Bart-Jan Kullberg^{2,19} , Katrien Lagrou^{20,21} , Cornelia Lass-Flörl²² , Russell E. Lewis²³ , 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. Rogers³³ , Jeroen A. Schouten^{34,35} , Isabel Spriet³⁶ , Lore Vanderbeke^{20,37} , Joost Wauters³⁷  and Frank L. van de Veerdonk^{2,19} 

EORTIC IFI criteria > non-classifiable

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

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

<i>Aspergillus</i> tracheobronchitis	IAPA in patients without documented <i>Aspergillus</i> tracheobronchitis
<p>Proven Biopsy or brush specimen of airway plaque, pseudomembrane or ulcer showing hyphal elements and <i>Aspergillus</i> growth on culture or positive <i>Aspergillus</i> PCR in tissue</p>	<p>Lung biopsy showing invasive fungal elements and <i>Aspergillus</i> growth on culture or positive <i>Aspergillus</i> PCR in tissue</p>
<p>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 <i>Aspergillus</i></p>	<p>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</p>

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

St Louis White, et al. • *Clin Infect Dis*. 2021 Oct 5;73(7):e1634–e1644.

Defining CAPA

AspICU	IAPA	CAPA-specific
<p>Putative:</p> <ul style="list-style-type: none"> 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 	<p>Putative:</p> <ul style="list-style-type: none"> Positive culture from BAL Positive GM-EIA in BAL ≥ 1.0 Positive GM-EIA in serum ≥ 0.5 	<p>Putative:</p> <ul style="list-style-type: none"> Non-specific radiology:^a Two or more positives across different test types or multiple positives within one test type, from the following: <ul style="list-style-type: none"> Positive culture from NBL/BAL Positive GM-EIA in NBL/BAL ≥ 1.0 Positive GM-EIA in serum ≥ 0.5 Positive <i>Aspergillus</i> PCR in BAL or blood Positive BDG in serum/plasma

^aIf 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, $\beta(1,3)$ -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

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}

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

	AspICU	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%)

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 Azoulay⁵ , Matteo Bassetti^{6,7} , Stijn Blot^{8,9} , Jochem B. Buil^{1,2} , Thierry Calandra¹⁰ , Tom Chiller¹¹ , Cornelius J. Clancy¹² , Oliver A. Cornely^{13,14,15} , Pieter Depuydt¹⁶ , Philipp Koehler^{13,14} , Katrien Lagrou^{17,18} , Dylan de Lange¹⁹ , Cornelia Lass-Flörl²⁰ , Russell E. Lewis²¹ , Olivier Lortholary^{22,23} , [Peter-Wei Lun Liu](#)^{24,25} , Johan Maertens²⁶ , M. Hong Nguyen¹² , Thomas F. Patterson^{27,28} , Bart J. A. Rijnders²⁹ , Alejandro Rodriguez³⁰ , Thomas R. Rogers³¹ , Jeroen A. Schouten^{32,33} , Joost Wauters³⁴ , Frank L. van de Veerdonk³⁵  and Ignacio Martin-Loeches^{36,37,38*} 

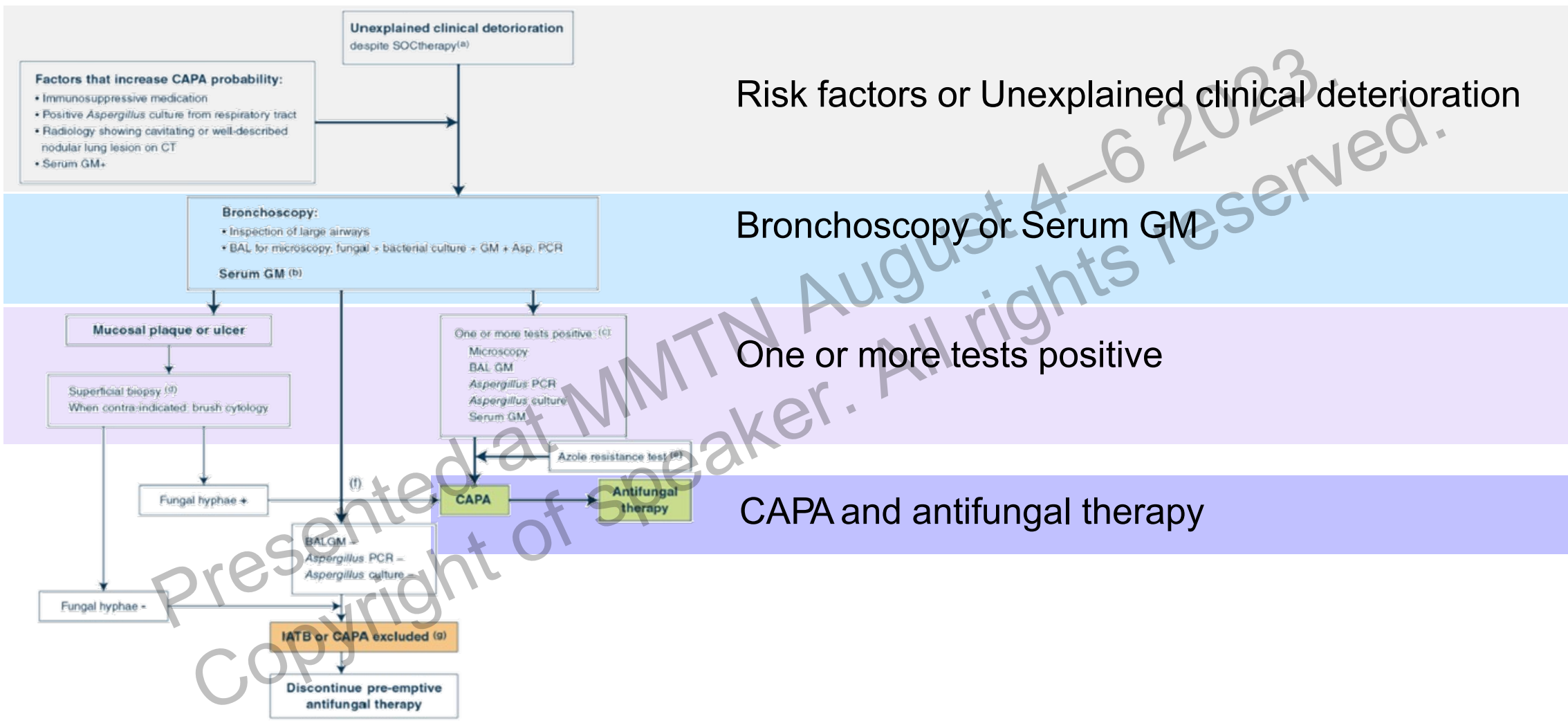
Proposed clinical guidance for the management of CAPA

