Management of invasive fungal infections in COVID-19 patients

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Many factors could influence the morbidity and mortality in COVID-19 patients,

among these,

opportunistic fungal infections

have a serious role.

There are three reasons for immunocompromised status in COVID-19 area:

- Significant decrease of different cell components, essentially microphages, neutrophils, and lymphocytes
- Downregulation of tight junction, integrity and barrier function of the epithelium of respiratory system.
- Immunosuppressive agents such as corticosteroids used in treatment

Candida species are the most isolated fungi responsible for invasive infection of **extrapulmonary sites** in COVID-19 patients.

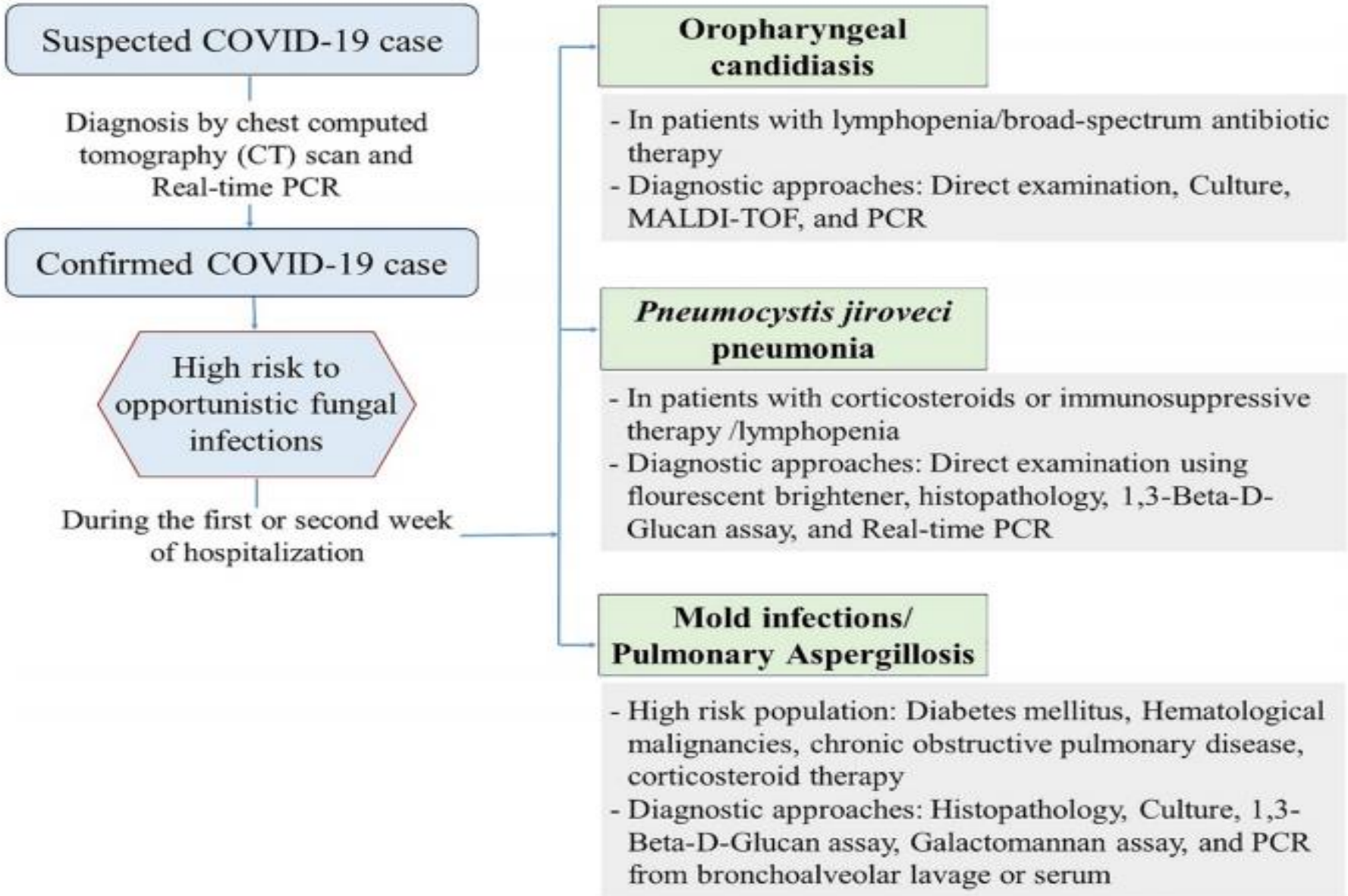
Mycopathologia (2020) 185:607–611
https://doi.org/10.1007/s11046-020-00472-7

OPINION ARTICLE

Opportunistic Fungal Infections in the Epidemic Area of COVID-19: A Clinical and Diagnostic Perspective from Iran

Mohammadreza Salehi · Kazem Ahmadikia · Hamid Badali · Sadegh Khodavaisy

- The role of opportunistic fungal infections in the morbidity and mortality of COVID-19 patients remains less defined.
- COVID-19 patients are most likely to develop **pulmonary aspergillosis**, **oral candidiasis**, or **pneumocystis pneumonia**.
- Other IFI are probable as the accurate diagnosis of opportunistic fungal infections remains challenging in resource-poor settings.


