Management of Invasive Aspergillosis Infection post COVID-19 Pneumonia

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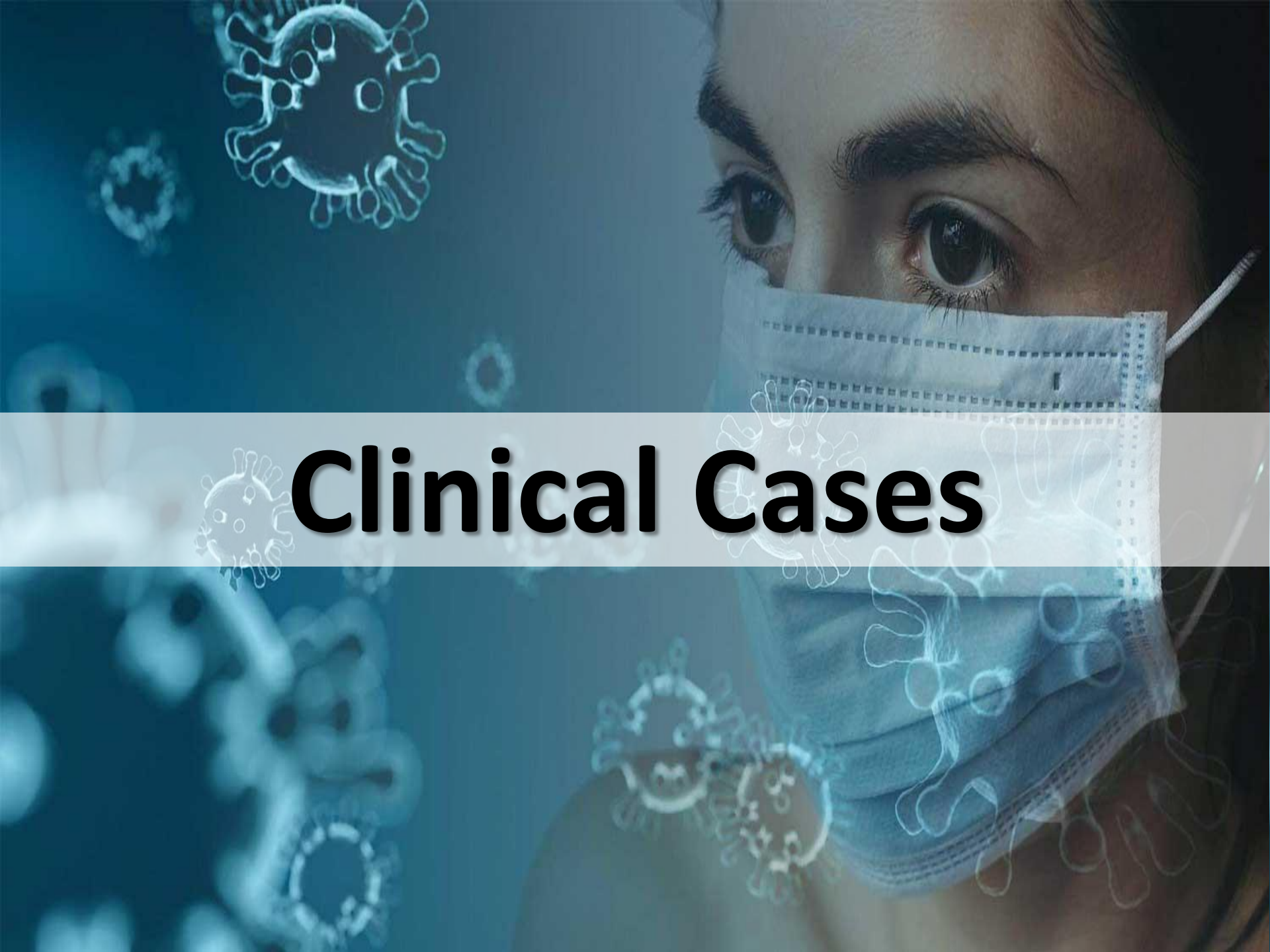
COVID-19

Overview

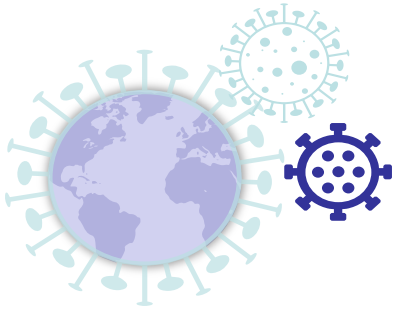
1. Clinical Cases
2. Introduction of COVID-19 associated pulmonary aspergillosis (CAPA)
3. Clinical challenges of CAPA and treatment overview


Clinical Cases

Case-1 ♂

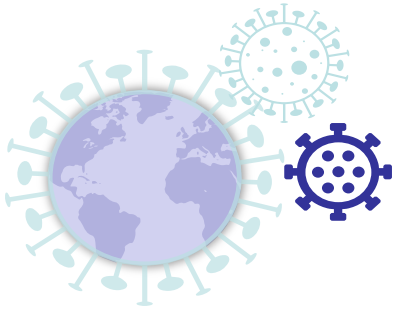
- 83 year-old male
- 178cm/ 68kg, Scr=0.66, GOT/GPT: 63/67, albumin 4.2
- Past medical history: nil; Allergy: NKA
- CC: general weakness, cough, fever
- TOCC: Wang-Hua tea house
- Diagnosis: COVID-19 pneumonia **(5/21 COVID PCR+, CT=14)**

Case-1



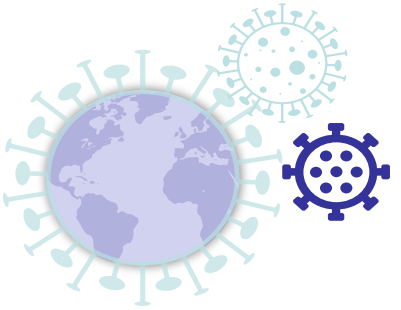
5/21	Admitted	To ward	COVID PCR (CT=14)
5/27	Pneumonia progression, unstable oxygen saturation	→**+Dexamethasone 6mg/day (5/27-6/5)** →**+Tocilizumab 8mg/kg stat (5/28)** →+Empirical levofloxacin (5/29-6/5) →+Remdesivir (5/30-6/3)	CRP=14.55mg/dL
5/31	CXR: pneumonia progression	**Admitted to ICU** →+Enoxaparin	COVID PCR (CT=33), CRP=4.35mg/dL D-dimer=3.74
6/3	CXR: Increasing infiltration **Suspect COPD lung** **GI bleeding**	→ +furosemide 20mg QD → +Spiolto → Hold enoxaparin → **+pantoprazole 40mg QDAC**	
6/8	unstable O2 , s/p ETT+MV	**+ Voriconazole 6mg/kg Q12H,** 4mg/kg Q12H since 6/8	**6/1 Serum Aspergillosis Ag (+) 0.921** (day11 post adm.) CRP=0.55mg/dL
6/9	PEA, shock	Expired	

Case-2 ♂



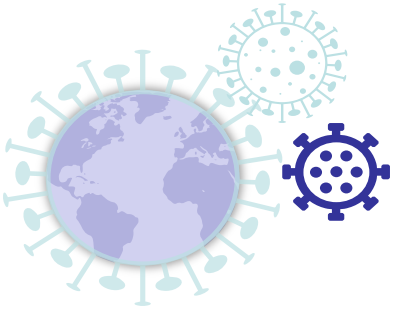
- 73 year-old male
- 165cm/ 80kg, Scr=1.39, GOT: 82, albumin: 3.6 g/dL
- Past medical history:
  - **DM: metformin 500mg TID**
  - CAD: aspirin 100mg QD
  - Hypertension: amlodipine 5mg QD, valsartan 160mg QD
  - Dyslipidemia: rosuvastatin 10mg QD, ezetimibe 5mg QD
- CC: Dyspnea with cold sweating, decreased appetite, cough
- CXR: bilateral diffuse infiltration
- Allergy: NKA; TOCC: denied
- Diagnosis: COVID-19 pneumonia **(5/29 COVID PCR+, CT=18)**

Case-2



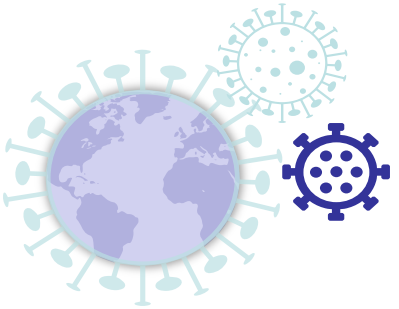
5/29	Admitted to ER, PaO2: 50%	General ward, non-rebreathing mask (NRM) use →**+Dexamethasone 6mg/day (5/29-6/8)**	CT=18
5/31	PaO2: 85-90% Admitted to ICU, (NRM: 15L/min)	→+Remdesivir (6/2-6/6) →+Enoxaparin →+**levofloxacin** (5/31)	HBV/HCV/HIV: all negative pneumococcus Ag (+)
6/4	Intermittent shallow respiration pattern.	→**+Tocilizumab 8mg/kg stat (6/4)**	CT=28, procalcitonin=0.25 CRP=8.95 (6/2) → 15 (6/4)
6/16	Conscious change, dyspnea, PEA, IHCA, shock, AKI	→ **On ETT+MV (6/16), CRRT** → +Norepinephrine CIVD → **+Hydrocortisone 50mg Q6H (6/16-22)** → +pip/tazo, vancomycin (6/16-)	PCT=1.17
6/20	Persisted shock	+ **anidulafungin** use (6/20-) → ceftazidime/avibactam, daptomycin → change CVC	**6/17 B/C: yeast (candidia albicans)** GOT/GPT: 23/29 (6/9)→385/492 (6/16) **6/20 B/C: (A-line)N, (CVC) CRKP, VRE** 6/20 PJP PCR: negative
6/23 -25	Shock improved Try weaning	→ **+ methylprednisolone 40mg Q8H (6/23- 26)** → CRRT switch back to regular HD → Switch to **fluconazole** → **Remove ENDO, switch to HFNC**	6/21-22 B/C , tip culture: N 6/25 GOT/GPT: 45/87

Case-2



6/29	CXR: pneumonia (no improvement) Hemoptysis	HFNC 50L/min → hold enoxaparin	D-dimer=2.91
6/30-7/1	PaO2: 65-85% CXR: Diffuse alveolar infiltrations Chest CT: 1. Bilateral diffuse patchy GGO & consolidation 2. Bilateral pleural effusion.	→**Plan bronchoscopy (6/30)** →**Re-on ENDO (7/1)** → **resume methylprednisolone 40mg Q8H (7/1-)** →+ furosemide → Fluconazole switch back to anidulafungin	COVID PCR: CT=30
7/6		Tracheostomy → **tapper steroid**	
7/7-10		Try weaning ventilator (PSV)	
7/11-13	NG coffee ground	→hold clopidogrel, → H2B to IV pantoprazole → **Discontinue steroid**	7/13 Hgb=5.1