Risk factors or Unexplained clinical deterioration

Bronchoscopy or Serum GM

One or more tests positive

CAPA and antifungal therapy

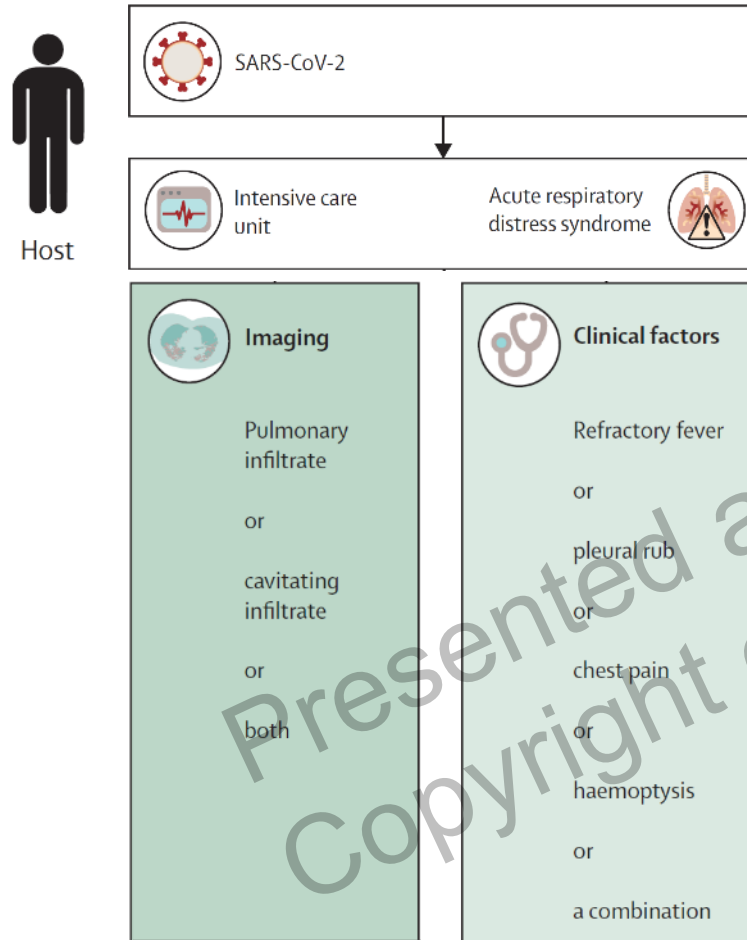


Asp., Aspergillus spp.; BAL, bronchoalveolar lavage; CAPA, COVID-19 associated pulmonary aspergillosis; CT, computerised tomography; GM, galactomannan; IATB, invasive Aspergillus tracheobronchitis; PCR, polymerase chain reaction; SOC, standard of care; TDM, therapeutic drug monitoring

Defining and diagnosing CAPA

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

Philipp Koehler, Matteo Bassetti, Arunaloake 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



