A Care Step Pathway for the Diagnosis and Treatment of **COVID-19–Associated Invasive Fungal Infections** in the Intensive Care Unit

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Background In March 2020, the World Health Organization declared COVID-19, caused by the SARS-CoV-2 virus, a pandemic. Patients with severe cases resulting in hospitalization and mechanical ventilation are at risk for COVID-19–associated pulmonary aspergillosis, an invasive fungal infection, and should be screened for aspergillosis if they have persistent hemodynamic instability and fever. Early detection and treatment of this fungal infection can significantly reduce morbidity and mortality in this population.
Objective To develop an evidence-based care step pathway tool to help intensive care unit clinicians assess, diagnose, and treat COVID-19–associated pulmonary aspergillosis.
Methods A panel of 18 infectious disease experts, advanced practice registered nurses, pharmacists, and clinical researchers convened in a series of meetings to develop the Care Step Pathway tool, which was modeled on a tool developed by advanced practice nurses to evaluate and manage side effects of therapies for melanoma. The Care Step Pathway tool addresses various aspects of disease management, including assessment, screening, diagnosis, antifungal treatment, pharmacological considerations, and exclusion of other invasive fungal coinfections.
Results The Care Step Pathway tool was applied in the care of a patient with COVID-19–associated aspergillosis. The patient was successfully treated.
Conclusion The Care Step Pathway is an effective educational tool to help intensive care unit clinicians consider fungal infection when caring for COVID-19 patients receiving mechanical ventilation in the intensive care unit, especially when the clinical course is deteriorating and antibiotics are ineffective. (*Critical Care Nurse*. Published online August 9, 2022)

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In December 2019, patients began presenting to hospitals in Wuhan, China, with severe respiratory disease. Shortly thereafter, researchers identified the novel coronavirus SARS-CoV-2, which resulted in a severe disease that was termed COVID-19. SARS-CoV-2 quickly swept through China and the world through respiratory transmission. In March 2020, the World Health Organization declared COVID-19 a pandemic; entire countries began to enter into national lockdowns to prevent the spread of disease as hospitals and intensive care units (ICUs) started to reach maximum patient capacity. Among patients admitted to the hospital for treatment, those most frequently requiring mechanical ventilation were male and of advanced age (older than 65 years) and had comorbidities such as hypertension, obesity, and diabetes.[1]

Influenza-associated aspergillosis in patients receiving mechanical ventilation has been previously described.[2,3] Patients with COVID-19 who were admitted to the ICU with the initiation of mechanical ventilation typically experienced prolonged and complicated hospitalizations. Among these patients, COVID-19–associated pulmonary aspergillosis (CAPA) was identified as a fungal disease that increased morbidity and mortality. The reported incidence of CAPA in this patient population varies, ranging from 3.8% to 35%.[4] This variation is believed to be due to differing diagnostic capabilities, clinical presentations, reporting and screening practices, and provider knowledge of the association between the conditions across ICU facilities. Reported mortality rates associated with CAPA are as high as 51.2%.[5] Common patient risk factors for CAPA include the presence of chronic lung disease, receipt of mechanical ventilation, and corticosteroid use.[2,6] Thus, awareness of CAPA is especially critical given the recommendation for use of dexamethasone in patients with severe disease due to SARS-CoV-2 infection.[7] Moreover, anti–interleukin-6 treatments such as tocilizumab are also attributed to increased patient susceptibility to invasive fungal infections, including CAPA.[2]

Diagnosing CAPA can be challenging. Traditional diagnosis of invasive pulmonary aspergillosis involves radiography, culture and histologic evaluation, and assessment of serum fungal biomarker levels from bronchoscopies.[8] Moreover, owing to aerosol production during the performance of bronchoscopies, these procedures are often limited to protect the health and safety of ICU staff members.[2] Upper respiratory tract samples are less helpful in diagnosing CAPA because they do not distinguish between colonization and invasive disease. This distinction is often difficult to make and warrants the use of algorithms to better assess, diagnose, and treat disease. Additionally, systemic inflammatory markers such as C-reactive protein and erythrocyte sedimentation rate are usually elevated in patients with severe COVID-19; therefore, these markers often cannot be used to determine the presence of other coinfections.[9] Diagnostic imaging can also be challenging when assessing patients with suspected CAPA. Patients are often unfit for imaging studies because of their poor clinical status and prone