Case-2

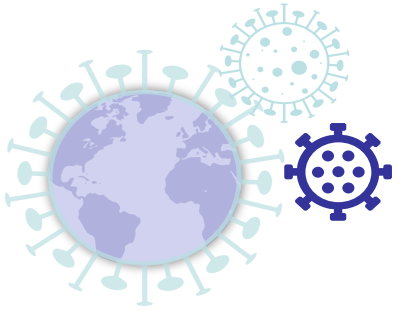


7/14-19	Shock 7/14 ABD and chest CT: 1. Small amount of ascites, partial bilateral hepatic infarction. 2. diffuse lung GGO and fibrosis	→+ norepinephrine CIVD, CRRT **Laparotomy for ischemic bowel necrosis (7/14)** → meropenem, **micafungin** →+ tigecycline, daptomycin	PCT=4.76 (7/14) →46 (7/16) Pus culture: MDRKP (S to tygacil) Blood culture: VRE (S to daptomycin) **6/30 BAL: Aspergillosis Ag (+) 1.334** (1 month after COVID diag.) **GOT/GPT: 982/1192**, T-bili=1.6
7/20	BP improved CXR: not improved	→ Tapper off norepinephrine	
7/21-22	**CXR: PN progression, With ARDS**	**+ Dexamethasone 20mg/day** **+** Midazolam, cisatracurium **+ Voriconazole 6mg/kg Q12H** **→ 2mg/kg Q12H IV (NPO)** + Ganciclovir 2.5mg/kg QD	GOT/GPT: 121/136→65/82 **T-bili=1.4→2.3,** albumin=1.7, INR=1.32, **CMV DNA: 72374**
7/23	Shock	→ Norepinephrine ↑ → Hydrocortisone 50mg Q6H	
7/24	Expired		Follow-up… **Serum Aspergillosis Ag: negative** CMV DNA: 15961 IU/mL B/C: Chryseobacter indologenes

Case-3

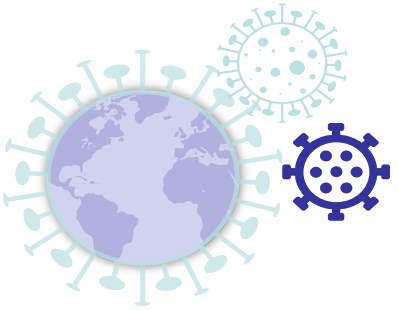
- 68 year-old female
- 158cm/ 81g, Scr=1.59, GOT: 101, albumin: 3.3
- Past medical history:
  - **DM:** metformin 850 mg BID, glimepiride 3mg BID, vildagliptin 50mg BID **(a1c: 10%)**
  - Hypertension: azilsartan 40mg QD
  - Dyslipidemia: atorvastatin 20mg QW1,4
  - CKD stage 3
- CC: headache with fever 39.6 celcius
- CXR: bilateral lung infiltration
- Allergy: valdoxan ; TOCC: 中和黃昏市場
- Diagnosis: COVID-19 pneumonia **(5/28 PCR+, CT=22)** with AKI

Case-3

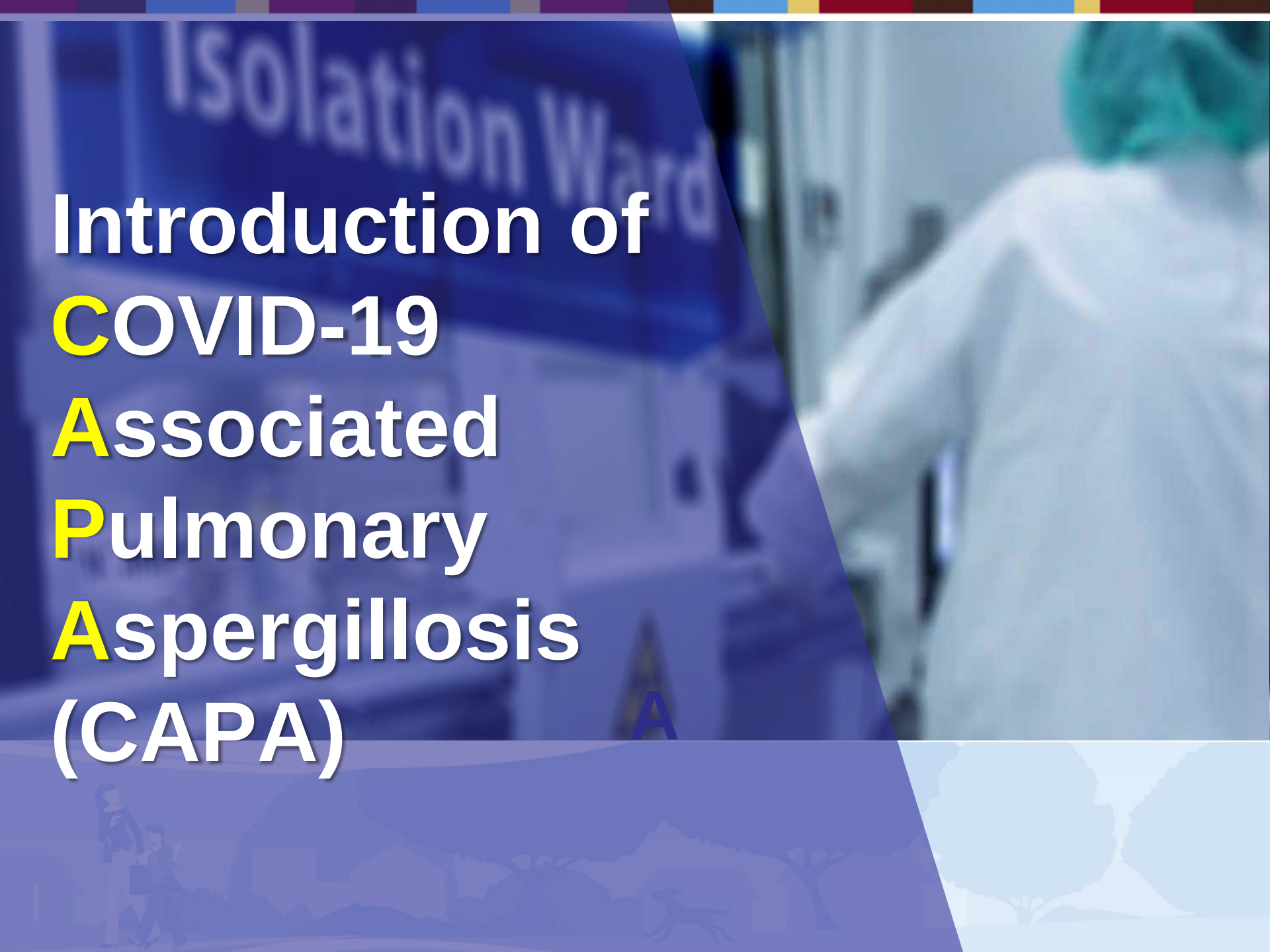


5/28	Admitted to ER	General ward → Ceftriaxone	COVID PCR (CT=22) **PCT=0.51 ng/mL,** S/C: N
5/30	PaO2: 85-90%	→**Dexamethasone 6mg QD (5/30-6/8)** →admitted to ICU	
5/31	PaO2: 55-60% (NRM) Respiratory failure AKI+ DKA **ARDS**	→**ETT+MV, Start HD** →**DKA: start RI pump** →Remdesivir (6/2-6/6) →Meropenem →Fentanyl, **midazolam,** cisatracurium(5/31-)	COVID PCR (CT=23) S/C: N; MTB, PJP, HIV: N **PCT=6.69**
6/12 -14	Bilateral infiltration progress and desaturation Shock	**+ Voriconazole 6mg/kg Q12H (d1),** **4mg/kg Q12H (6/14-) IVD (NPO)** → Norepinephrine CIVD → Switch HD to **CRRT**	**6/12 sputum culture: mold** (2 weeks after COVID diag.) **6/14 serum Aspergillosis Ag (+) 2.778** (S/C: aspergillus flavus)
6/17 -19	Shock persisted	→+Ampicillin →+Levofloxacin	B/C: Enterococcus faecalis S/C: Stenotrophomonas maltophilia
6/21 -25	Shock improved ARDS improved	Tapper off norepinephrine **DC midazolam**, cisatracurium (6/21-)	CRP: 4.69, PCT=0.71

Case-3

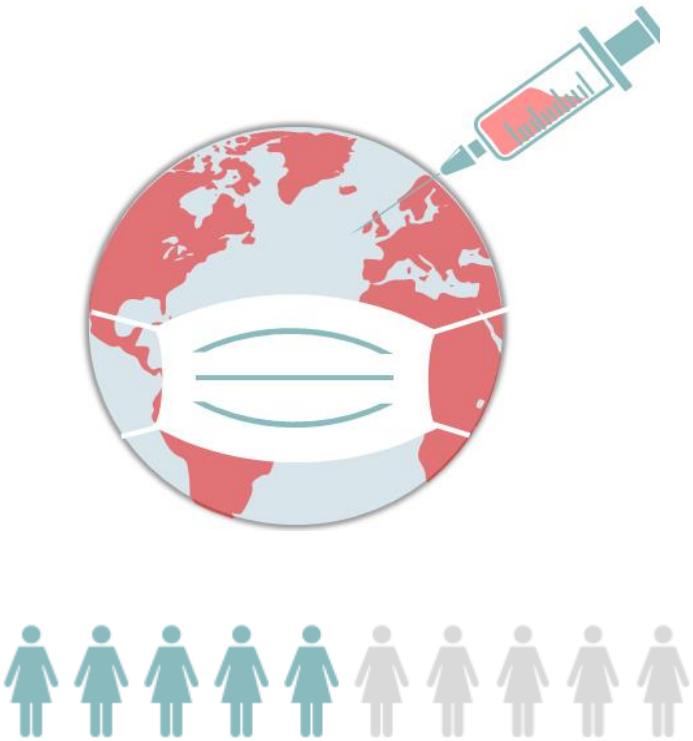


6/28- 7/10	Poor digestion GI bleeding CXR: persist lung infiltration **→Chest CT & A+P CT** - **Liver cirrhosis** - Massive ascites - Pleural effusion - Patchy infiltration of bilateral lung consistent with pneumonia	Hold enoxaparin → H2B to **pantoprazole 40mg Q12H** **Child-Pugh score=B** **Adjust voriconazole to 2mg/kg Q12H**	6/23 B-bili/ T-bili=0.6/1.5 6/25 B-bili/ T-bili=0.8/1.8 **6/28 B-bili/ T-bili=1.0/2.3** 7/2 B-bili/ T-bili=0.8/1.4 **7/6 B-bili/ T-bili=0.6/1.0**
7/12	CXR: improved Vital sign improved No active GI bleeding	**CRRT→HD** **Switch to PO voriconazole 100mg BID** Try weaning ventilator	**7/7 serum Aspergillosis Ag: N** 7/7 CMV IgM: negative
7/23	CXR: lung fibrosis Still drowsy conscious	Tracheostomy	**7/24 BZD (urine)(藥物濃度)** **>900.0 ng/mL [<200.0]** 7/26 B-bili/ T-bili=0.4/0.7
7/25 8/2		Weaning ventilator To ward	



Introduction of COVID-19 Associated Pulmonary Aspergillosis (CAPA)

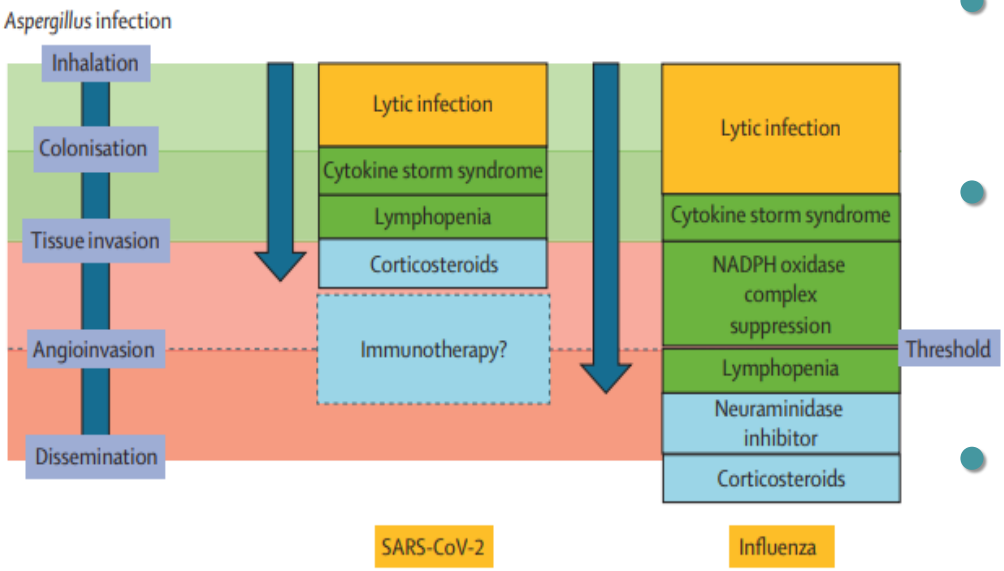
COVID-19 associated Pulmonary Aspergillosis (CAPA)



- Prevalence: **19-33%**
- Diagnosed a median of **10 days** after COVID disease diagnosis
  - 2-21 days after hospital admission
  - 2-11 days after ICU admission
- Most common species:
  - Aspergillus fumigatus, Aspergillus flavus.