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

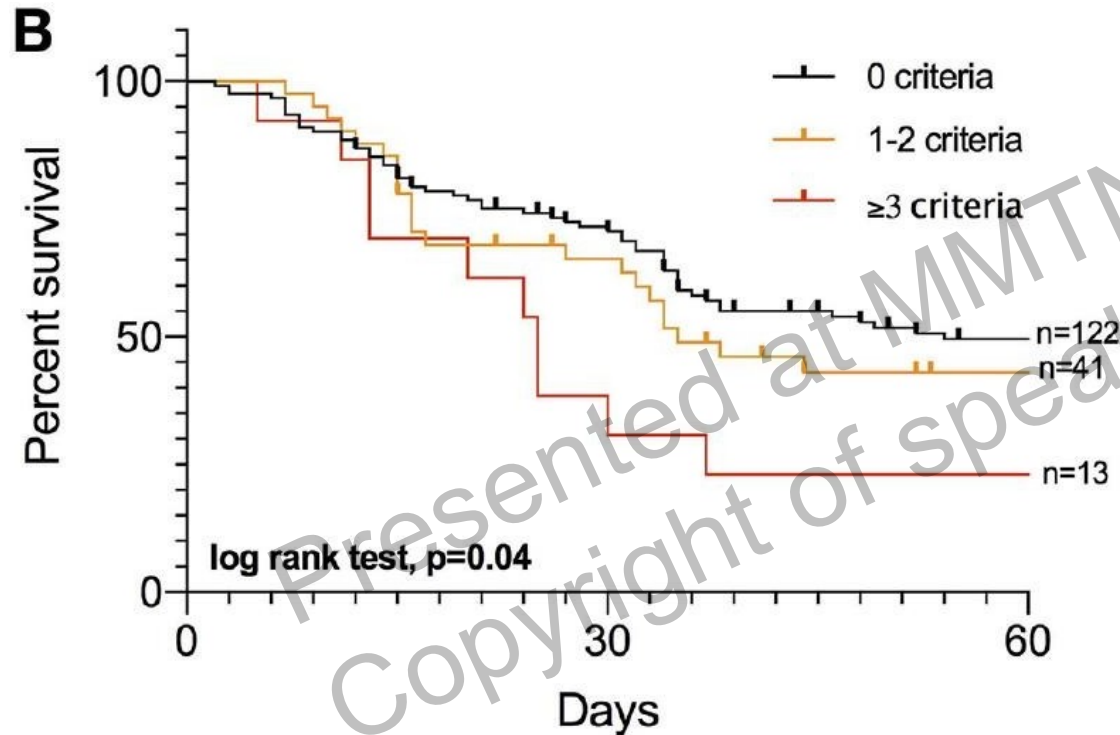
GM > 0.5 or LFA > 0.5

or 2 or more **positive PCR**

1 PCR positive in serum and in BAL

Combination of mycological criteria: A better surrogate to identify CAPA patients and evaluate prognosis?

To evaluate seven mycological criteria and their combination in a large homogenous cohort of patients. All successive patients (n = 176) hospitalized for COVID-19 requiring mechanical ventilation.



From respiratory specimens:

- (i) Direct respiratory sample examination with branched hyphae suggestive of *Aspergillus*-type hyphae,
- (ii) respiratory sample culture growing *Aspergillus* sp.,
- (iii) galactomannan in bronchoalveolar lavage (index of >1.0),
- (iv) *Aspergillus* qPCR in respiratory sample with quantitative cycle (Cq) of <36;

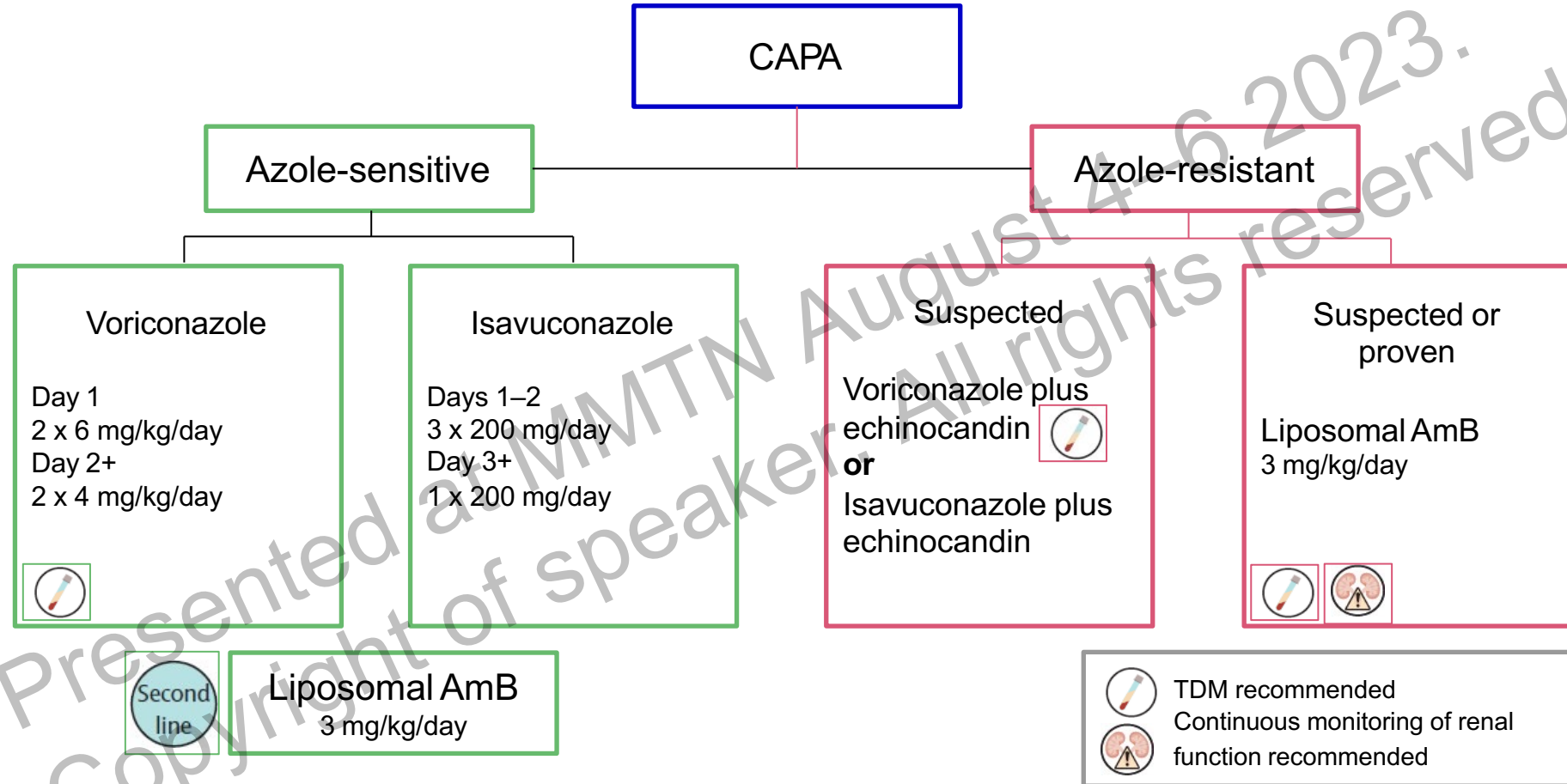
From serum:

- (i) galactomannan in blood (index of >0.5),
- (ii) positive *Aspergillus* qPCR in blood with Cq of <40,
- (iii) blood BDG of >80 pg/mL.