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positioning given associated severe acute respiratory distress syndrome (ARDS). Furthermore, chest radiographs and computed tomographic scans in COVID-19 patients often reveal diffuse pulmonary opacities consistent with ARDS, thus making it difficult to see distinct aspergillus crescent signs associated with CAPA.[10,11] Finally, in the busy ICU setting, the activities of caring for the COVID-19 patient receiving mechanical ventilation leave little time for nurses to consider fungal diagnostic assessment and screening in a setting of persistent deterioration despite treatment for bacterial infections.

Objective

To address the diagnostic challenges surrounding CAPA as well as lack of awareness of the disease process, our team set out to develop an evidence-based care step pathway (CSP) to assist bedside nurses and health care providers in assessing, diagnosing, and treating CAPA. In developing this tool, we built on a CSP that was previously developed by the Melanoma Nursing Initiative.[12] The purpose of the CAPA CSP was to improve early assessment, screening, diagnosis, and treatment of CAPA, as well as consideration of other invasive fungal infections. It also addresses a variety of pharmacological issues that affect treatment of these patients, who may be receiving multiple medications and supportive treatment modalities, including extracorporeal membrane oxygenation. The following case report illustrates the clinical complexity of CAPA in patients receiving mechanical ventilation in the ICU. The patient provided written consent to share his case for publication.

Case Report

A 66-year-old Hispanic man was admitted to the hospital because of COVID-19 pneumonia after a 2-week history of worsening dyspnea, pyrexia, myalgia, anosmia (loss of smell), nausea, and anorexia. He received dexamethasone and tocilizumab (a monoclonal antibody directed against the interleukin-6 receptor). He spent 2 days in the hospital and was discharged to home in a stable condition. His medical history included obstructive sleep apnea with use of a continuous positive airway pressure machine, obesity (body mass index, calculated as weight in kilograms divided by height in meters squared, 35.1), hypertension, and hyperlipidemia, with outpatient medications consisting of lisinopril 40 mg daily, rosuvastatin 20 mg daily, and pantoprazole 40 mg daily.

Within 24 hours of discharge, the patient was readmitted with increasing shortness of breath and tachypnea, up to 36 breaths per minute. On admission, he was hypoxic with an oxygen saturation of approximately 80% on room air and required initiation of a high-flow nasal cannula (oxygenation rate, 60 L/min with 100% oxygen). His chest radiograph showed ground-glass opacities. Within 24 hours he required intubation and admission to the ICU owing to worsening hypoxia. He did not meet the requirements for administration of remdesivir but received convalescent plasma and was continued on dexamethasone for a total of 10 days. Figure 1 shows his hospital course from day –17 to day 34. During the hospital course, he experienced worsening hypoxia and leukocytosis and was found to have ventilator-associated pneumonia with *Enterobacter aerogenes* and methicillin-sensitive *Staphylococcus aureus*. However, by day 20 and with antimicrobial therapy, his fever returned, and he experienced leukocytosis along with increased ventilator and vasopressor requirements, including initiation of norepinephrine.

On day 24, bronchoscopy with bronchoalveolar lavage was performed owing to an increase in fever to 40 °C, leukocytosis with leukocyte count up to 22 400/μL, and hemodynamic worsening requiring the addition of vasopressin. Within 24 hours, the galactomannan index (*Aspergillus* antigen) from the bronchoalveolar lavage sample was found to be positive at 4.721 (negative: < 0.5 index), with a serum galactomannan of 0.156 and (1,3) β-D-glucan considered negative at less than 0.31 pg/mL. The patient had been receiving intravenous (IV) micafungin, 100 mg every 24 hours, as empiric therapy for fever and sepsis but was switched to IV isavuconazonium sulfate because of the positive galactomannan index and a new diagnosis of CAPA. The patient started to improve after a few days, and he eventually required a tracheostomy on day 28 owing to continued ventilator dependency. On day 30, repeat computed tomography angiography of the chest showed severe bilateral lower lobe consolidation with extensive ground-glass opacities (Figures 2 and 3).