Emerg Infect Dis 27:1077–1086 Journal of Microbiology, Immunology and Infection (2021) 54, 46e53

Factors Attribute to Invasive Aspergillosis



- **Virus**
  - Cytokine storm, lymphopenia
- **Underlying disease**
  - DM, COPD, liver disease
  - solid tumor, MM
- **Malnutrition**
  - Lower BMI, hypoalbuminemia
- **Treatment**
  - Corticosteroid, anti IL-6, azithromycin

Lancet Respir Med 2021; 9: 795–802; Diagnostics 2020, 10, 807 ; Crit Care Explor. 2020;2

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

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

	CAPA N=30 (%)	Non-CAPA N=73 (%)	p
Demographics			
Age, years, mean (±SD)	63 (57-70)	63 (57-70)	0.86
Male	24 (80)	83 (77)	0.80
Underlying diseases			
Obesity	10 (37)	34 (49)	0.36
BMI, median (IQR)	28 (26-31)	29 (26-31)	0.92
Hypertension	16 (59)	49 (65)	0.64
Diabetes mellitus	5 (17)	13 (17)	0.99
Coronary disease	3 (10)	9 (11)	0.99
Cerebrovascular disease	3 (10)	1 (1.4)	0.06
Chronic kidney disease	6 (20)	6 (8)	0.08
COPD	4 (13)	13 (17.8)	0.10
Malignancies	2 (7)	5 (6)	0.99
Solid organ transplant	1 (3)	4 (5)	0.99
Chronic steroid treatment	5 (17)	2 (3)	0.02
Haemodialysis	3 (13)	3 (5)	0.36
Charlson index, median (IQR)	3 (1-4)	2 (1-4)	0.51

	CAPA N=30 (%)	Non-CAPA N=73 (%)	p
Laboratory tests at admission			
White Blood Cells (10^9/L) median (IQR)	9.7 (4.9-14.0)	7.1 (5.2-10.1)	0.13
Neutrophils (10^9/L) median (IQR)	8.0 (3.9-13.4)	5.9 (4.0-8.8)	0.24
Lymphocytes (10^9/L) median (IQR)	0.76 (0.55-1.10	0.84 (0.50-1.01)	0.67
Creatinine (mg/dL), median	1.0 (0.77-2.05)	1.00 (0.77-1.38)	0.38
CRP (mg/dl), median (IQR)	11 (5-18)	11.8 (6.5-19.9)	0.37
LDH (IU/L), median (IQR)	375 (311-500)	389 (286-524)	0.67
SOFA score	3 (2-4)	3 (1-4)	0.81
COVID19 treatment			
Hydroxychloroquine	28 (93)	73 (94)	0.99
Azithromycin	9 (30)	31 (40)	0.38
Lopinavir	12 (40)	27 (35)	0.61
Darunavir	2 (7)	6 (8)	0.99
Remdesivir	3 (10)	5 (6)	0.68
Tocilizumab	22 (73)	57 (78)	0.80
Corticosteroids	18 (60)	34 (46.6)	0.29

The only factor associated to CAPA was chronic steroid therapy at dosage $\geqq$ prednisone 16 mg/day for at least 15 days

BartolettiM, et al. Clin Infect Dis. 2020.

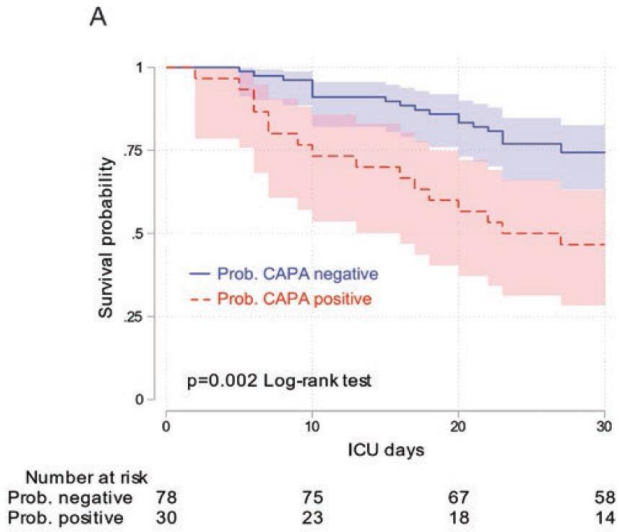
Risk factors associated with COVID-19-associated pulmonary aspergillosis in ICU patients: a French multicentric retrospective cohort

Comparison of patients with severe coronavirus disease 2019 (COVID-19) with and without probable invasive pulmonary aspergillosis (IPA)

	Total ($n = 108$)	Without IPA ($n = 87$)	With IPA ($n = 21$)	OR	95%CI	p
Male *n (%)*	88 (81.5)	72 (82.8)	16 (76.2)	0.7	0.2–2.1	—
Age *median (Q1–Q3)*	62 (56–68)	62 (56–68)	63 (56.75–68.25)	—	—	0.63 [a]
Mechanical ventilation *n (%)*	105 (97.2)	85 (97.7)	20 (95.2)	0.5	0.04–5.3	
COVID risk factors						
HTA *n (%)*	64 (59.3)	50 (57.5)	14 (66.7)	1.5	0.5–4.0	—
Diabetes *n (%)*	40 (37.0)	31 (35.6)	9 (42.9)	1.4	0.5–3.6	—
Obesity *n (%)*	35 (32.4)	31 (35.6)	4 (19.0)	0.4	0.1–1.3	—
Coronary disease *n (%)*	15 (13.9)	13 (14.9)	2 (9.5)	0.6	0.1–2.9	—
BMI *median (Q1–Q3)*	28 (25–31)	28 (26–32)	28 (25–29)	—	—	0.70 [a]
Other patient characteristics						
Asthma *n (%)*	5 (4.6)	3 (3.4)	2 (9.5)	2.9	0.5–18.9	—
COPD *n (%)*	2 (1.9)	2 (2.3)	0 (0.0)	0.8	0.04–17.2	—
Immunocompromised patient *n (%)*	10 (9.3)	8 (9.2)	2 (9.5)	0.6	0.1–2.9	—
Long-term corticosteroids *n (%)*	11 (10.2)	8 (9.2)	3 (14.3)	1.6	0.4–6.8	—
Specific COVID therapy						
Lopinavir–ritonavir *n (%)*	16 (14.8)	10 (11.5)	6 (28.6)	3.1	0.9–9.8	
Hydroxychloroquine *n (%)*	34 (31.5)	27 (31.0)	7 (33.3)	1.1	0.4–3.1	
Azithromycin + hydroxychloroquine *n (%)*	29 (26.9)	22 (25.3)	7 (33.3)	1.4	0.5–4.1	
Immunoglobulins *n (%)*	3 (2.8)	3 (3.4)	0 (0.0)	0.6	0.03–11.3	
Sarilumab *n (%)*	1 (0.9)	1 (1.1)	0 (0.0)	4.3	0.3–71.8	
Eculizumab *n (%)*	6 (5.6)	4 (4.6)	2 (9.5)	2.2	0.4–12.8	
Tocilizumab *n (%)*	4 (3.7)	2 (2.3)	2 (9.5)	4.5	0.6–33.8	
Therapy with cumulative dose before sampling						
Azithromycin >1500 mg total dose *n (%)*	26 (24.1)	17 (19.5)	9 (42.9)	**3.1**	**1.1–8.5**	
Dexamethasone >1000 mg *n (%)*	16 (14.8)	10 (11.5)	6 (28.6)	3.1	1.0–9.8	
Any β-lactam >3 days *n (%)*	90 (83.3)	74 (85.1)	16 (76.2)	0.6	0.2–1.8	

Clinical Microbiology and Infection 27 (2021) 790.e1e790.e5

Outcomes of Invasive Aspergillosis in COVID infection

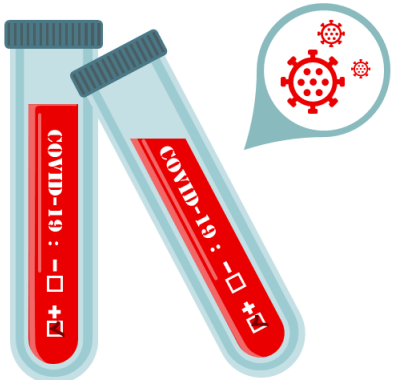


- **<u>Advancing in severity</u>** twice as fast
- **<u>Intubated</u>** twice as long
- Longer **<u>hospital length of stay</u>**
- Higher **<u>mortality rate</u>** (50-60%)
  - Receive appropriate antifungal therapy : 46.7%
  - Not receive appropriate antifungal therapy 100%

Clin Infect Dis. 2021 Mar 9 : ciab223. . Clin Infect Dis. 2020 Jul 28 : ciaa1065; Clin Infect Dis . 2020 Aug 29;ciaa1298.