IDSA guidelines for the 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

Treatment of CAPA



AmB, amphotericin B; CAPA, COVID-19-associated pulmonary aspergillosis; TDM, therapeutic drug monitoring

IDSA guidelines for the management of aspergillosis

Treatment duration:

- Minimum of 6–12 weeks

Depends on:

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

Therapeutic drug monitoring (TDM) of antifungal agents

- Weekly TDM in patients with CAPA is recommended, specifically for voriconazole and posaconazole.
- For voriconazole, a plasma trough concentration of 2–6 mg/L is recommended.
- For posaconazole, the lower threshold is 1 mg/L.
- No isavuconazole target concentration has been defined, but TDM might be warranted in patients who are on RRT or ECMO or with obesity.
- In a prospective observational study, 34 ICU patients were receiving voriconazole for the treatment of invasive fungal infection, 35% (12/34) of the voriconazole plasma trough levels were not within the therapeutic range.*

Take-home messages

- Diagnosis of IPA in ICU populations requires a high index of suspicion.
- Critically ill patients without classic risk factors (e.g. COPD, cirrhosis, severe Influenza, severe COVID-19, steroid use) should start adequate antifungal therapy upon suspicion of IPA, before obtaining definitive proof of infection
- A diagnostic work-up for IPA is recommended in clinically deteriorating patients with no other explanation or with cavitary and/or nodular lesions on CT scan.
- Integrating all mycological tests would be useful (including GM, LFA, qPCR, culture)
- First-line treatment: voriconazole or **isavuconazole**
- Salvage/azole-resistance: liposomal amphotericin B

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

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

ICU

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

Severe ARDS (P/F ratio 84)

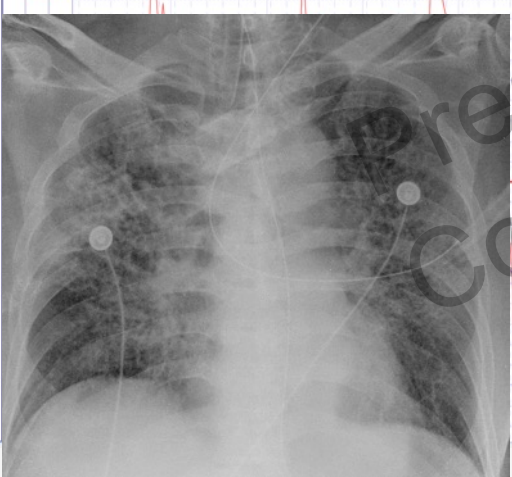
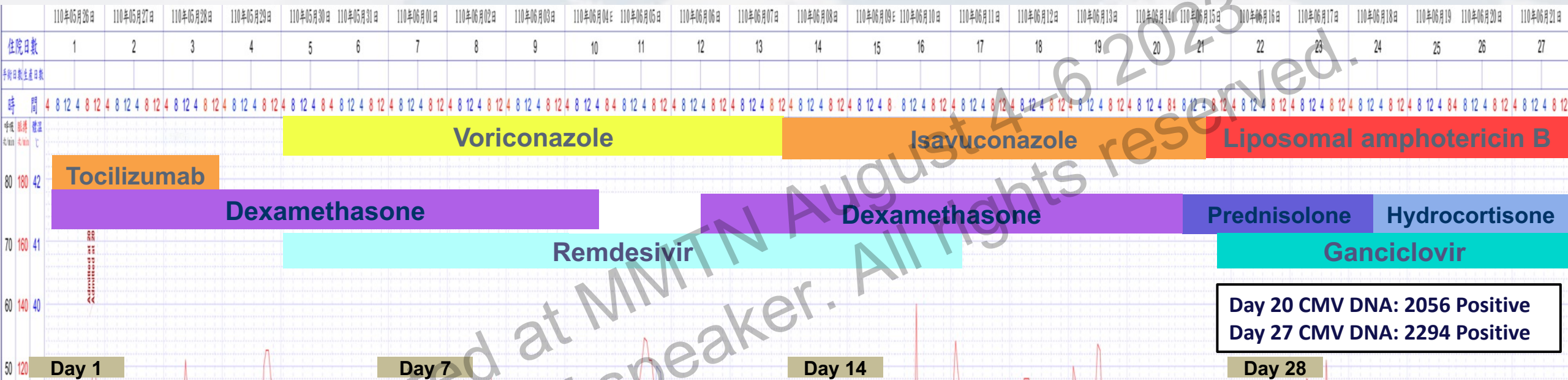