The case report illustrates the clinical complexity of COVID-19–associated pulmonary aspergillosis in patients receiving mechanical ventilation in the ICU.

One week after the initiation of antifungal therapy, the patient's fever gradually lowered, and he began to

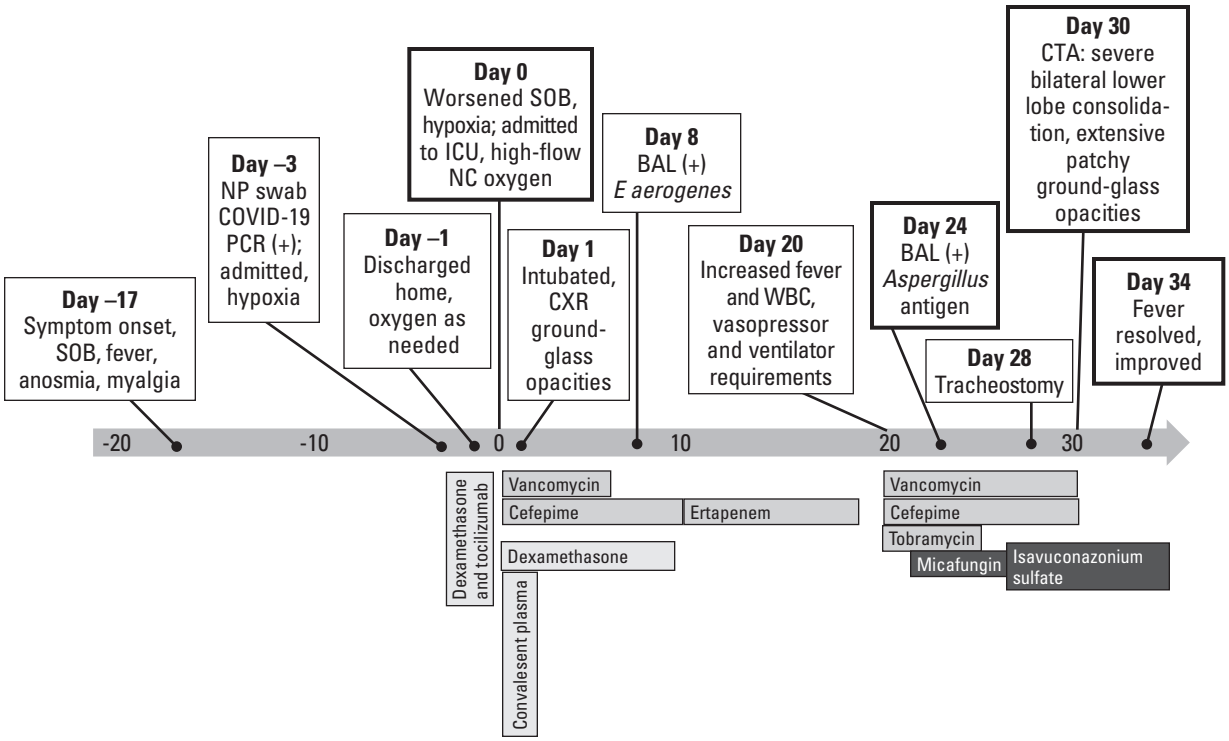

Figure 1 Hospital course, day –17 to day 34.

Abbreviations: BAL, bronchoalveolar lavage; CTA, computed tomography angiography; CXR, chest radiograph; *E aerogenes, Enterobacter aerogenes;* ICU, intensive care unit; NC, nasal cannula; NP, nasopharyngeal; PCR, polymerase chain reaction; SOB, shortness of breath; WBC, white blood cell count.