Who Should be Screening for CAPA? (2020 ECMM/ISHAM consensus)

- Refractory respiratory failure for >5-14 days, plus:
  - **Aspergillus culture** from the respiratory tract
  - **Refractory fever** for >3 days
  - **New fever** after a period of defervescence >48hrs during appropriate ABX therapy without other cause
  - **Worsening** respiratory status
  - Haemoptysis, pleural friction rub, or chest pain



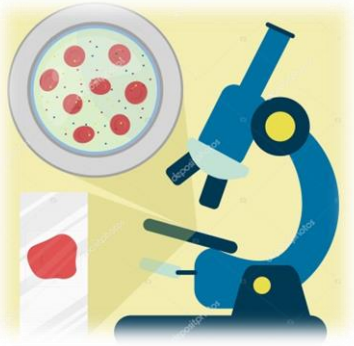
Lancet Infect Dis 2021; 21: e149–62

IDSA: Invasive fungal disease (2021)

☑ Proven IPA:

1. Needle **aspiration or biopsy** in which *Aspergillus* spp **hyphae** are seen with associated **tissue damage**

2. *Aspergillus* spp. **culture from a normally sterile site** and clinically or radiologically abnormal site consistent with an infectious-disease process



IDSA: Invasive fungal disease (2021)

☑ Probable IPA:

Host factor	Clinical/ radiological	Mycological
• Neutropenia (ANC ≤500 cells/mm^3 • Chronic respiratory airway Dx • Decompensated cirrhosis • Hematological malignancies • SOT or HSCT • HIV • Immunosuppressants use during the past 90 days • **Glucocorticoid treatment (prednisone≥ 20 mg/d)** • **Severe viral pneumonia, such as COVID-19**	• Dense, well-circumscribed lesions +/- halo sign • Air crescent sign • Cavity • Wedge-shaped & segmental or lobar consolidation • Tracheobronchial ulceration, pseudomembrane, nodule, plaque, or eschar detected by bronchoscopy (for Aspergillus tracheobronchitis)	• Cytology, direct microscopy, or culture of Aspergillus spp. in a lower respiratory tract specimen • **GM Ag>0.5** in plasma/serum; • **GM Ag>0.8** in BALF

EORTC/MSGERC consensus (2020)

Any 1 of the following:
Single serum or plasma: ≥1.0
BAL fluid: ≥1.0
Single serum or plasma: ≥0.7 and BAL fluid ≥0.8

*GM: Galactomannan

Challenges in CAPA Diagnosis/Management

- Most CAPA **without classic host risk factors** except steroid use
- Difficult to distinguish CAPA from severe COVID-19 alone for their similar **radiology feature**
- Difficult to distinguish btw aspergillus **colonization and invasive** disease from sputum or tracheal aspirate
- Decreased use of diagnostic bronchoscopy
- Low sensitivity of detection of **circulating biomarker in serum** (galatomannan test: 0-40%; BDG: 0-50% not specific for CAPA)

Lancet Infect Dis 2021; 21: e149–62

Challenges in CAPA Diagnosis/Management

- **High mortality in CAPA despite antifungal therapy**
  - Lack of high quality studies evaluate drug of choice in this population
- **Drug interactions with antifungal use :**
  - e.g. corticosteroid, FQ, PPI, BZD…
- **PK/PD changes in critical illness status:**
  - Liver, renal impairment
  - Decrease enteral absorption; NPO status
  - Altered fluid balance, protein binding, inflammation condition
  - ECMO, renal replacement therapy

Lancet Infect Dis 2021; 21: e149–62

COVID-19 Associated Pulmonary Aspergillosis Management

Recommended Treatment Algorithm
(2020 ECMM/ISHAM consensus criteria)

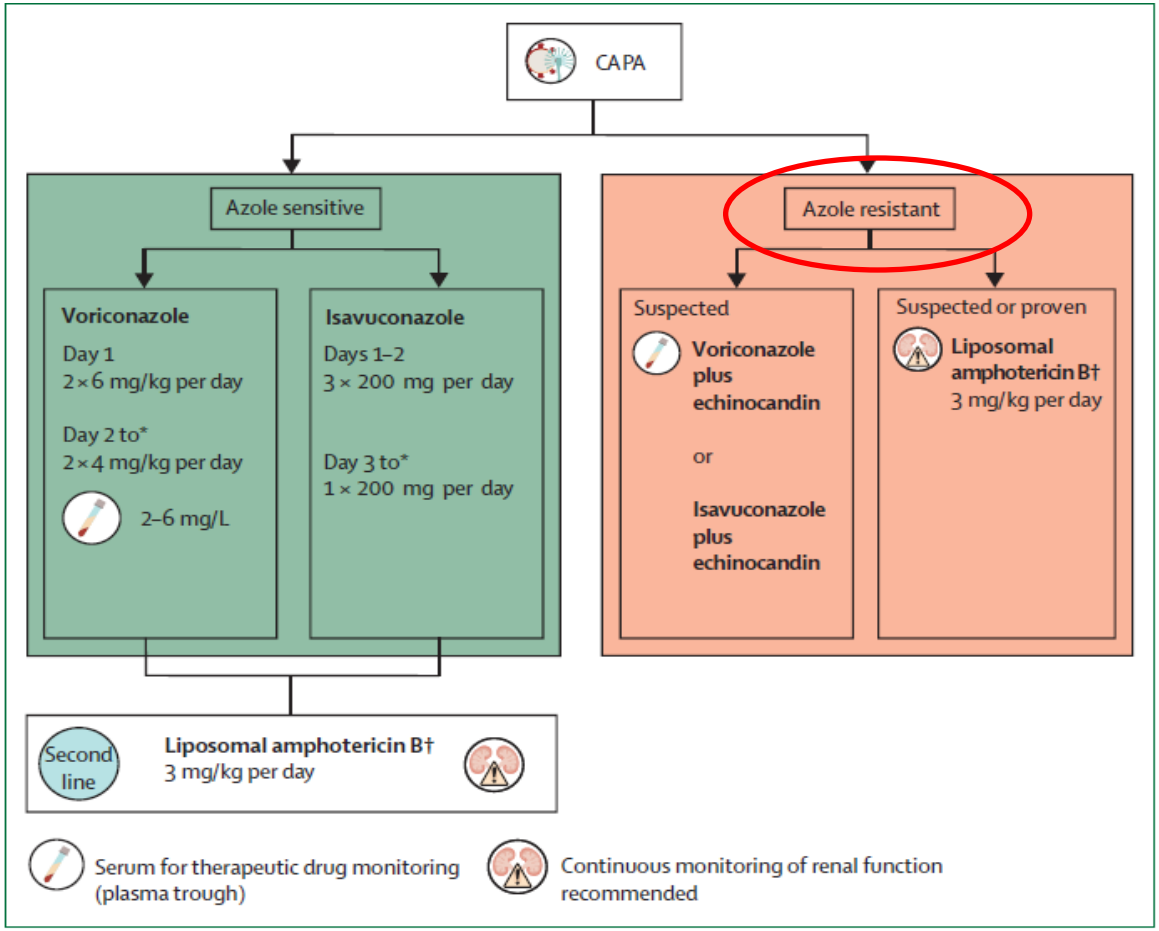


Figure 3: Recommended treatment for CAPA

- Based on
  - MIC?
  - Local prevalence?
  - Clinical response?
  - History of azole use?

Guideline	Isavuconazole	Voriconazole	Liposomal amphotericin B
ECIL-6[30]	AI	AI	BI
ESCMID/ ECMM 2018[31]	AI–AII	AI–AII	BII
IDSA 2016[56]	AII	AI	AII

Lancet Infect Dis 2021; 21: e149–62

Voriconazole

- **First-line therapy for IA**
- **Dose:** (Loading) 6mg/kg Q12H*2 doses; (Maintenance) 4mg/kg Q12H
  - **Renal impairment:** CrCl <50 mL/min: risk of SBECD accumulation
    - ✓ **Oral form is recommended** unless benefit> risk;
    - ✓ Closely monitor scr, change to PO form when possible
  - **Liver impairment:** (Child-Pugh A-B) 50% dose reduction
- **Treatment consideration:**
  - Highly variable nonlinear pharmacokinetics
  - Narrow therapeutic window
  - Drug-drug interactions

Voriconazole

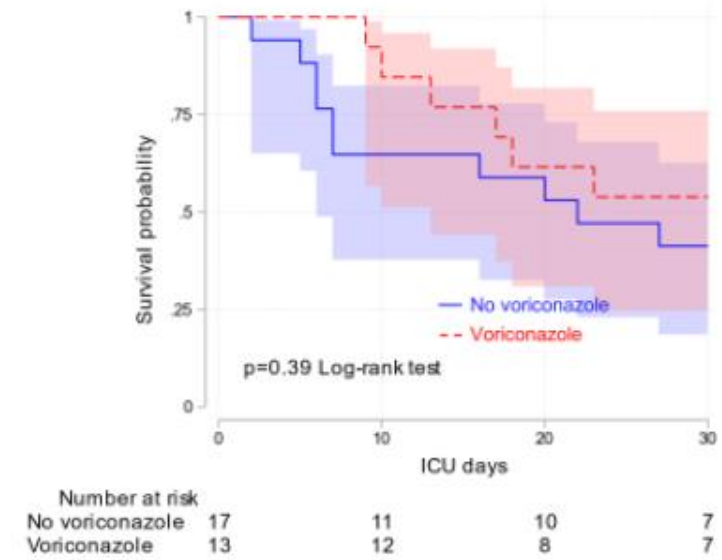
- The **most commonly prescribed** antifungal agent in CAPA[1]

  → Show **a trend** toward **lower mortality** and **reduction of GM index**[2]

Table 1. Clinical characteristics, treatment and outcomes in patients with COVID-19-associated pulmonary aspergillosis (CAPA) who survived or died. Data are presented as N (%), unless otherwise indicated.

Parameter	Total	Survived	Died	*p*-Value
N	85	39	46	
None	15 (18)	5 (13)	10 (22)	0.28
Mold-active triazole (MAT: vori-, posa-, isavuconazole)	61 (72)	31 (79)	30 (65)	0.61
Voriconazole	55 (65)	29 (74)	26 (57)	0.11
Isavuconazole	6 (7)	2 (5)	4 (9)	0.68
Echinocandin (caspo-, mica-, anidulafungin)	14 (16)	7 (18)	7 (15)	0.78
Amphotericin-B	21 (25)	11 (28)	10 (22)	0.62

* Total > 100% since one patient was coinfected with *A. fumigatus* and *A. flavus*. ** Total >100% since patients may have received combination or sequential antifungals.



1. Diagnostics 2020, 10, 807 2. Clin Infect Dis. 2020 Jul 28 : ciaa1065.

Isavuconazole

- **First-line therapy for IA**
- **Prodrug:** Isavuconazonium sulfate (Cresemba®)
- **Dose:** (Loading) 200 mg Q8H * 6 doses; (Maintenance) 200 mg QD
  - ✓ start 12-24 hours after loading dose
  - **Renal impairment:** no dosage adjustment necessary
  - **Liver impairment:**

    (Child-Pugh A-B) no dosage adjustment

    (Child-Pugh C): no data

Isavuconazole

SECURE trial (phase 3, non-inferior RCT)

- **P:** suspected invasive mould disease
- **I:** Isavuconazole IV 200mg TID d1-2, 200mg QD (IV/PO)
- **C:** Voriconazole 6mg/kg BID d1, 4mg/kg BID IV (PO 200mg BID D3~)
- **O:** All-cause mortality; safety

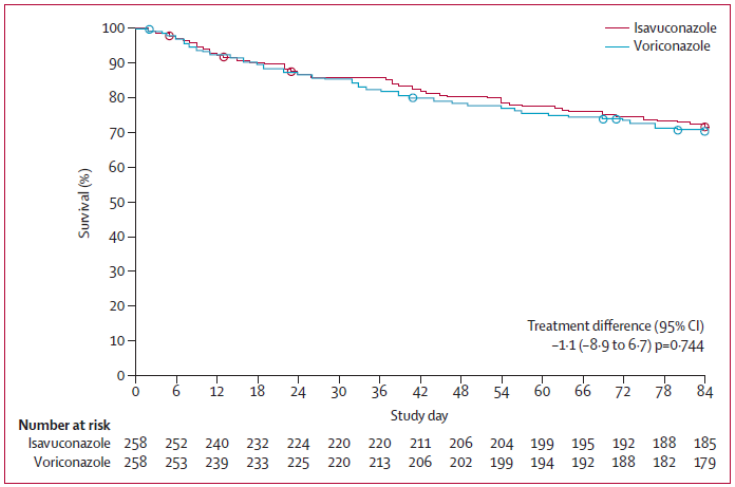


Figure 2: **Survival from first dose of study drug to day 84**
Patients were censored on the day of their last known survival status, represented by the circles. Figure shows data for ITT population. ITT=intention to treat; all randomised patients who received study drug.