ICU Day 1

ICU Day 14

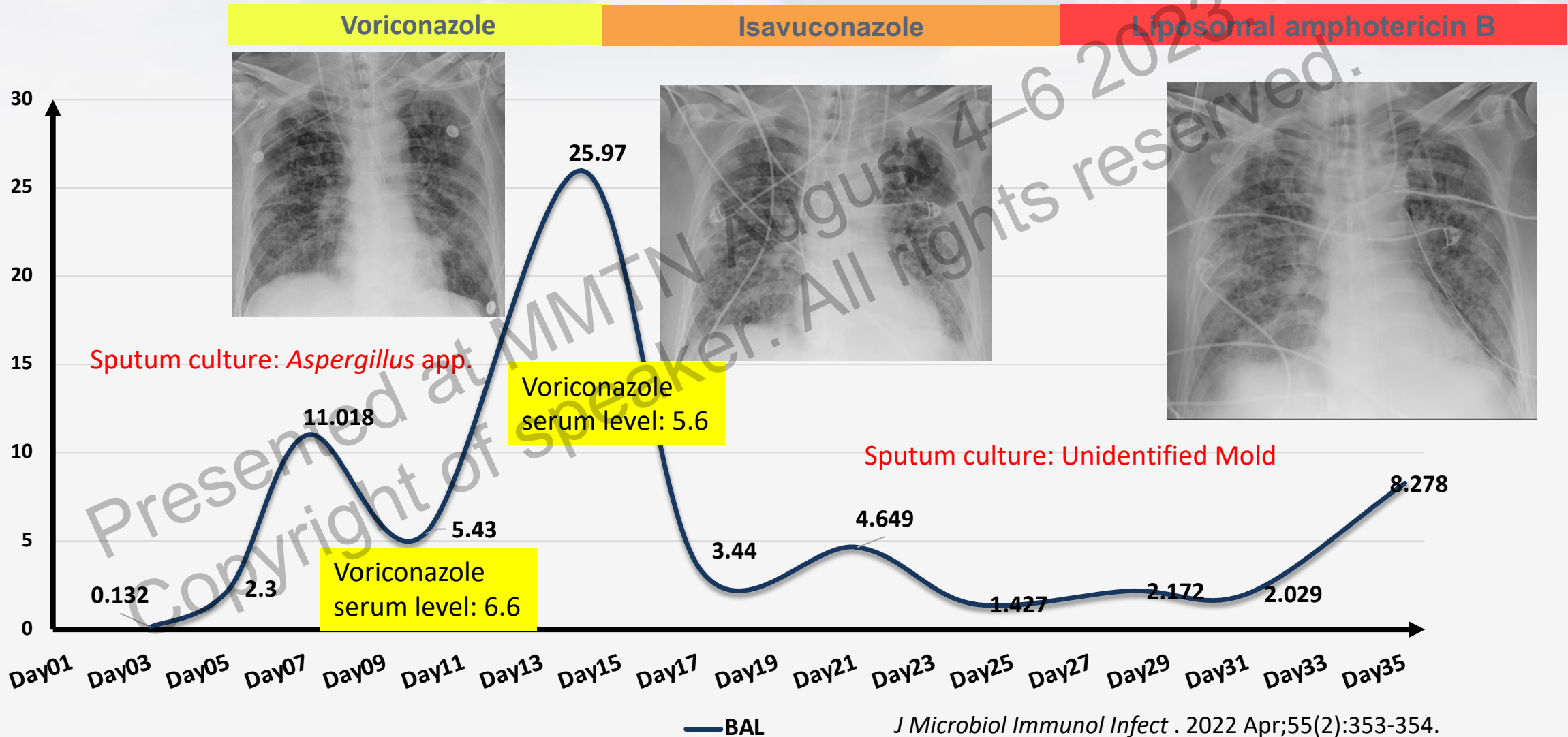
Clinical course

Day 13 Elevated *Aspergillus* Ag level :
5.430 (06/03) → **25.970** (06/07)