Suspected COVID-19 case
Diagnosis by chest computed tomography (CT) scan and Real-time PCR
Confirmed COVID-19 case
High risk to opportunistic fungal infections
During the first or second week of hospitalization
Oropharyngeal candidiasis
- In patients with lymphopenia/broad-spectrum antibiotic therapy
- Diagnostic approaches: Direct examination, Culture, MALDI-TOF, and PCR
Pneumocystis jiroveci pneumonia
- In patients with corticosteroids or immunosuppressive therapy /lymphopenia
- Diagnostic approaches: Direct examination using flourescent brightener, histopathology, 1,3-Beta-D-Glucan assay, and Real-time PCR
Mold infections/ Pulmonary Aspergillosis
- High risk population: Diabetes mellitus, Hematological malignancies, chronic obstructive pulmonary disease, corticosteroid therapy
- Diagnostic approaches: Histopathology, Culture, 1,3-Beta-D-Glucan assay, Galactomannan assay, and PCR from bronchoalveolar lavage or serum

Mycoses
Diagnosis, Therapy and Prophylaxis of Fungal Diseases

ORIGINAL ARTICLE | Free Access

Oropharyngeal candidiasis in hospitalised COVID-19 patients from Iran: Species identification and antifungal susceptibility pattern

Mohammadreza Salehi, Kazem Ahmadikia, Shahram Mahmoudi, Saeed Kalantari, Saeidreza Jamalimoghadamsiahkali, Alireza Izadi, Mohammad Kord, Seyed Ali Dehghan Manshadi, Arash Seifi, Fereshteh Ghiasvand, Nasim Khajavirad, Saeedeh Ebrahimi, Amirhossein Koohfar, Teun Boekhout, Sadegh Khodavaisy ✉

First published: 01 July 2020 | https://doi.org/10.1111/myc.13137 | Citations: 23

Patients and Methods

- hospitalized COVID-19 patients with OPC were studied.
- Relevant clinical data were mined.
- Strain identification was performed by 21-plex PCR .
- Antifungal susceptibility testing was performed according to the CLSI broth dilution method.

Results

- During the period of this study, **53 (5%) out of 1059** Iranian patients with confirmed COVID-19 infection had OPC.
- Almost **80%** of the patients (n = 42) were **≥50 years of age**, which was significantly associated with OPC (P = .03).
- The **mean time interval** between diagnosis of COVID-19 and clinical presentations of OPC leading to specimen collection was **8 days**.
- Cardiovascular diseases (28/53; 52.8%) and diabetes (20/53; 37.7%) were the principal underlying conditions.
- ***Seventy-one per cent of patients showed lymphopaenia*** (a median lymphocyte count of 1000 cells/mm) (P < .001).
- **C. albicans** (46/6; 70.7%) was the most prevalent yeast species.
- In general, there was a **high level of susceptibility** to all the tested antifungal drugs.

Risk factors		
Recipient broad-spectrum antibiotics	49	92
Corticosteroid therapy	25	47
Admission to ICU	26	49
Mechanical ventilation	16	30

OPC treatment is as follows:

- Mild: Nystatin suspension four times a day for 1-2 weeks, or 10 mg clotrimazole troche five times a day for 1-2 weeks
- Moderate to severe: 100-200 mg oral daily fluconazole for 1-2 weeks
- Refractory to fluconazole: 200 mg itraconazole solution once a day for up to 4 weeks

Journal de Mycologie Médicale 30 (2020) 101012

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Letter to the Editor

Critically ill patients with COVID-19 and candidaemia: We must keep this in mind

Usually and in relation to our local epidemiology, the annual incidence rate is **1.07 – 2.19** candidaemia for every **1000 patients admitted to the ICU**

C. albicans is the most commonly isolated species (50%) in blood cultures, followed by C. parapsilosis (20%), C. glabrata (13%), C. tropicalis (10%) and C. krusei (7%).

Journal of Global Antimicrobial Resistance 23 (2020) 290–291

Contents lists available at ScienceDirect

Journal of Global Antimicrobial Resistance

journal homepage: www.elsevier.com/locate/jgar

Incidence of bacterial and fungal bloodstream infections in COVID-19 patients in intensive care: An alarming "collateral effect"

Maria Adriana Cataldo*, Nardi Tetaj, Marina Selleri, Luisa Marchioni, Alessandro Capone, Emanuela Caraffa, Antonino Di Caro, Nicola Petrosillo, the INMICOVID-19 Co-infection Group[1]

National Institute for Infectious Diseases Lazzaro Spallanzani-IRCCS, Rome, Italy

Table 1
Aetiological agents isolated from blood cultures of 28 patients with bloodstream infection.

Aetiological agent	Number of patients
Pseudomonas aeruginosa	6
Pseudomonas aeruginosa + *Enterococcus faecium*	1
Pseudomonas putida	1
Enterococcus faecalis	3
Enterococcus faecium	4
Klebsiella aerogenes + *Enterococcus faecium*	1
Klebsiella aerogenes	1
Klebsiella pneumoniae	1
Escherichia coli	1
Enterobacter cloacae	1
Stenotrophomonas maltophilia	1
Enterococcus casseliflavus/gallinarum	2
Candida albicans	2
Candida parapsilosis	2
Candida glabrata + *Candida parapsilosis*	1

Journal of Fungi

MDPI

Article

Candidemia among Iranian Patients with Severe COVID-19 Admitted to ICUs

Amir Arastehfar [1], Tahmineh Shaban [2], Hossein Zarrinfar [3], Maryam Roudbary [4], Mona Ghazanfari [5,6], Mohammad-Taghi Hedayati [5,6], Alireza Sedaghat [7], Macit Ilkit [8], Mohammad Javad Najafzadeh [2,*] and David S. Perlin [1,*]

In this retrospective study, investigators assessed **COVID-19-associated candidemia (CAC)** epidemiology in the intensive care units (ICUs) of two COVID-19 centers in Mashhad, Iran, from early November 2020 to late January 2021.

Results

- Among 1988 patients with COVID-19 admitted to ICUs, seven had fungemia (7/1988; 0.03%).
- The mortality of the limited CAC cases was high and greatly exceeded that of patients with COVID-19 but without candidemia (100% (6/6) vs. 22.7% (452/1988).
- In total, nine yeast isolates were collected from patients with fungemia: **five Candida albicans**, three C. glabrata, and one Rhodotorula mucilaginosa.
- Half of the patients infected with C. albicans (2/4) were **refractory to both azoles and echinocandins**.