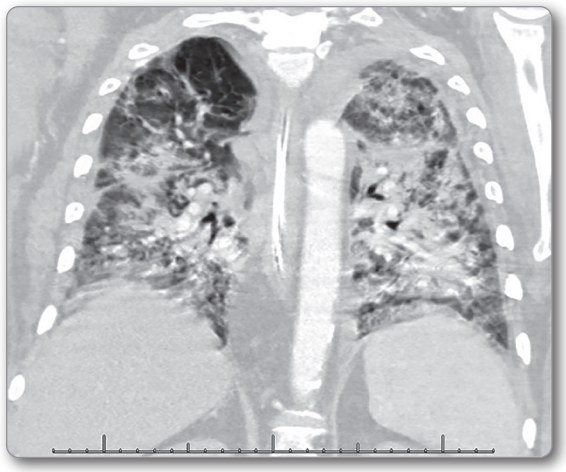

Figure 2 Computed tomography angiography of the chest, coronal view, showing severe bilateral lower lobe consolidation with extensive ground-glass opacities.

Image courtesy of Jose Vazquez, MD.

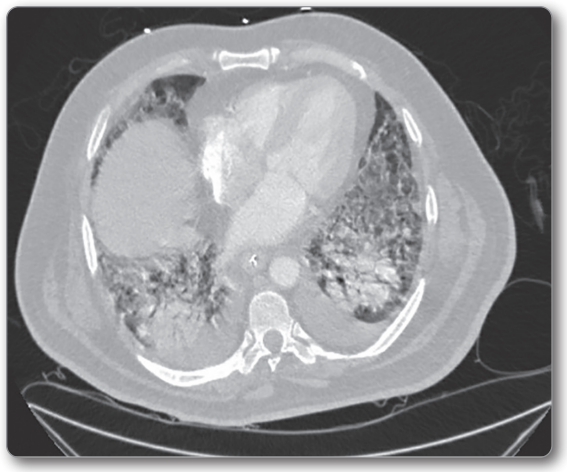

Figure 3 Computed tomography angiography of the chest, axial view, showing severe bilateral lower lobe consolidation with extensive ground-glass opacities.

Image courtesy of Jose Vazquez, MD.

show signs of clinical improvement and oxygenation by day 34. The patient remained ventilator dependent until day 68, when he was ultimately weaned to Trilogy (Phillips) bilevel positive airway pressure (BiPAP). Four days after he was transitioned to BiPAP, he was transferred from the ICU to a general medical ward (Figure 4). On day 75,