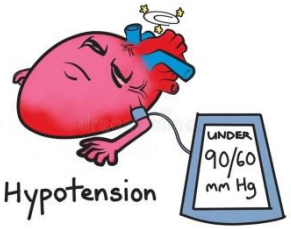
	Isavuconazole (n=257)	Voriconazole (n=259)	p value
Overall	247 (96%)	255 (98%)	0·122
Gastrointestinal disorders	174 (68%)	180 (69%)	0·705
Infections and infestations	152 (59%)	158 (61%)	0·719
General disorders and administrative site conditions	148 (58%)	144 (56%)	0·658
Respiratory, thoracic, and mediastinal disorders	143 (56%)	147 (57%)	0·859
Metabolism and nutrition disorders	108 (42%)	121 (47%)	0·289
Nervous system disorders	95 (37%)	89 (34%)	0·582
Skin and subcutaneous tissue disorders*	86 (33%)	110 (42%)	0·037¶
Investigations (abnormal laboratory tests)	85 (33%)	96 (37%)	0·357
Blood and lymphatic system disorders	77 (30%)	82 (32%)	0·703
Psychiatric disorders†	70 (27%)	86 (33%)	0·151
Musculoskeletal and connective tissue disorders	69 (27%)	77 (30%)	0·495
Vascular disorders	67 (26%)	77 (30%)	0·378
Renal and urinary disorders	55 (21%)	58 (22%)	0·832
Cardiac disorders	43 (17%)	57 (22%)	0·148
Eye disorders‡	39 (15%)	69 (27%)	0·002¶
Injury, poisoning, and procedural complications	33 (13%)	39 (15%)	0·526
Hepatobiliary disorders§	23 (9%)	42 (16%)	0·016¶
Immune system disorders	20 (8%)	25 (10%)	0·533
Neoplasms benign, malignant and unspecified	19 (7%)	31 (12%)	0·101
Ear and labyrinth disorders	14 (5%)	13 (5%)	0·846
Reproductive system and breast disorders	8 (3%)	13 (5%)	0·373
Endocrine disorders	5 (2%)	3 (1%)	0·503

- Isavuconazole is **non-inferior** to voriconazole
- Well tolerated with **less hepatobiliary, eye, and skin side effects**

Lancet 387:760, 2016

Amphotericin B

- **Alternative therapy**
  - Preferred regimen if intolerant to voriconazole
  - May be 1st line therapy in region with >10% azole resistance
- **Dose:**
  - **Standard prep: 0.25-1 mg/kg/day**
    - ✓ No dose adjustment necessary for renal or hepatic
  - **Liposomal amphotericin B: 3-5mg/kg/day**
    - ✓ 健保給付：限用於侵入性黴菌感染且腎功能不全患者。



Posaconazole

- **Alternative therapy of IA**
  - Indicated for IA prophylaxis
  - ECMM/ISHAM: 2nd line for IA
    - ✓健保給付:對amphotericin B或itraconazole或voriconazole治療無效或不能忍受之成人侵入性麴菌病的第二線用藥。
- **Dose:**
  - (IV or delayed release tab) 300mg BID on day 1, then 300mg QD
  - (Suspension): 200mg QID, then 400mg BID after stabilization

Posaconazole

	Posaconazole group	Voriconazole group	Treatment difference (95% CI)*	p value
All-cause mortality				
ITT population				
Day 42 all-cause mortality†	44/288 (15%)	59/287 (21%)	−5·3% (−11·6 to 1·0)‡	<0·0001§
Day 84 all-cause mortality	81/288 (28%)	88/287 (31%)	−2·5% (−9·9 to 4·9)	NA
FAS population				
Day 42 all-cause mortality†	31/163 (19%)	32/171 (19%)	0·3% (−8·2 to 8·8)	NA
Day 84 all-cause mortality	56/163 (34%)	53/171 (31%)	3·1% (−6·9 to 13·1)	NA
Global clinical response in the FAS population				
Success at week 6	73/163 (45%)	78/171 (46%)	0·6% (−11·2 to 10·1)	NA
Complete response¶	11/163 (7%)	9/171 (5%)	..	..
Partial response‖	62/163 (38%)	68/171 (40%)	..	..
Stable response, progression of fungal disease, death, or unable to assess at week 6	90/163 (55%)	93/171 (54%)	..	..
Stable response**	12/163 (7%)	22/171 (13%)	..	..
Progression††	27/163 (17%)	21/171 (12%)	..	..
Death	34/163 (21%)	33/171 (19%)	..	..
Unable to assess	17/163 (10%)	17/171 (10%)	..	..
Success at week 12	69/163 (42%)	79/171 (46%)	−3·4% (−13·9 to 7·1)	NA
Complete response¶	20/163 (12%)	19/171 (11%)	..	..
Partial response‖	49/163 (30%)	60/171 (35%)	..	..
Stable response, progression of fungal disease, death, or unable to assess at week 12	94/163 (58%)	92/171 (54%)	..	..
Stable response**	9/163 (6%)	7/171 (4%)	..	..
Progression††	13/163 (8%)	19/171 (11%)	..	..
Death	56/163 (34%)	51/171 (30%)	..	..
Unable to assess	16/163 (10%)	15/171 (9%)	..	..

- 26 countries, 2013 -2019, phase 3, non-inferiority RCT
- **P:** ≥13 y/o, proven/probable/possible IA (N=575)
- **I:** POSA 300mg BID (d1), 300mg QD (d2-84) IV or PO
- **C:**VORI 6mg/kg BID IV (or 300mg BID PO) d1, 4mg/kg BID (or 200mg BID PO) d2-84
- **O:** **(1st)** all-cause mortality on d42 ; **(2nd)** IA death on d42, d84, clinical response, safety

	Posaconazole group (n=288)	Voriconazole group (n=287)	Treatment difference (95% CI)*
Participants with treatment-emergent adverse events	281 (98%)	280 (98%)	0·0% (−2·8 to 2·8)
Serious	178 (62%)	172 (60%)	1·9% (−6·1 to 9·8)
Deaths	86 (30%)	87 (30%)	−0·5% (−7·9 to 7·0)
Leading to discontinuation of study drug	93 (32%)	102 (36%)	−3·2% (−11·0 to 4·5)
Participants with treatment-related adverse events	86 (30%)	115 (40%)	−10·2% (−17·9 to −2·4)
Serious	16 (6%)	20 (7%)	−1·4% (−5·6 to 2·7)
Deaths	0	3 (1%)	−1·0% (−3·0 to 0·3)
Leading to discontinuation of	18 (6%)	28 (10%)	−3·5% (−8·1 to 1·0)

Posaconazole is non-inferior to voriconazole for the treatment of IA, and is well tolerated compared with voriconazole

- **VORI:** Eyes disorders(10%); GOT/GPT (6%), GGT (4%); Hallucination (4%); Nausea (4%)
- **POSA:** GOT/GPT (6-8%); Hypokalaemia (4%); Nausea/Vomiting (3-4%);

Lancet . 2021 Feb 6;397(10273):499-509.

PK/PD of Triazoles

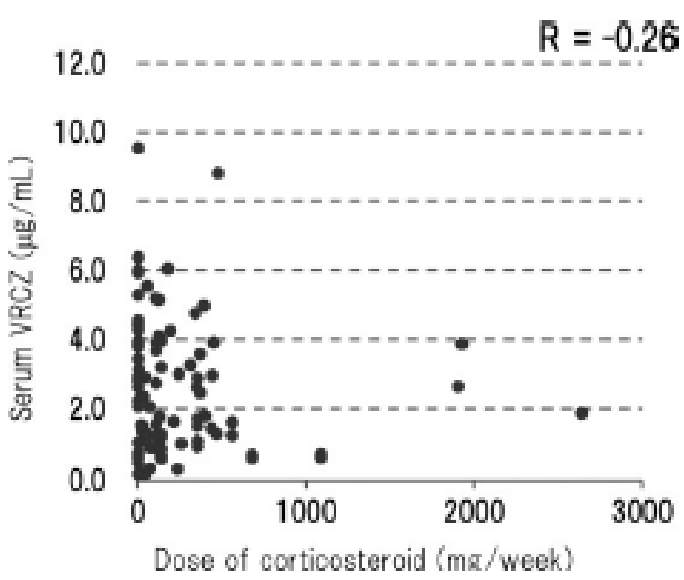
	Voriconazole	Isavuconazole	Posaconazole
Absorption	• Oral: 96% • Time to peak: 1-2 hours (PO)	• Oral: 98% • Time to peak: 2-3 hours (PO)	• Oral : (tablet) 54%; (suspension) well absorbed • Time to peak: 4 hours (PO)
Distribution	• Extensive tissue distribution • Adults: 4.6 L/kg • **Protein binding: 58%**	• V_{ss}: 450 L (IV) • **Protein binding: >99%**	• Vd: 287 L (PO); 261 L (IV) • **Protein binding: >98%**
Metabolism	• **Hepatic** ✓ ↑AUC 3.2-fold in mild to moderate hepatic impairment (Child-Pugh class A and B)	• **Hepatic** ✓ Rapidly hydrolyzed in the blood from isavuconazonium sulfate (prodrug)	• **Hepatic:** ✓ primarily glucuronidation ✓ substrate of P-gp and UDP-glucuronidation
Excretion	• **Half-life: 6-8hrs** ✓ Steady-state: achieved by day 3 ✓ Accumulation of the IV vehicle (SBECD) occurs in patients with renal impairment • **Poorly dialyzed[3]** **(SBECD can be removed by CRRT)**	• **Half-life: 130 hrs** ✓ feces (33% as unchanged isavuconazole) ✓ Urine (<1% as unchanged isavuconazole); • **Not dialyzable**	• **Half-life: 26-35hrs** ✓ Steady-state: achieved by day 7-10 • **Not dialyzable[3]**

1. Lexicomp; 2. Micromedex; 3. 2013 Dialysis of Drugs; 4. Cresemba® product information

	Voriconazole	Isavuconazole	Posaconazole
ECMO	• **May initially underdosing (**extracted in ECMO circuit**);** • **May overdosing at discontinuation (**once circuit saturated, "re-dosing" of patient can occur**)**	• Exposure may be **reduced by 50%**	-
Critically illness	• Unpredictable • **Elevated exposures** are reported in the setting of systemic inflammation	-	-
Drug interactions	✓ Proton Pump Inhibitor (↑voriconazole serum conc.) ✓ Glucocorticoid (↓voriconazole serum conc.) ✓ **Midazolam** (↑midazolam AUC by 3-10 fold)	✓ **Glucocorticoid** (↑dexamethasone serum conc**.)** ✓ **Midazolam** (↑midazolam AUC by 2-fold)	✓ **Proton Pump Inhibitor** (↓ posaconazole serum conc.) ✓ **Glucocorticoid** (↑dexamethasone serum conc.) ✓ **Midazolam** (↑midazolam AUC by 3-6 fold)
TDM	• Goal trough: 1-5.5(6) mg/L • Suggest frequency: weekly (twice in the first week)	• Routine TDM may not be necessary	• Goal trough: 1-3.75 mg/L • Suggest frequency: weekly (twice in the first week)