Candidemia in Nonneutropenic Patients

- For nonneutropenic patients, an **echinocandin** is recommended as initial therapy.
- If the isolate is **susceptible to fluconazole** and the patient is clinically stable, the echinocandin should be switched to fluconazole.
- Although **voriconazole** is effective for candidemia, it is recommended primarily when additional mold coverage is desired or as step-down oral therapy for candidemia due to **C. krusei** or cases due to voriconazole susceptible **C. glabrata**.
- A lipid formulation of AMB is an alternative if the patient is intolerant to other antifungals or has an isolate resistant to other antifungals.

Executive summary: clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;62:409–417.

CVCs should be removed as early as possible in the course of candidemia when the source is presumed to be the CVC and the catheter can be removed safely; this decision should be individualized for each patient.

Executive summary: clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;62:409–417.

Follow-up blood cultures every day or every other day until demonstration of clearance of Candida from the bloodstream are helpful to establish the appropriate duration of antifungal therapy.

Executive summary: clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;62:409–417.

If there are no metastatic complications of candidemia, the **duration of therapy** with systemic antifungal agents should be **14 days** following documented clearance of Candida species from the bloodstream and resolution of signs and symptoms attributable to infection.

Executive summary: clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;62:409–417.

Pneumocystis pneumonia (PJP)

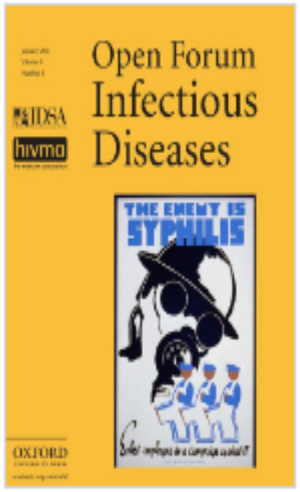
in COVID-19 Patients

Pneumocystis pneumonia (PJP), an opportunistic fungal infection, is caused in immunocompromised individuals, specially immunodeficiency virus (HIV).

Open Forum Infectious Diseases

IDSA Infectious Diseases Society of America

hivma hiv medicine associ



Volume 8, Issue 1

January 2021

Pneumocystis and Severe Acute Respiratory Syndrome Coronavirus 2 Coinfection: A Case Report and Review of an Emerging Diagnostic Dilemma

Carlos Rubiano, Kathleen Tompkins ✉, Subhashini A Sellers, Brian Bramson, Joseph Eron, Jonathan B Parr, Asher J Schranz Author Notes

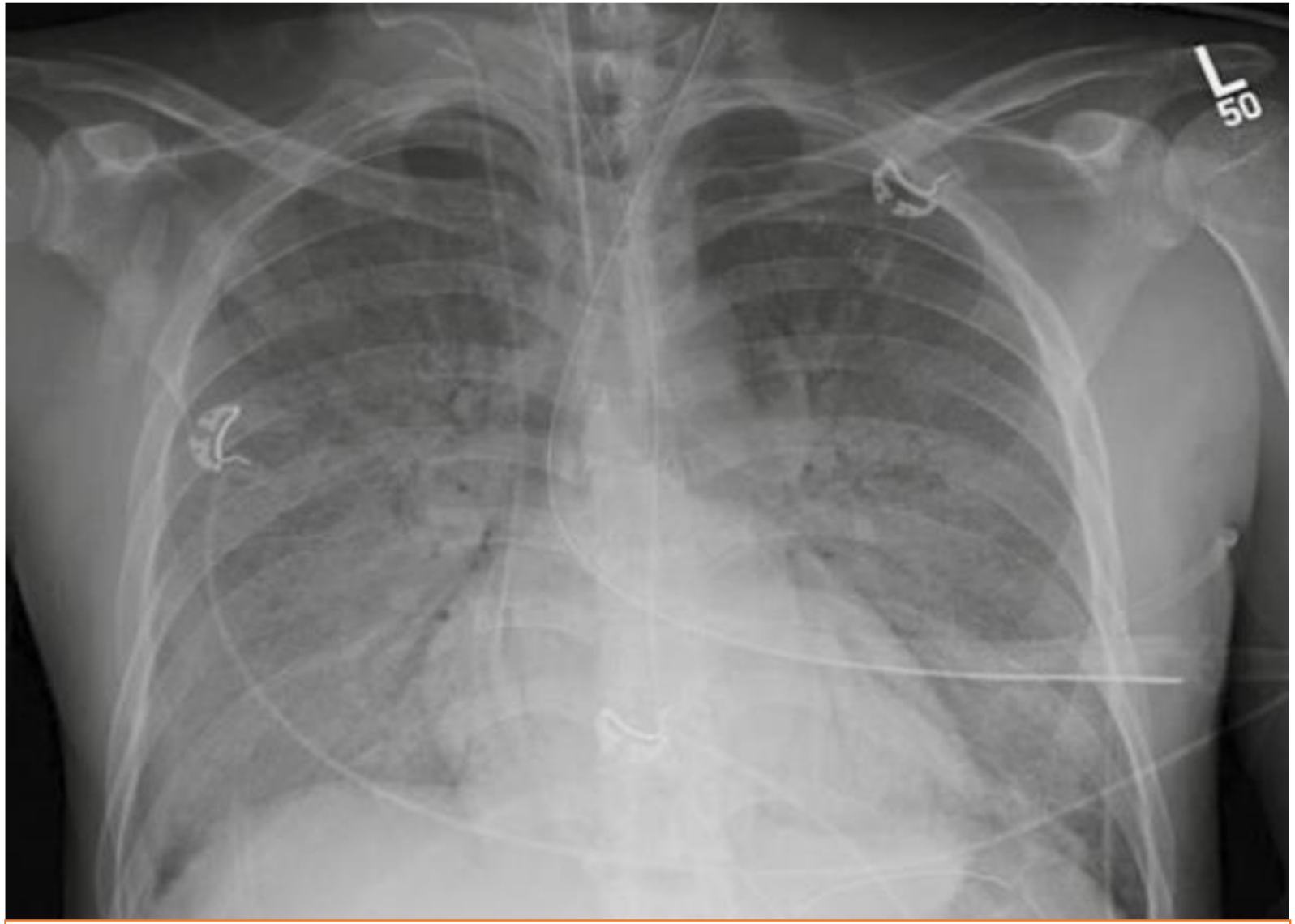
Open Forum Infectious Diseases, Volume 8, Issue 1, January 2021, ofaa633,

https://doi.org/10.1093/ofid/ofaa633

Published: 18 December 2020 **Article history** ▼

CASE REPORT

- They present a case of a critically ill patient with coronavirus disease 2019 (COVID-19).
- Chest CT Scan showed diffuse bilateral ground-glass opacifications.
- HIV-1/2 antigen/antibody test was performed and reactive.
- He took Remdesivir , a transfusion of COVID-19 convalescent plasma, and antibacterial medications (ceftriaxone and azithromycin).