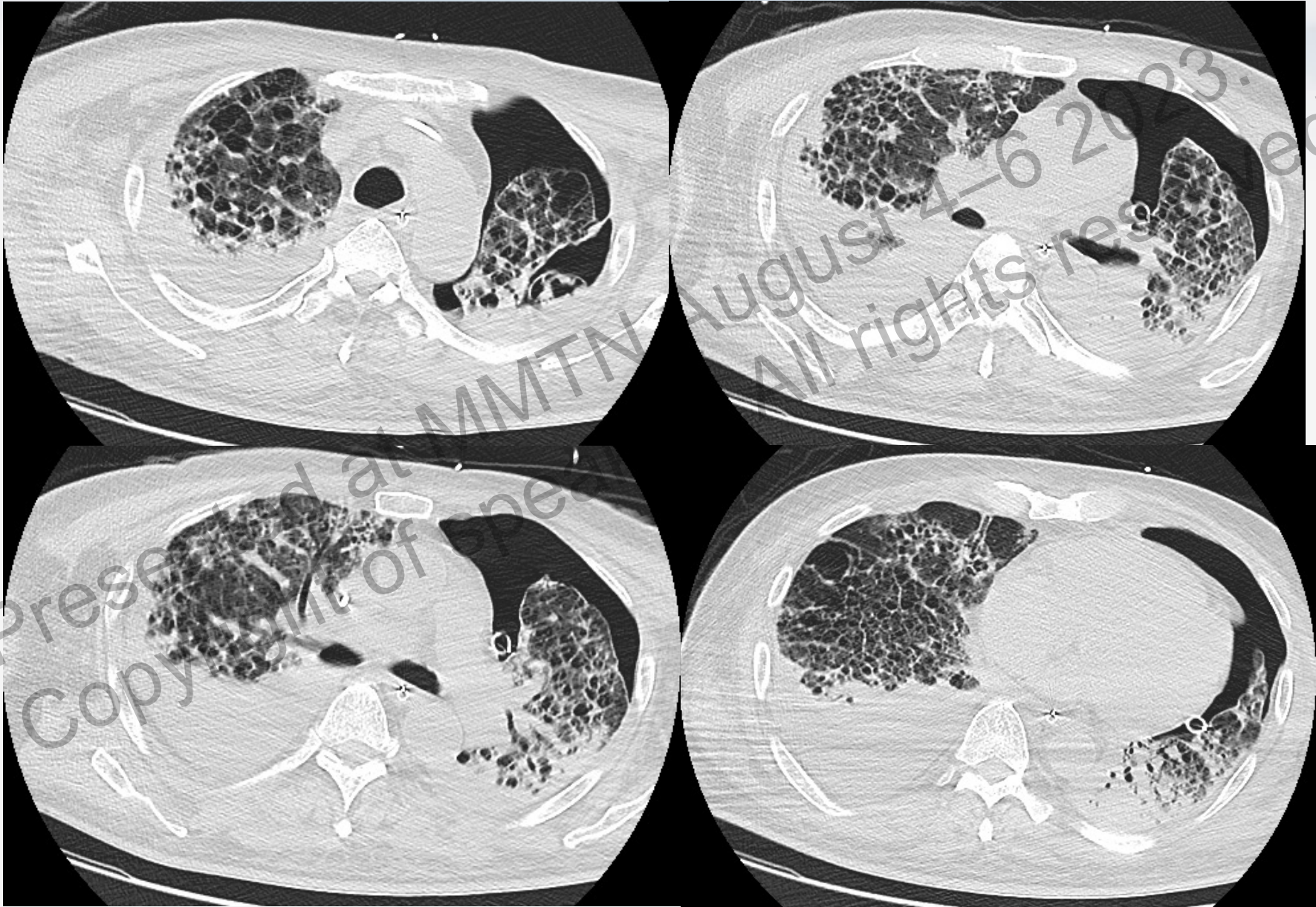


Peter WL Liu, personal case and images.

Non-directed bronchoalveolar lavage *Aspergillus* Ag



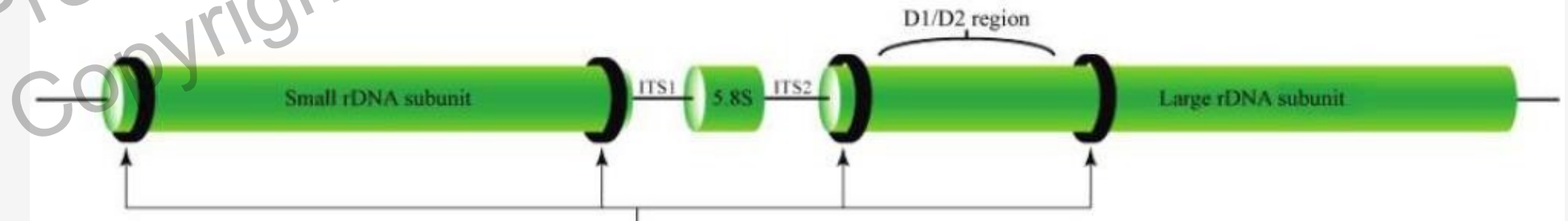
Chest CT scan



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

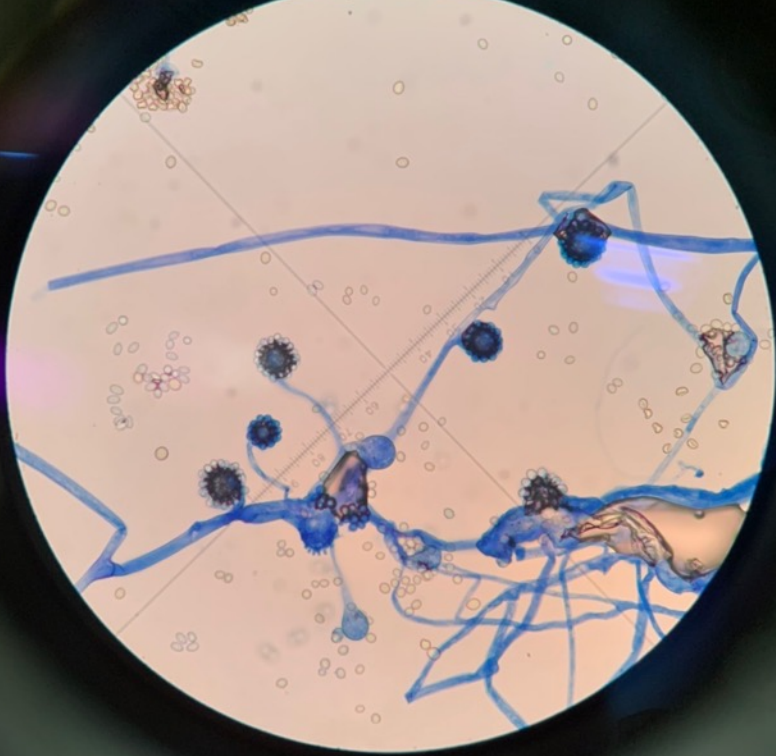


Final ID		AmB MIC	ITC MIC	VRC MIC	PSC MIC	ISC MIC	AND MEC	AND MIC
Cunninghamella bertholletiae	CLSI M38-A2	2	> 16 (1)	>16	>8 (0.5)	>8	>8	>8
Aspergillus terreus	CLSI M38-A2	2	0.12	1	0.03	0.5	<0.004	>8