Lancet Infect Dis 2021; 21: e149–62; Lexicomp: drug interact

Voriconazole Concentration Inversely Correlated with Corticosteroid Use



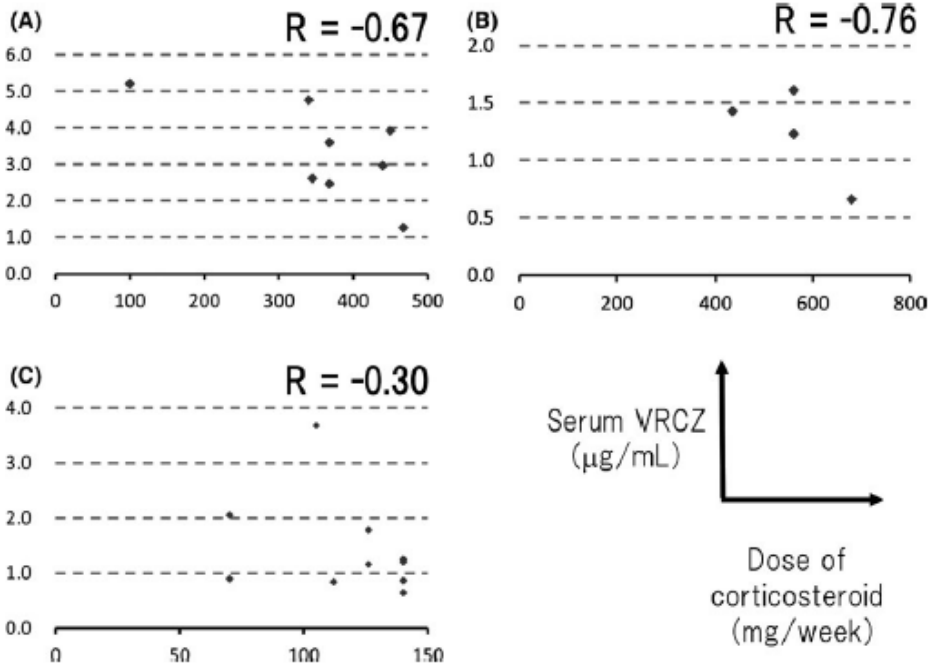
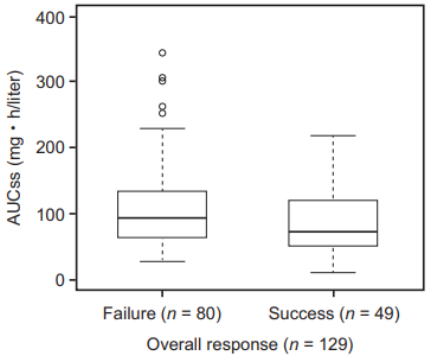


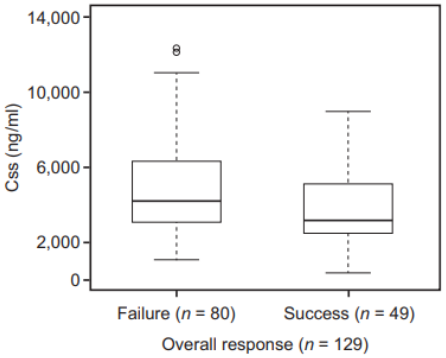
FIGURE 1 Association between VRCZ concentration and corticosteroid dose. A, VRCZ concentration was inversely correlated with corticosteroid dose ($r = -.26$); B, 1/VRCZ concentration per body weight was weakly correlated with corticosteroid dose ($r = .17$)

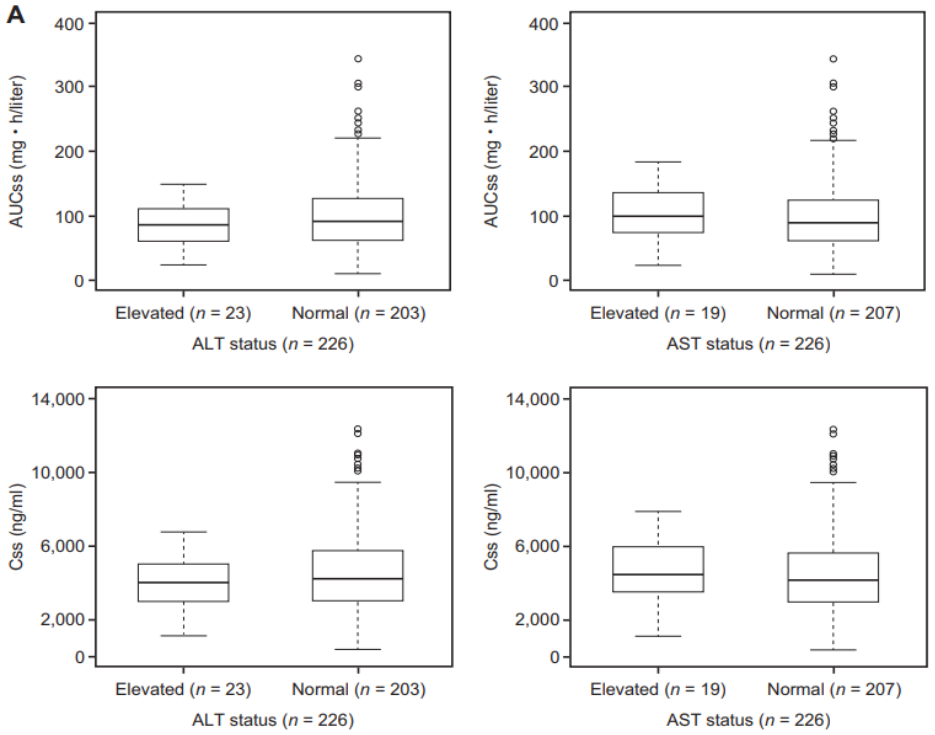
Transpl Infect Dis. 2018;20:e12886.

Exposure-Response Relationship of Isavuconazole

- **No statistically significant relationships** were observed for the **exposure** of isavuconazole with **efficacy or safety** profiles.
- Routine TDM may not be necessary



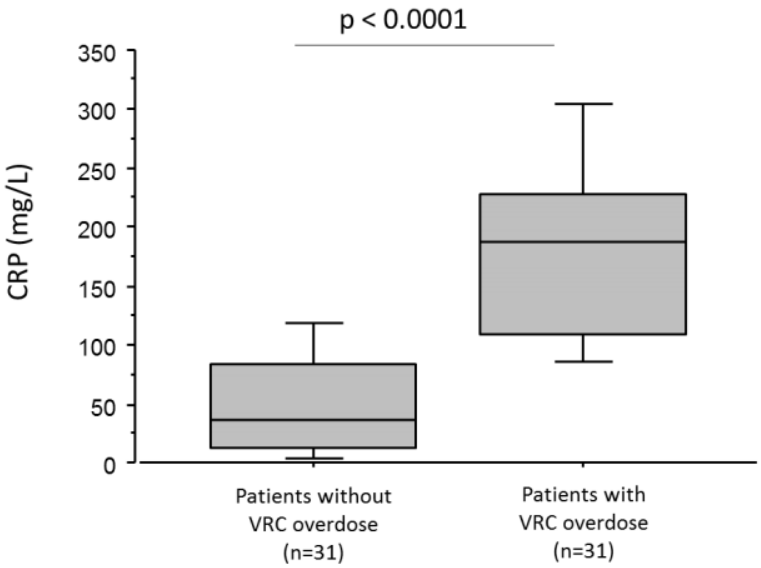




Antimicrob Agents Chemother 61:e01034-17

Elevated Voriconazole Exposure has been Shown in the Setting of Systemic Inflammation

- With 0.015mg/L increase in voriconazole Cmin for every 1mg/L increase in CRP → Increase risk of voriconazole overdose



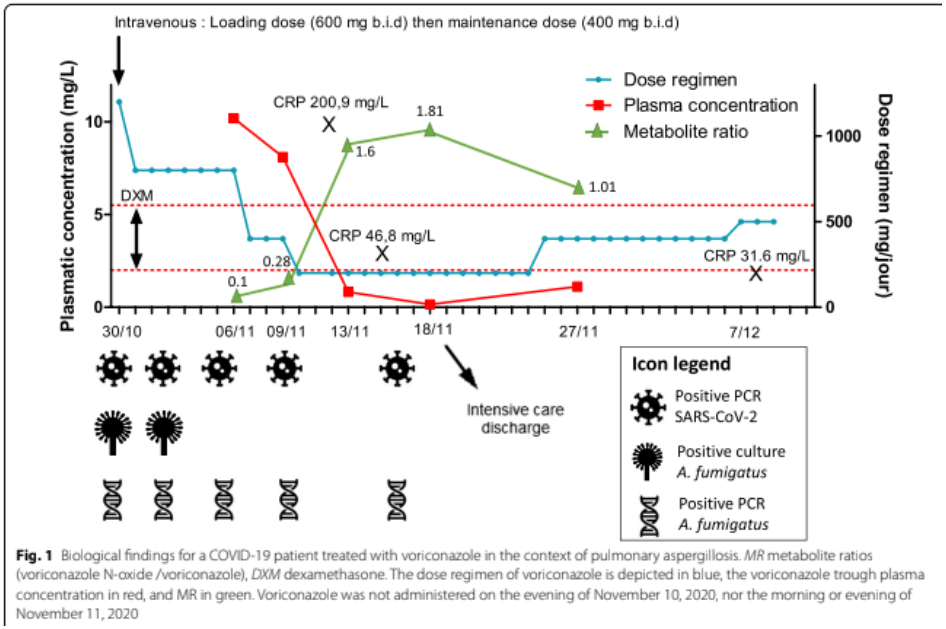


Fig. 1 Biological findings for a COVID-19 patient treated with voriconazole in the context of pulmonary aspergillosis. *MR* metabolite ratios (voriconazole N-oxide /voriconazole), *DXM* dexamethasone. The dose regimen of voriconazole is depicted in blue, the voriconazole trough plasma concentration in red, and MR in green. Voriconazole was not administered on the evening of November 10, 2020, nor the morning or evening of November 11, 2020

Intensive Care Medicine volume 47, pages819–834 (2021); Fundam Clin Pharmacol. 2018;fcp.12422.

PPI Decreased the Metabolism of Voriconazole

- Co-administered with LAN, OME and ESO significantly increased the plasma VRC trough levels ($p < 0.05$)
- There was no significant association between VRC concentration and PAN or ILA use.