Based on subacute symptoms and x-ray findings, an evaluation for PCP was undertaken and he was started on empiric trimethoprim-sulfamethoxazole and prednisone.

- A tracheal aspirate acid-fast stain, bacterial culture, and P jirovecii direct fluorescent antibody stain (DFA) were all negative.
- **Positive** serological studies included **(1→3)-β-D-glucan >500** pg/mL.
- On hospital day 7, he underwent **bronchoscopy with bronchial alveolar lavage** that yielded **positive Pneumocystis DFA and PCR tests, positive SARS-CoV-2 PCR**, and bacterial, fungal, and mycobacterial cultures that remain negative to date.
- The patient completed a course of remdesivir. He received a 21-day course of trimethoprim-sulfamethoxazole and prednisone for PCP, and he started dolutegravir with combination tenofovir alafenamide/emtricitabine for HIV.

He continued to experience refractory hypoxemia despite maximal ventilator settings, paralytic agents, and prone positioning. On hospital day 26, he developed asystolic cardiac arrest and died.

International Journal of Infectious Diseases 99 (2020) 119–121

Contents lists available at ScienceDirect

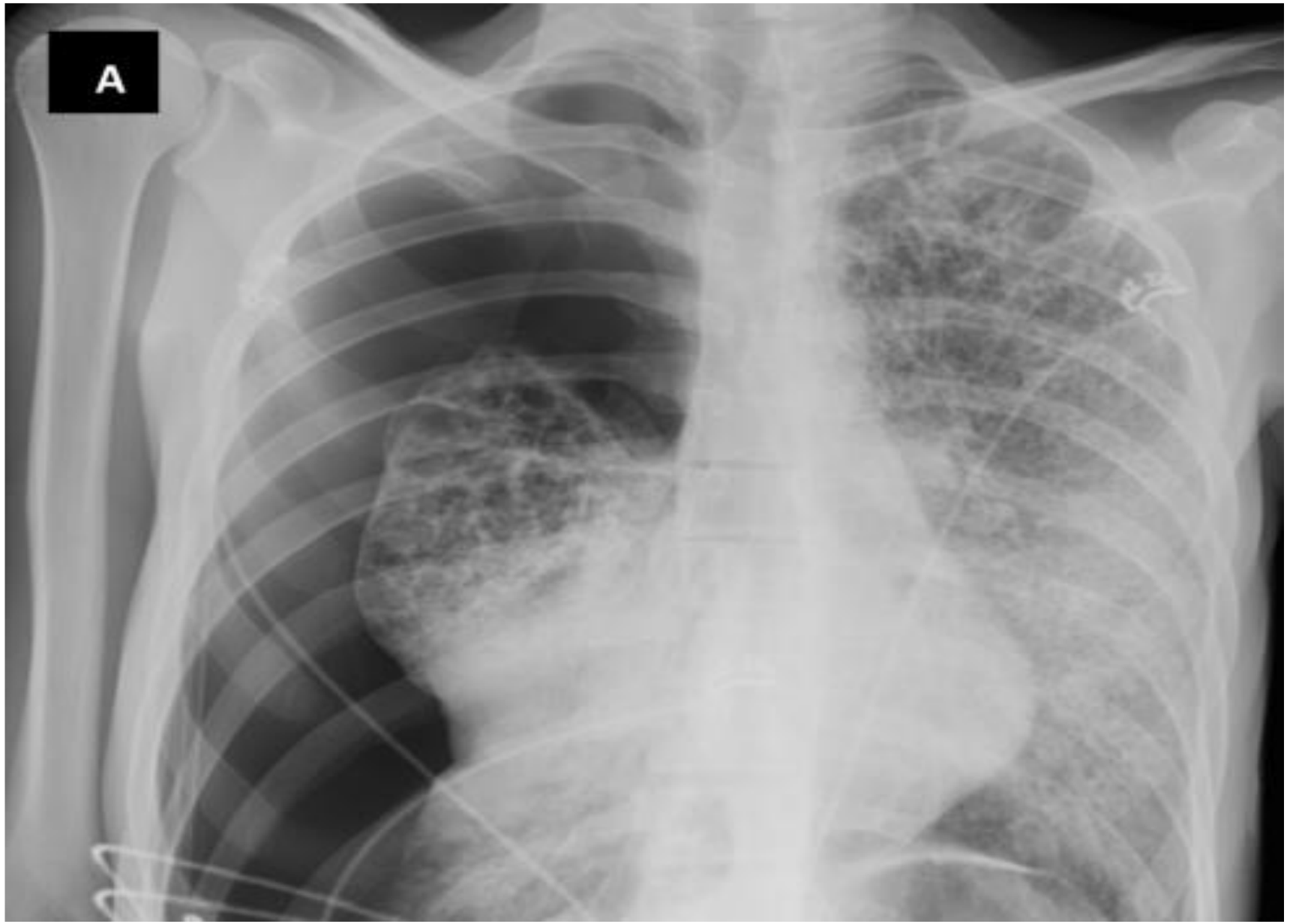
International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