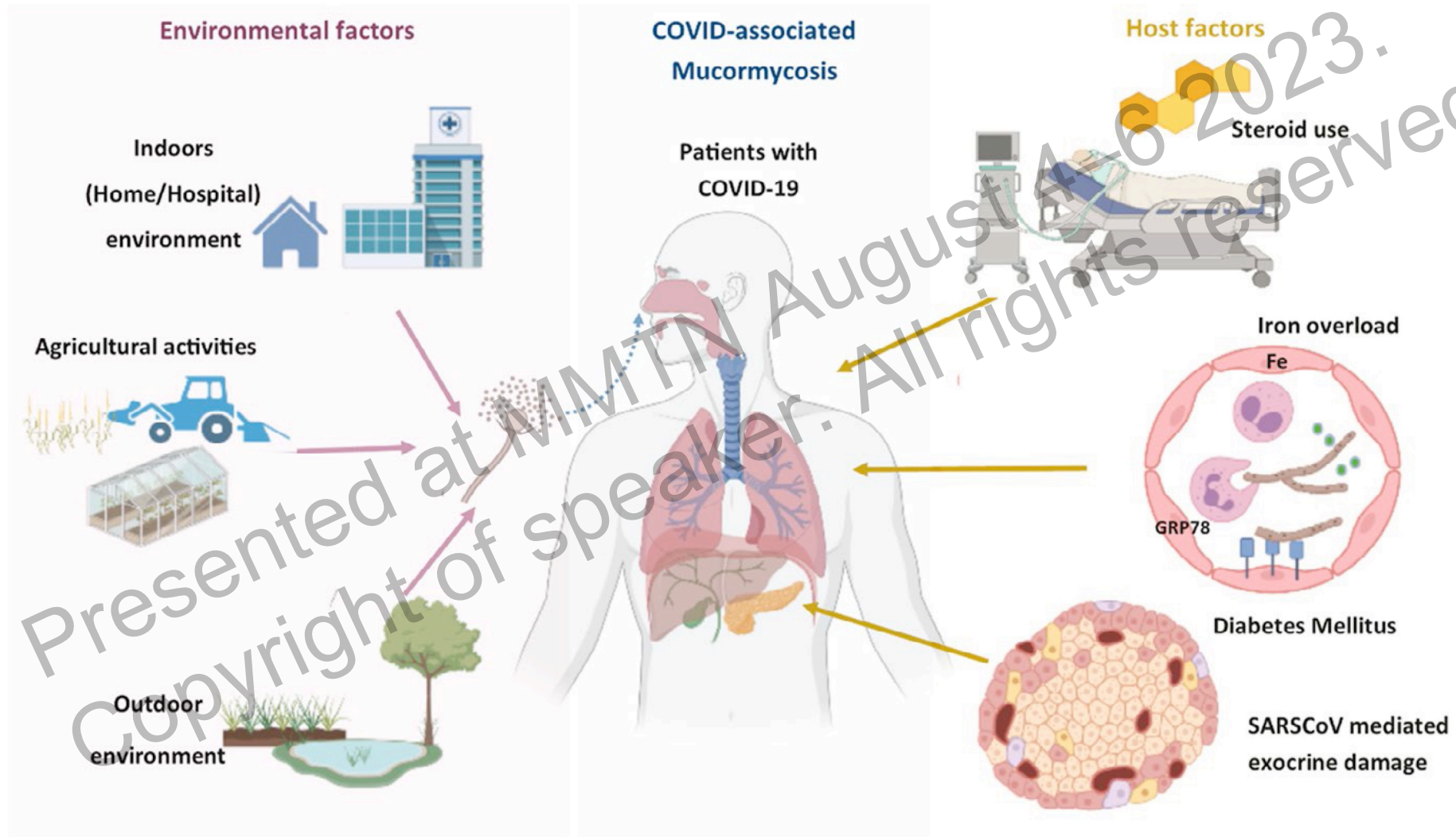


Conserved areas targeted by primers

Cunninghemella bertholletiae



Risk factors of COVID-associated mucormycosis



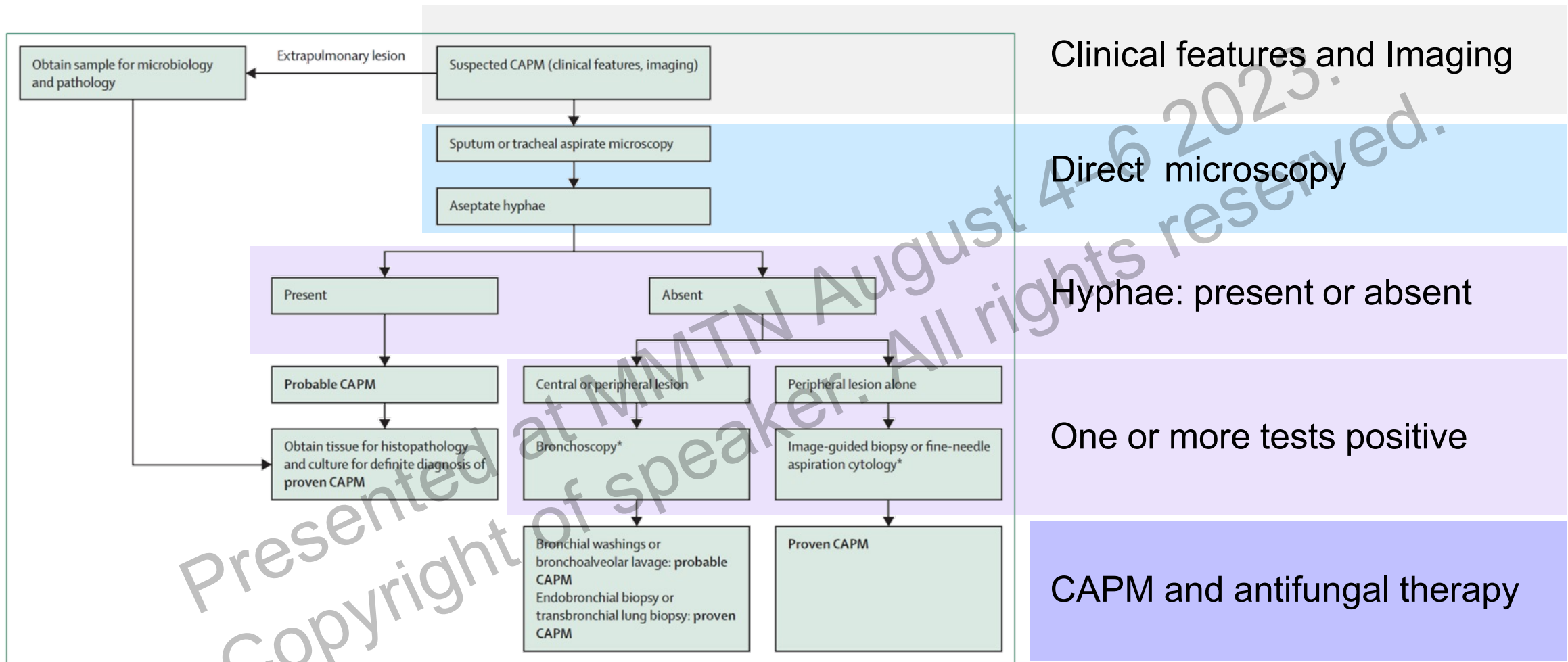
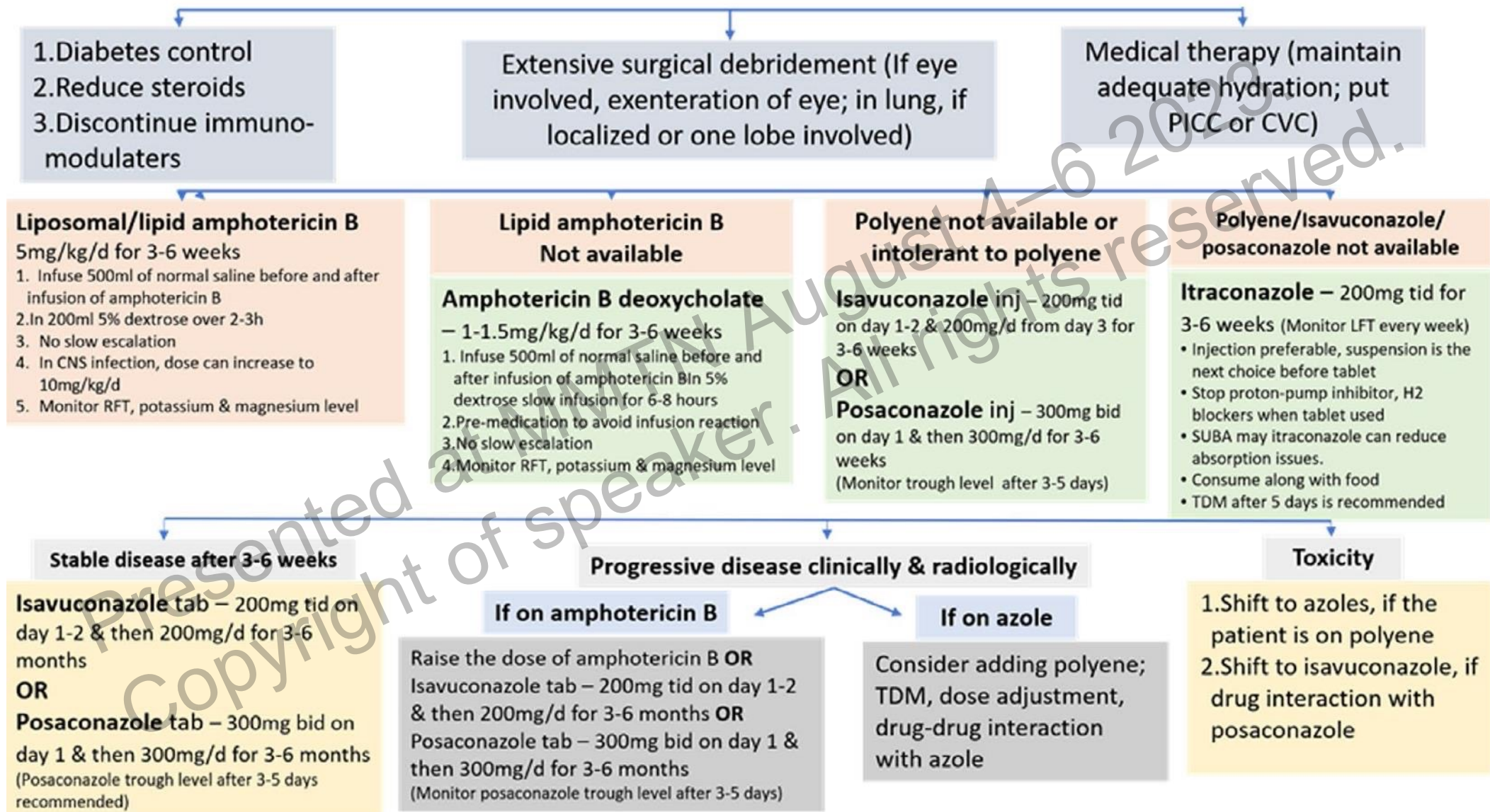


Figure 1: Diagnostic algorithm for evaluating suspected CAPM

CAPM=COVID-19-associated pulmonary mucormycosis. *Direct microscopy or histopathology showing broad aseptate hyphae.

CAPM, COVID-19-associated pulmonary mucormycosis

Treatment algorithm for CAPM



CAPM is a rare but under-reported complication of COVID-19.

- **Flexible bronchoscopy** is recommended as an early diagnostic tool for CAPM infection.
- **Liposomal amphotericin B** (5 mg/kg per day) and **early surgery** are recommended as central to the management of mucormycosis in patients with COVID-19.
- **Posaconazole or isavuconazole** was recommended as **maintenance therapy** following initial response. In patients with stable or progressive disease, the experts recommended **salvage therapy with posaconazole or isavuconazole**.