Biomedicine & Pharmacotherapy 108 (2018) 60–64

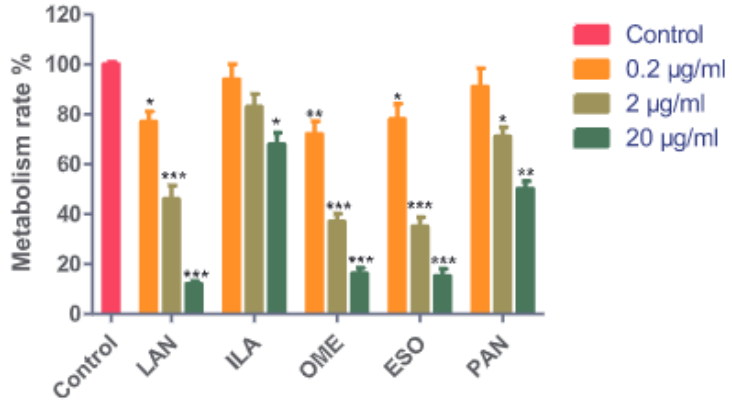
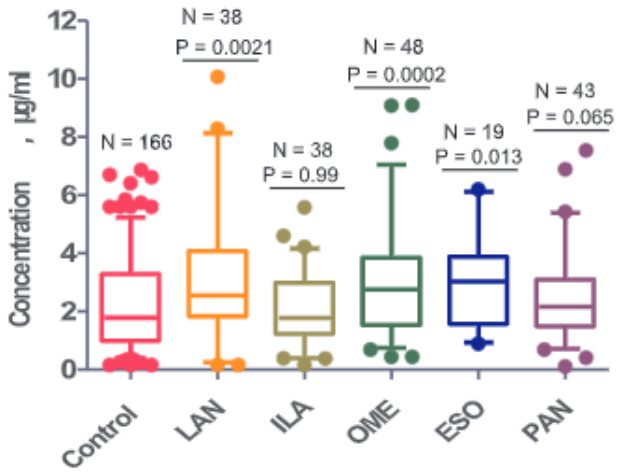


Fig. 1. Concentration-dependent inhibition of VRC metabolism by Five PPIs. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ compared with the control group. Statistical analyses were performed by the unpaired Student's test.



***LAN:** lansoprazole; **ESO:** esomeprazole; **OME:** omeprazole;
***PAN:** pantoprazole**; ILA:** ilaprazole; ***VRC:** voriconazole

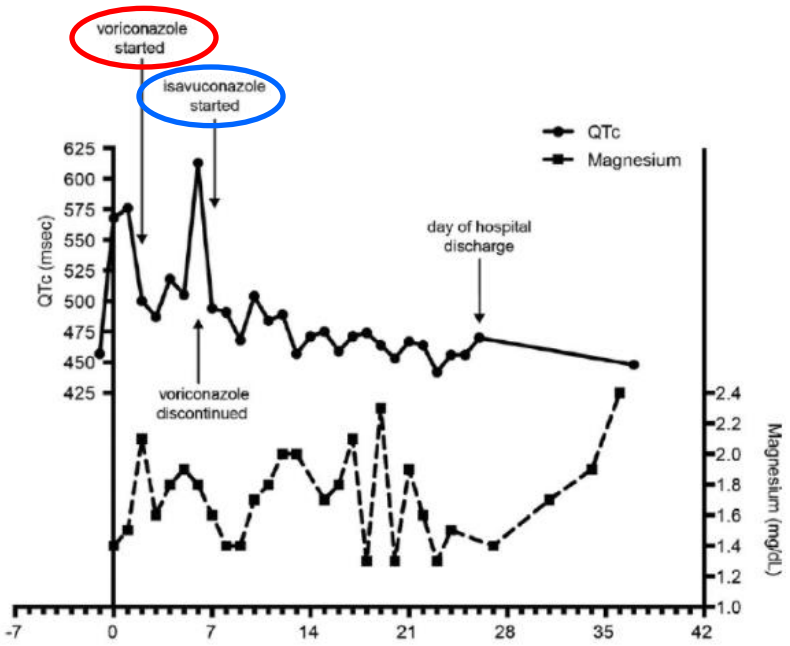
Biomed Pharmacother Biomed Pharmacother. 2018;108:60–4.

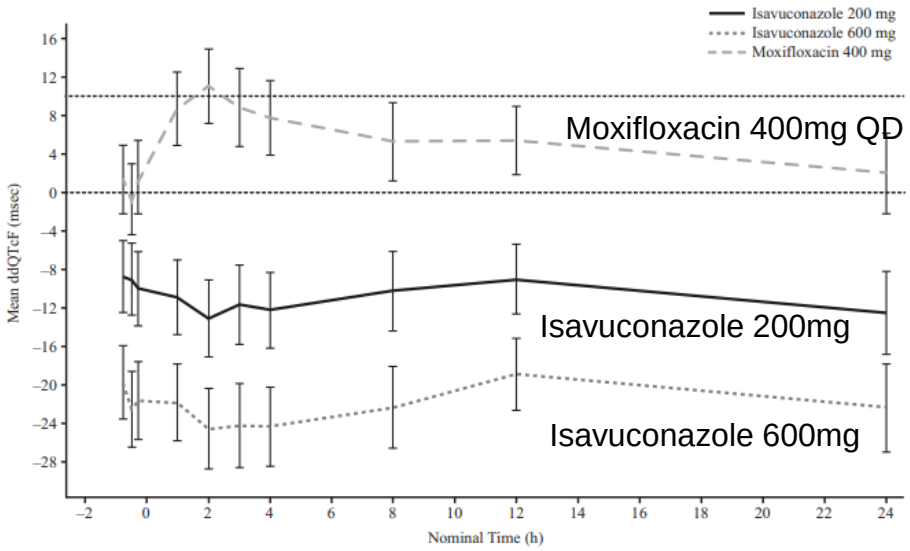
Triazoles and QT Abnormalities

- **Voriconazole[1], posaconazole** increase risk of QT interval prolongation, especially in combination with FQ, macrolide

  → ventricular arrhythmias, Torsades de Pointes

- **Isavuconazole** shortens the QT interval in a **dose-dependent** manner[2]





1. Transpl Infect Dis. 2017;19:e12712. 2.Clin Pharmacol Ther. 2017;101(6):782–790

Echinocandins

- **Only caspofungin has indication for invasive aspergillosis**

	Caspofungin	Anidulafungin	Micafungin
FDA-approved indications		-	
- empiric febrile neutropenia	+	-	-
- candidemia	+	-	+
- candidal abscess	+	-	+
- esophageal candidiasis	+	+	+
- Candida peritonitis	+	-	+
- invasive aspergillosis	+ (2nd line)	-	-
- Candida prophylaxis	-	+ (in HSCT)	-
Dosing (labeled)	50 mg	100 mg	100 mg
Loading dose	70 mg	no	200 mg
Renal insufficiency	no adjustment	no adjustment	no adjustment
Hepatic insufficiency	reduce dose, if moderate	no adjustment	no adjustment
Pregnancy	category C	category C	category C
Breast feeding	unknown-caution	unknown-caution	unknown-caution
Drug-drug interactions	tacrolimus cyclosporine rifampin phenytoin carbamazepin examethasone efavirenz nevirapine	sirolimus nifedipine	-

AVFT [online]. 2010, vol.29, n.3, pp. 44-50 .

Echinocandins as monotherapy in IA

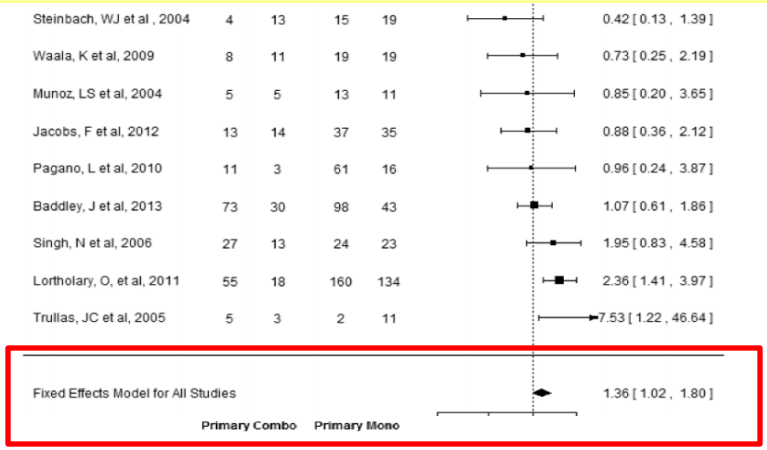
Reference	Study design	Patient group	Intervention	Control	Outcome
Viscoli C, 2009 (EORTC study)	Phase II, non-comparative, multicentre study	Proven or probable IA in HM or undergo HSCT (N=61)	**Caspufungin** (70mg (d1), then 50mg QD)	-	• **Response rate 33%** • Mortality rate: **34% (w6) , 47% (w12)**
Raad II, 2015	Retrospective cohort study	Proven or probable IA in HM (N=181)	**Caspofungin** (70mg (d1), then 50mg QD)	Voriconazole	• **Response rate:** → caspo 27%; VORI 47% (primary) → caspo 29%; VORI 46% (salvage) • **IA-mortality rate (12 weeks):** → caspo **47%;** VORI 8% (primary) → caspo **47%;** VORI 17%(salvage) • **VORI was associated with lower IA-mortality** than CASPO (HR = 0.2, 95% CI 0.06–0.96; P = 0.04)
Denning DW, 2006	Open-labeled, multinational, non-comparative study	Proven or probable pulmonary IA (N=225)	**Micafungin** (75-150mg/day)	-	• **Response rate: 35.6%** → 50% (primary), → 41% (salvage) • **IA mortality rate: 58.5%**
Kontoyiannis DP, 2009		Proven or probable (pulmonary) IA in HSCT (N=98)	**Micafungin** (75-150mg/day)	-	• **Response rate: 38%** → 50% (primary); → 0% (refractory); 100% (toxicity, n=2)

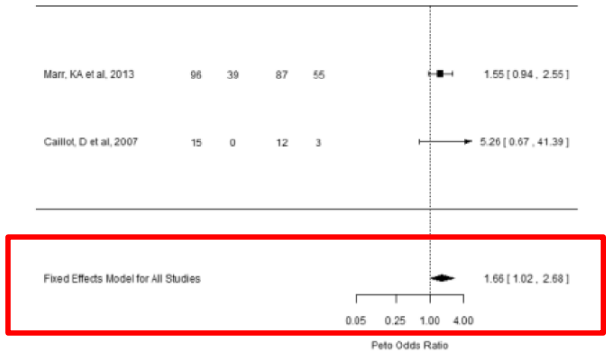
HM: haematological malignancies ; HSCT: hematopoietic stem cell transplantation

Echinocandins as combination therapy in IA

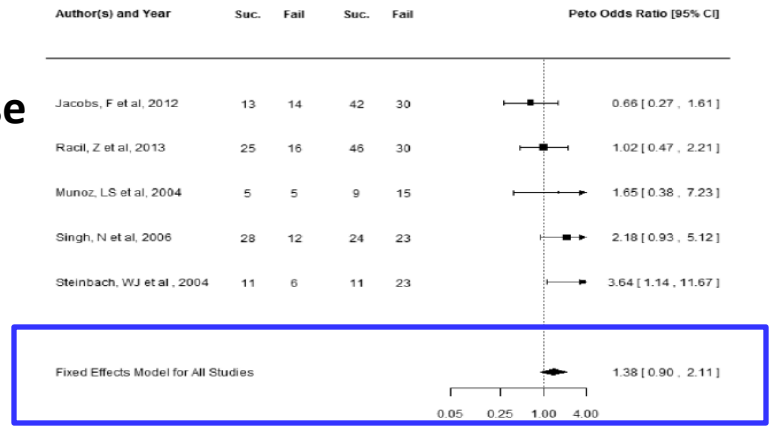
Combination antifungals for IA in the **primary setting** demonstrate **improvement in survival**, but **no significant** difference in **response rate**