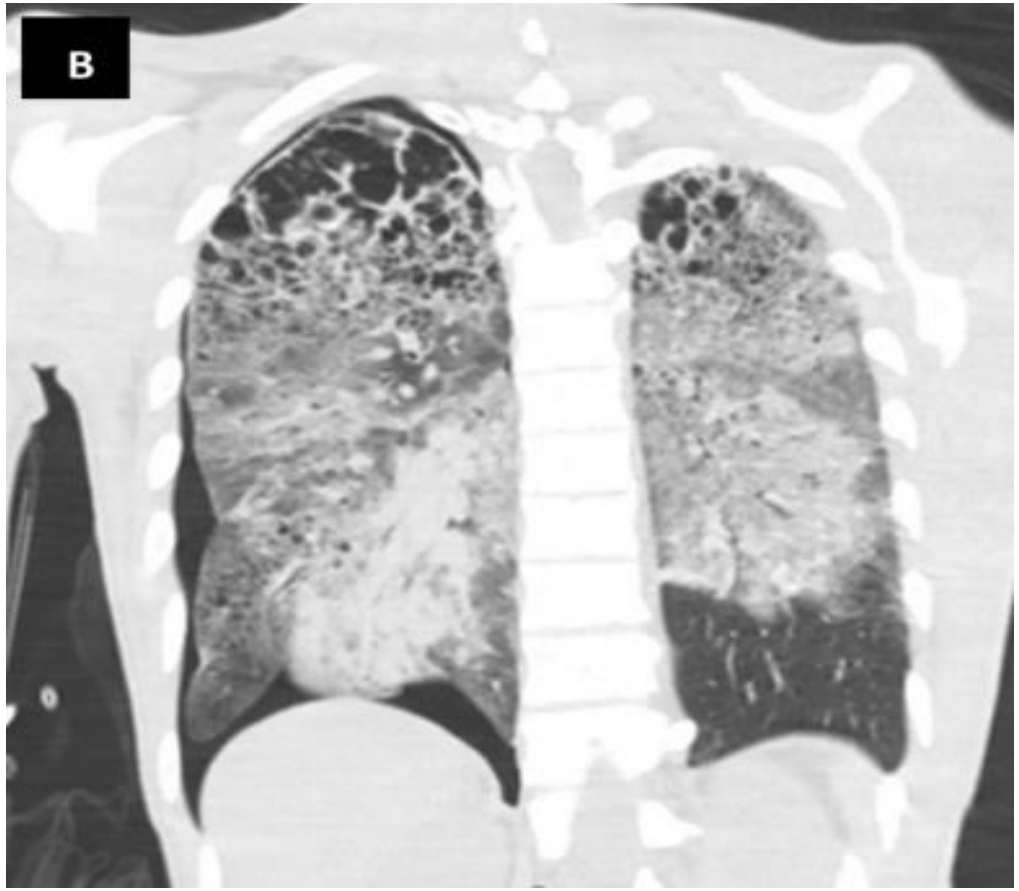
Medical Imagery

Concurrent COVID-19 and Pneumocystis jirovecii pneumonia in a severely immunocompromised 25-year-old patient

A 25-year-old male presented with profound hypoxemia during SARS-CoV-2 pandemic.
Chest X-ray showed a large right pneumothorax and extensive interstitial disease.


A

SARS-CoV-2 PCR was positive.
HIV serology was positive and his absolute CD4+ count was 32 cells/mm3.



- Pneumocystis pneumonia (PCP) was confirmed by bronchoscopic Pneumocystis RT PCR.
- Trimethoprim–sulfamethoxazole, prednisone, and Remdesivir was started.
- The patient improved clinically and was successfully extubated 21 days later.
- Multifocal ground-glass opacities are the principal finding in both PCP and SARS-CoV-2 infection, making radiographic differentiation potentially difficult, especially in the immunocompromised host.
- Cystic lesions can occur in one third of patients with advanced PCP.

Journal of the International AIDS Society 2020, **23**:e25533
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25533/full | https://doi.org/10.1002/jia2.25533

JIAS
JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

LETTER TO THE EDITOR

It's not all about COVID-19: pneumocystis pneumonia in the era of a respiratory outbreak

Chiaw Yee Choy[1,2] and Chen Seong Wong[1,2,3,§]

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They present two cases of
newly diagnosed advanced HIV infection with Pneumocystis pneumonia (PCP) that were initially managed as suspect cases of COVID-19, and in whom HIV was not initially considered.
PCP frequently occurs when the CD4 count drops below 200 cells/lL, which can manifest as lymphopenia

COVID-19–associated pulmonary aspergillosis (CAPA)

Received: 13 November 2020 | Revised: 3 February 2021 | Accepted: 8 February 2021

DOI: 10.1111/myc.13255

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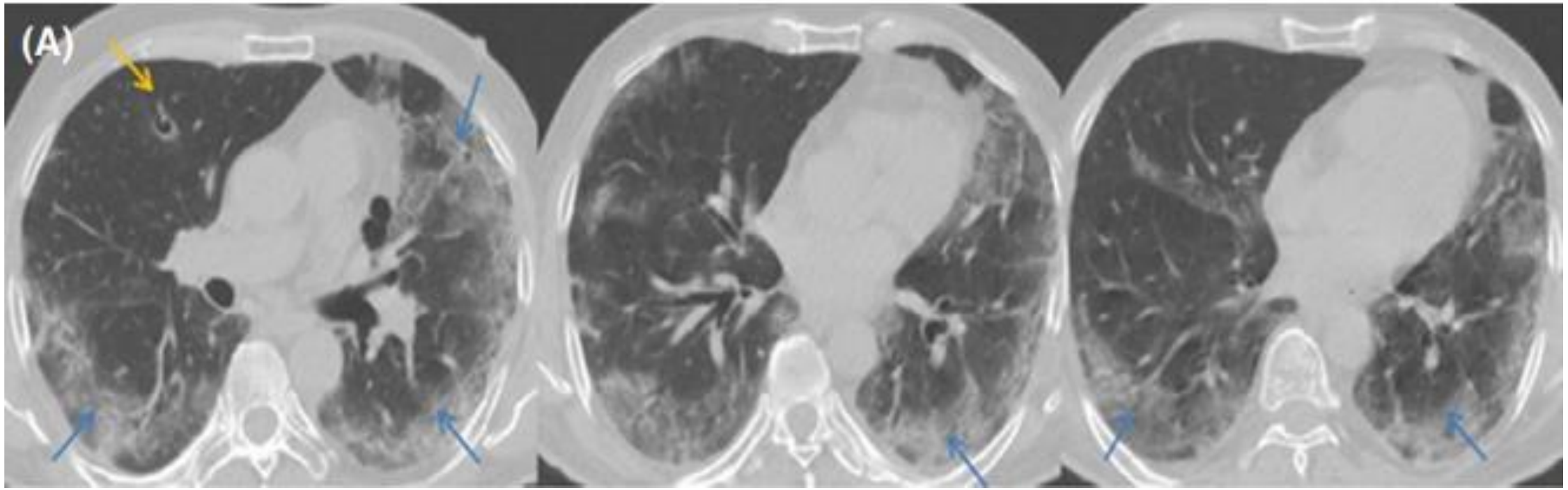
Diagnosis, Therapy and Prophylaxis of Fungal Diseases

WILEY

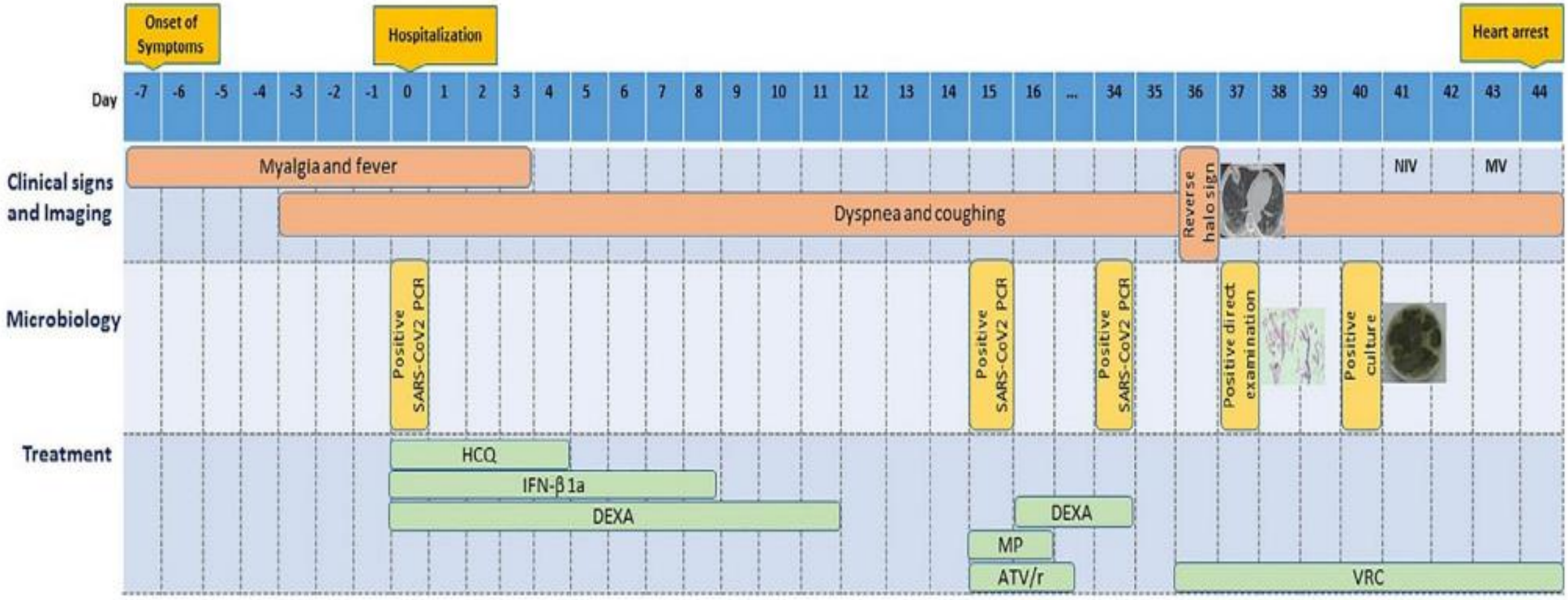
REVIEW ARTICLE

Proven *Aspergillus flavus* pulmonary aspergillosis in a COVID-19 patient: A case report and review of the literature

Mohammadreza Salehi[1] | Nasim Khajavirad[2] | Arash Seifi[1] | Faeze Salahshour[3] | Behnaz Jahanbin[4] | Hossein Kazemizadeh[5] | Sayed Jamal Hashemi[6] | Seyed Ali Dehghan Manshadi[1] | Mohammad Kord[6] | Paul E. Verweij[7] | Sadegh Khodavaisy[6]