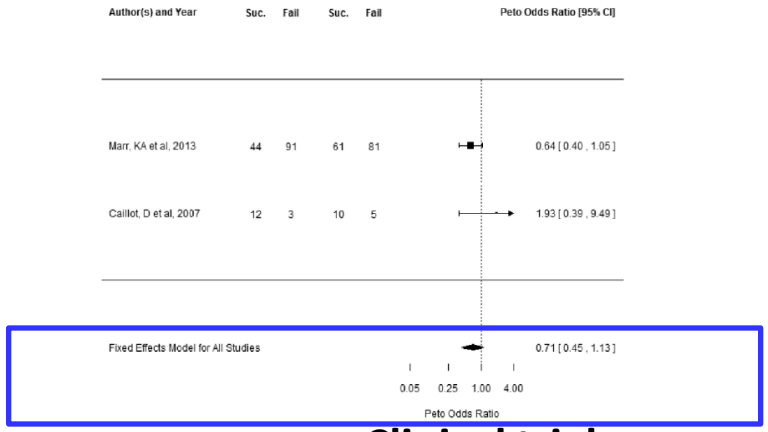
Survival rate





Response rate





Observational study

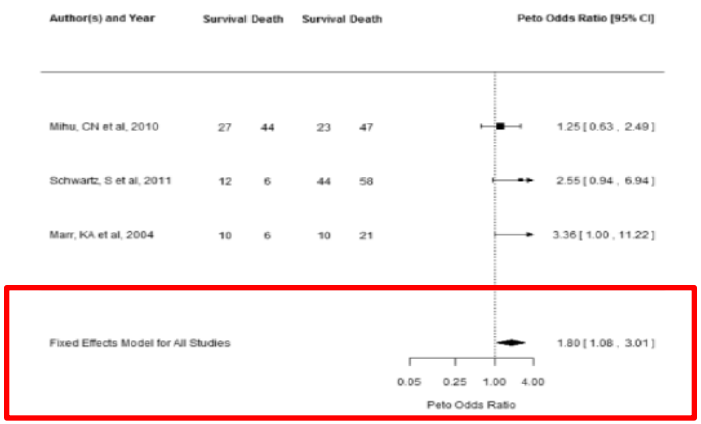
Clinical trials

International Journal of Infectious Diseases 28 (2014) 80–94

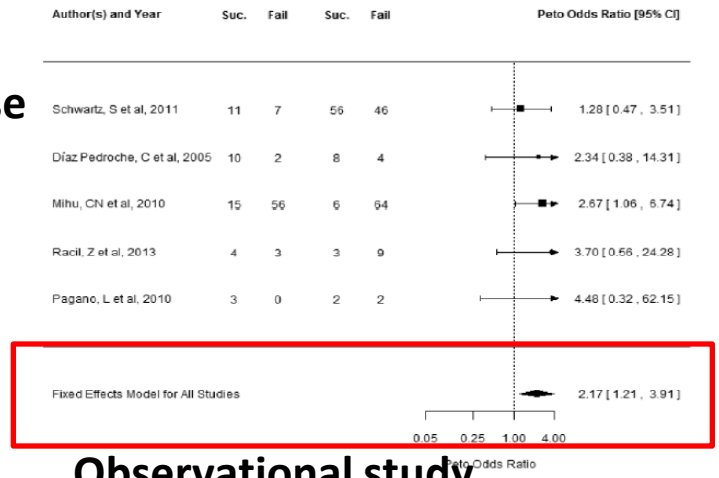
Echinocandins as combination therapy in IA

Combination antifungals for IA in the **salvage setting** demonstrate **improved clinical outcomes** over monotherapy in **observational studies**

Survival rate

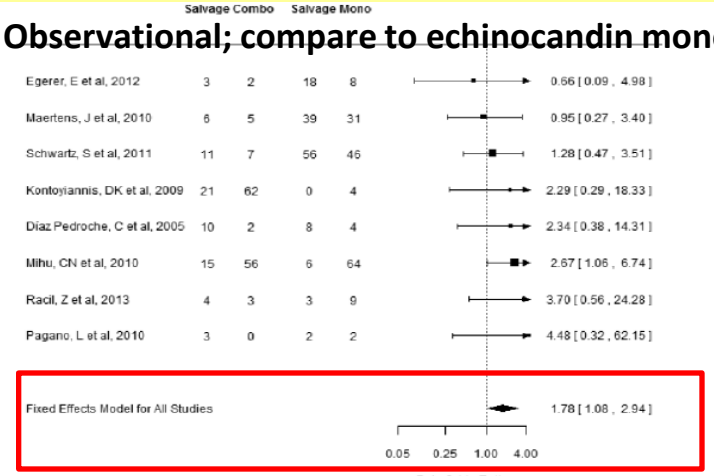


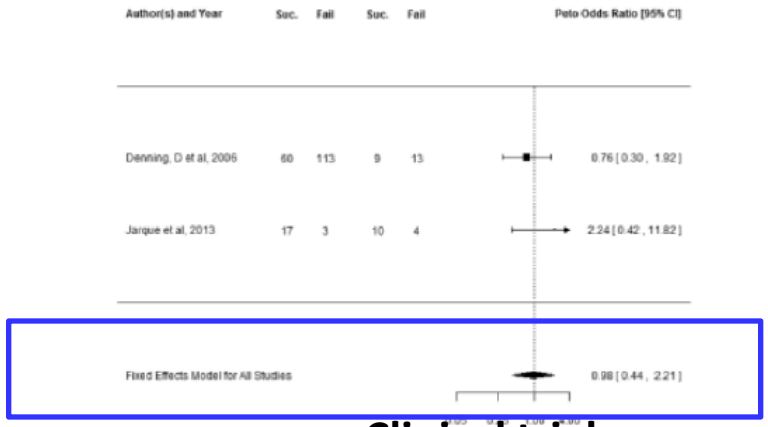
Response rate



Observational study

Observational; compare to echinocandin mono





Clinical trials

International Journal of Infectious Diseases 28 (2014) 80–94

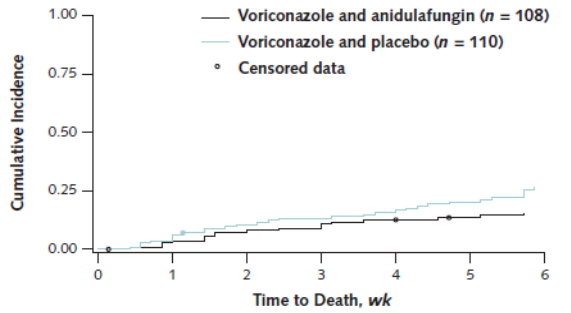
Echinocandins as combination therapy in IA

Prospective, double-blind, multicenter RCT (93 international sites).
P: 454 patients with HM or HCT and suspected or documented IA
I: Voriconazole + Anidulafungin
VORI 6mg/kg Q12H IV (d1), 4mg/kg Q12H IV (or PO 300mg Q12H after wk 1) * 6wks; Anidulafungin 200mg (d1), 100mg QDx 2-4 wks
C: Voriconazole + Placebo
O: (1st) all cause mortality at 6 weeks (2nd)all-cause mortality at W6, W12

Table 2. Mortality Outcomes in the Modified Intention-to-Treat Population, by Regimen

Variable	Deaths, *n/N* (%)*		Treatment Difference (95% CI), *percentage points*†
	Monotherapy	Combination Therapy	
Overall	39/142 (27.8)	26/135 (19.5)	−8.3 (−19.0 to 1.5)
Overall 12-wk mortality	55/142 (39.4)	39/135 (29.3)	−10.1 (−21.4 to 1.1)
Neutropenia§			
Yes	21/86 (24.4)	18/77 (23.5)	−0.9 (−14.0 to 12.2)
No	15/47 (33.2)	7/52 (13.7)	−19.5 (−36.1 to −2.8)
Geographic region			

Figure 3. Outcomes in the positive galactomannan subgroup.



- VORI+ anidulafungin shows **a trend towards reduced mortality**
- **All-cause mortality is significantly lower** in the combination group in GM(+) patients. (15.7% vs. 27.3%, P = 0.037)

Ann Intern Med 2015; 162: 81–89.

* HM: hematologic malignancies (HMs)
* HCT: hematopoietic cell transplantation (HCT)

Possible Role for Echinocandins in IA

TABLE 1 Possible role and indications for echinocandins in the treatment of invasive aspergillosis

Indication	Aim[a]	Situation	Level of evidence (Ref.)
First-line treatment (monotherapy)	To treat IA when no alternative regimen (or potential risks outweighing benefits for other regimens)	Relative contraindications to azoles (underlying liver disease, drug-drug interactions, prolonged QT interval); relative contraindications to AMB (underlying kidney disease, nephrotoxic comedications)	Noncomparative prospective or retrospective studies (overall success rate, 30–90%) (62)
Second-line treatment (monotherapy)	To treat IA when first-line antifungals have failed or need to be discontinued	Toxicity of triazoles (hepatic test disturbances, visual/neurological side effects); toxicity of AMB (acute renal failure); failure of previous antifungal regimens	Noncomparative prospective or retrospective studies (overall success rate, 30–70%) (62)
In combination with triazoles or AMB	To obtain synergistic interactions (triazoles, AMB)	Severe and/or disseminated IA, galactomannan-positive IA; in case of failure of previous regimen or breakthrough IA; for IA due to azole-resistant *A. fumigatus*	One randomized controlled trial (trends, benefit limited to subgroup analyses) (81); expert opinion; murine models (75, 77)
	To palliate potential PK/PD defect until first-line drug achieves appropriate serum level (triazoles)	In severe and/or disseminated IA	Expert opinion
	To palliate potential inefficacy of first-line drug (triazoles)	For empirical treatment, if suspicion or high local prevalence of azole-resistant *A. fumigatus*; breakthrough IA	Expert opinion (82)
	To obtain synergistic interactions on biofilms (triazoles, AMB)	For *Aspergillus* endocarditis or osteomyelitis with presence of prosthetic material	*In vitro* studies (79)

[a]AMB, amphotericin B; IA, invasive aspergillosis; PK/PD, pharmacokinetic/pharmacodynamic.

Antimicrob Agents Chemother 63:e00399-19.

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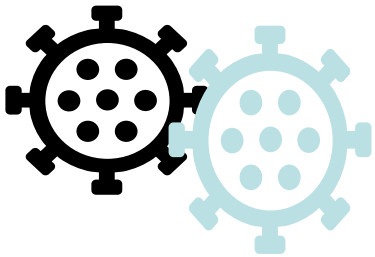
Duration of treatment

- **The optimal duration** of CAPA treatment is unknown
- Expert panel **suggest 6-12 weeks** according to:
  - clinical condition (resolution of infiltration)
  - host factor (malignancy, immunosuppressant)
  - microbiology (GM index in respiratory/serum)

Antimicrob Agents Chemother 63:e00399-19.

Conclusion

- The **dose and duration of corticosteroid** use in COVID patient should be carefully evaluated
- **Voriconazole** and **isavuconazole** are so far the most commonly recommended antifungals for CAPA
  - Posaconazole was non-inferior to VORI for the treatment of IPA
  - **Amphotericin B** can be salvage therapy or initial therapy if local azole resistance is high.
  - **Echinocandins** are not recommended as monotherapy, but may be used in combination with azole as salvage therapy or high risk of azole resistance.
- **Drug interactions, adverse effects, costs, & capability of TDM** should be considered in choosing the best strategy of CAPA management especially in critically ill status

COVID-19

THANK YOU