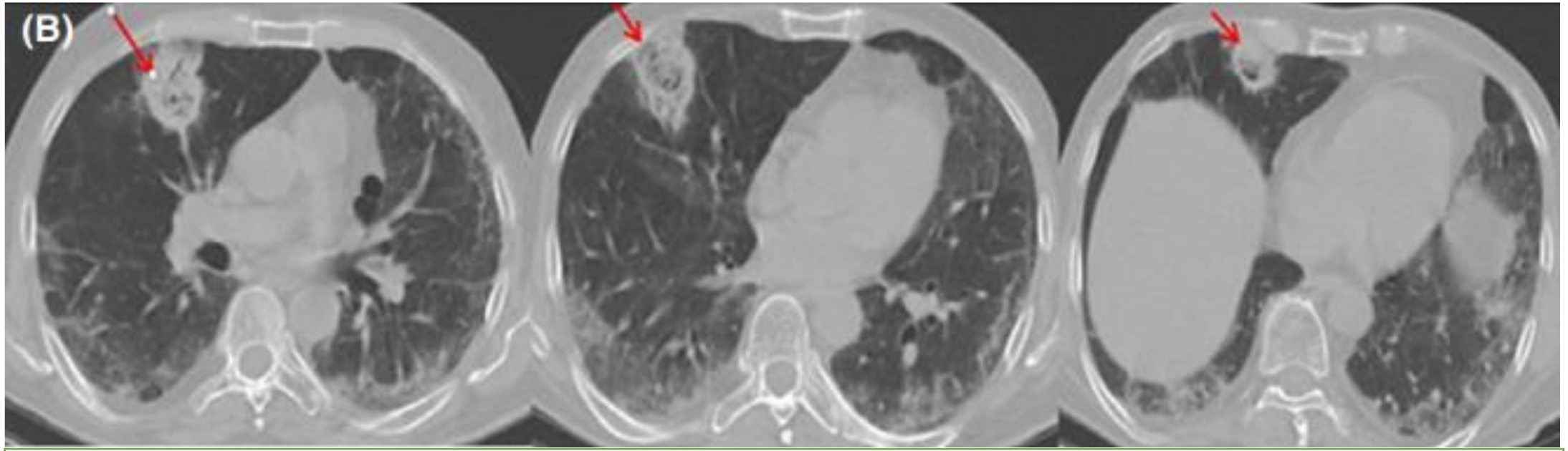


A 70-year-old man with a history of recent hospital admission due to SARS-CoV-2 infection with the diagnosis of exacerbation of viral pneumonia that was had been referred to Imam Khomeini Hospital complex

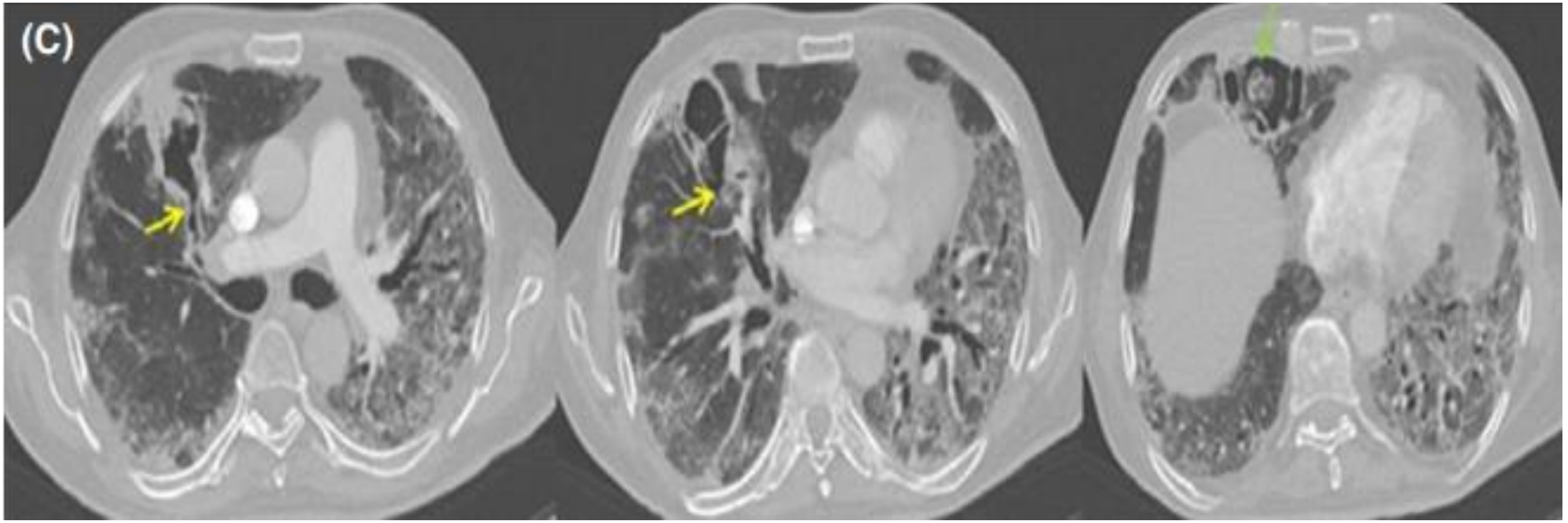


Abbreviations: MP, Methylprednisolone; DEXA, Dexamethasone; HCQ, Hydroxychloroquine; IFN-β 1a, Interferon beta-1a; ATV/r, atazanavir/ritonavir; VRC, voriconazole; NIV, Non invasive ventilation; MV, Mechanical ventilation.

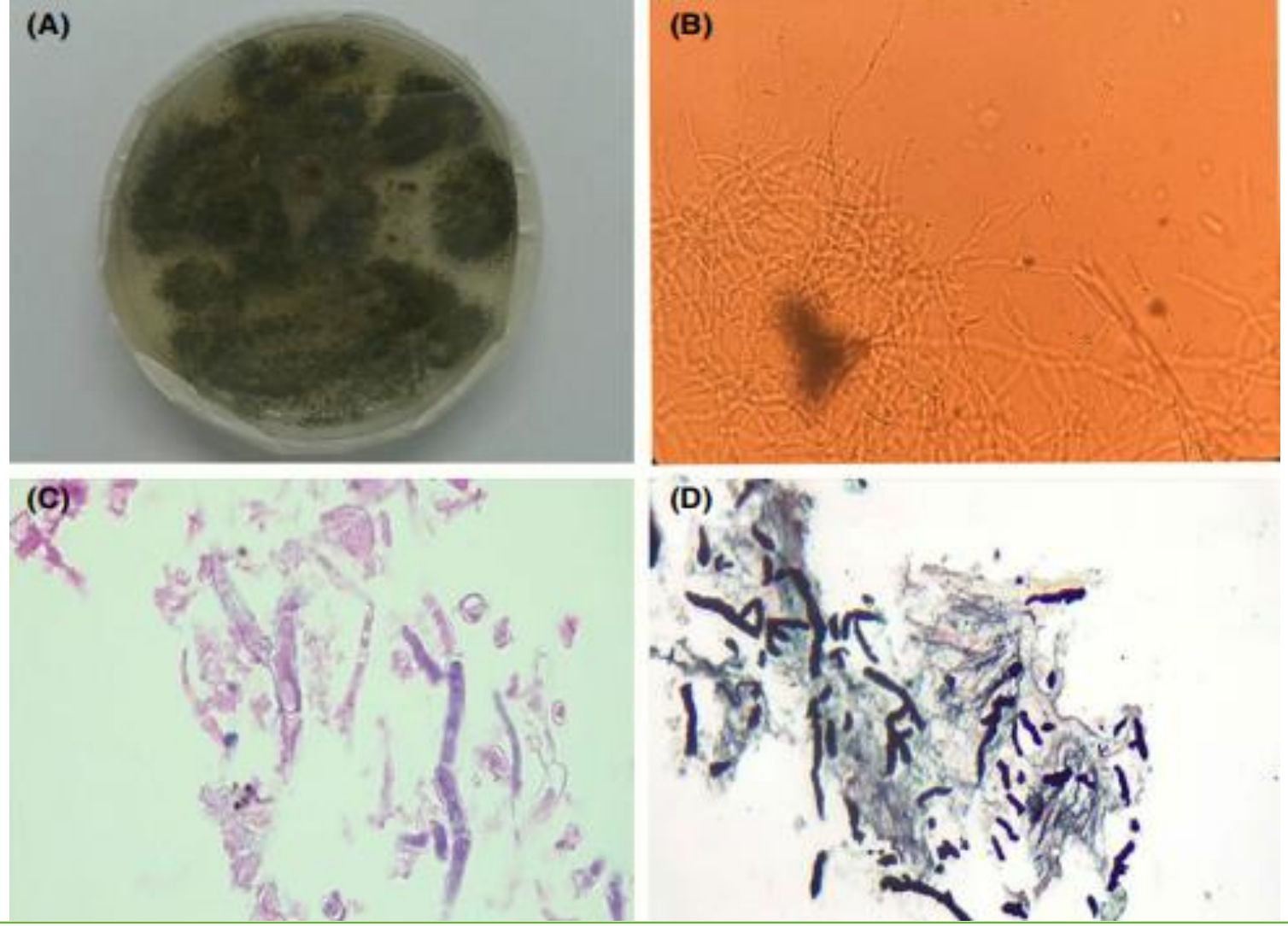
FIGURE 1 Timeline of the patient with COVID-19–associated pulmonary aspergillosis



The reduced ground-glass opacities and three new foci of peripheral wedge-shaped air-space opacities with reverse halo developed in the right middle lobe



The yellow arrows depict the foci of bronchial wall defects. The green arrow shows sloughed debris mimicking invasive aspergillosis



A, Culture on Sabouraud dextrose agar produced green, powdery surface colonies; B, Direct examination of the sample with KOH 10% show hyaline and septated hyphae; C H&E staining show branched and septated hyphae with acute angle hyphae; D, Gomori's methenamine silver (GMS) staining highlights acute angle hyphae

Clinical Infectious Diseases

MAJOR ARTICLE

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]

[1]Infectious Diseases Unit, Department of Medical and Surgical Sciences, Policlinico Sant'Orsola, Bologna, Italy, [2]Operative Unit of Microbiology, University of Bologna, Policlinico Sant'Orsola, Bologna, Italy, [3]Intensive Care Unit, Department of Medical and Surgical Sciences, Policlinico Sant'Orsola, Bologna, Italy, [4]Intensive Care Unit, Maggiore Hospital, Bologna, Italy, and [5]Cardio-Thoracic Anesthesiology Unit, S. Orsola Malpighi University Hospital, Bologna, Italy

Background & method

- They evaluated the incidence of invasive pulmonary aspergillosis among intubated patients with critical COVID-19 and evaluated different case definitions of invasive aspergillosis.
- Prospective, multicenter study in adult patients with microbiologically confirmed COVID-19 receiving mechanical ventilation. All included participants underwent a screening protocol for invasive pulmonary aspergillosis with bronchoalveolar lavage galactomannan and cultures performed on admission at 7 days and in case of clinical deterioration.
- Cases were classified as coronavirus-associated pulmonary aspergillosis (CAPA) according to previous consensus definitions. The new definition was compared with putative invasive pulmonary aspergillosis (PIPA).

Results

- 108 patients were enrolled. Probable CAPA was diagnosed in **30 (27.7%)** patients after a median of 4 (2–8) days from intensive care unit (ICU) admission.
- Kaplan-Meier curves showed a significantly higher 30-day mortality rate from ICU admission among patients with either **CAPA (44% vs 19%, P = .002)** or PIPA (74% vs 26%, P < .001) when compared with patients not fulfilling criteria for aspergillosis.
- Among patients with CAPA receiving voriconazole treatment (13 patients; 43%) a trend toward lower mortality (46% vs 59%; P = .30) and reduction in galactomannan index in consecutive samples were observed.

Treatment

- Invasive aspergillosis is often rapidly progressive and has a high mortality. Therefore, **rapid institution of therapy** in patients in whom invasive aspergillosis is suggested may be lifesaving.
- When the patients develop a compatible clinical picture, **empiric treatment** for aspergillosis should be initiated as diagnostic testing is undertaken.
- **Voriconazole** is now considered the drug of choice for invasive aspergillosis because of better tolerance and improved survival in comparison with amphotericin.
- **Posaconazole, Caspofungin, amphotericin B**, or amphotericin B lipid formulations may be considered as empiric therapy in critically ill patients.

Treatment

- **Combination antifungal therapy** is sometimes used for patients whose disease progresses while on single-drug therapy.
- ***Concomitant therapy with azole antifungals and amphotericin is controversial*** because the azole antifungals decrease amphotericin-binding sites and may therefore diminish its effectiveness.
- Newer antifungal azoles are under study (**ravuconazole**) and may be available for compassionate use in patients in whom other therapies have failed.
- Consider **reducing immunosuppression** if possible based on the underlying disease.
- Patients with invasive aspergillosis or CNPA who respond to initial inpatient treatment may require **several weeks** of antifungal therapy.

Thank you for your attention