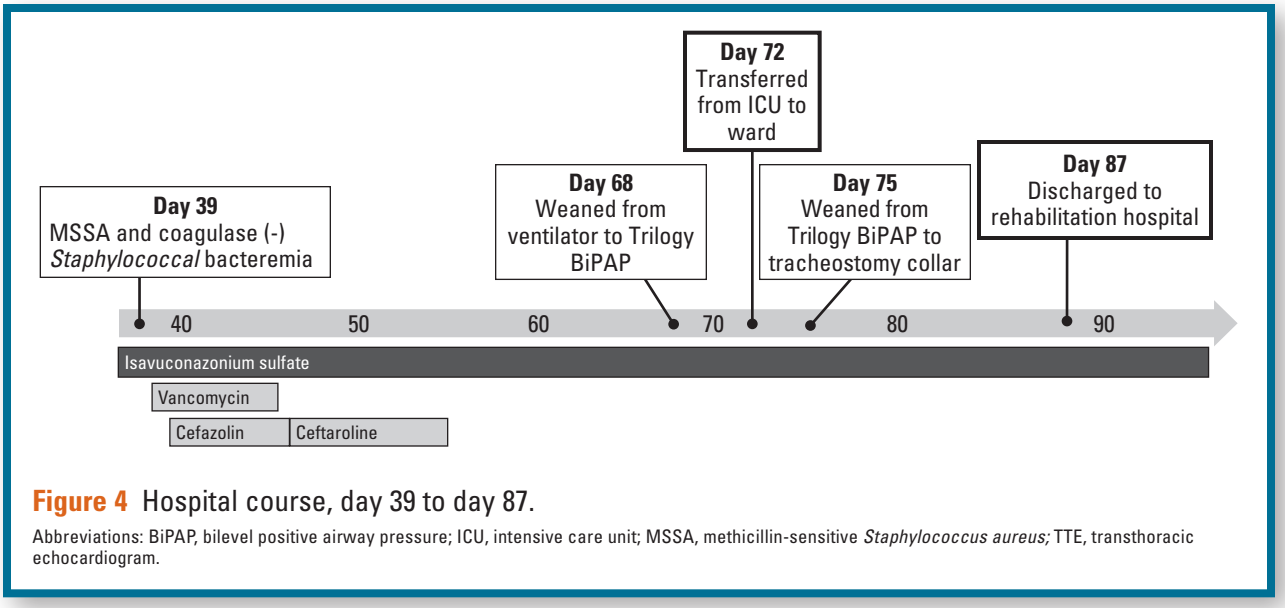

Figure 4 Hospital course, day 39 to day 87.

Abbreviations: BiPAP, bilevel positive airway pressure; ICU, intensive care unit; MSSA, methicillin-sensitive *Staphylococcus aureus;* TTE, transthoracic echocardiogram.

he was weaned from BiPAP to a tracheostomy collar. He remained in the acute care hospital until day 87, when he was discharged to a rehabilitation hospital. Antifungal therapy was continued, and he was switched to oral antifungal treatment for another 10 days.

Challenges of this case included recognizing that there was an occult infectious process causing the poor outcomes. Moreover, once the team was considering fungal infection, the challenge became establishing the etiology using the diagnostic tools at hand. Finally, once the patient was started on antifungal therapy, it became a challenge to ensure that the course of therapy was continued and transitions occurred from IV to oral therapy across settings.

Methods

The CAPA CSP was developed as part of a collaborative agreement between the Centers for Disease Control and Prevention (CDC), the University of Alabama at Birmingham, the Mycoses Study Group Education and Research Consortium, and Terranova Medica, LLC. Given the morbidity and mortality associated with CAPA and the difficulty in traditional diagnosis of pulmonary aspergillosis, our collaboration was guided by the urgent educational need to raise awareness of CAPA and illustrate appropriate screening, diagnosis, and management of this infection.

The steering committee leadership consisted of 3 infectious diseases physicians, an advanced practice nurse, and a certified continuing education professional, all specializing in invasive fungal infections. The CSP content faculty consisted of 10 additional invasive fungal infection physician specialists, a critical care pulmonologist, an infectious diseases pharmacist, and an advanced practice ICU nurse. These content development faculty members worked in 6 targeted subgroups to create evidence-based recommendations. The groups focused on the following topics: (1) clinical assessment (including prescreening and awareness); (2) screening (conducting a series of diagnostic tests for aspergillosis); (3) evaluation (applying diagnostic criteria for proven or possible CAPA for treatment decision-making); (4) treatment with antifungal treatment regimens for probable and proven CAPA; (5) evaluation of other invasive fungal infections (including nonpulmonary aspergillosis, infection caused by molds, *Pneumocystis jirovecii* pneumonia, cryptococcal species infection, other endemic mycoses, and candidiasis); and (6) pharmacological considerations (including drug-drug interactions and toxicity management) (Figure 5).

Challenges of this case included recognizing that there was an occult infectious process causing the poor outcomes.

The 6 expert groups met by video conferencing and corresponded via email to review current CAPA research, case reports, and clinical experiences to inform evidence-based content. Multiple rounds of content were developed over a 6-month period to ensure full consensus of the groups for the CSP tool. A final editing round served to finalize the tool. On June 18, 2021, the content was released

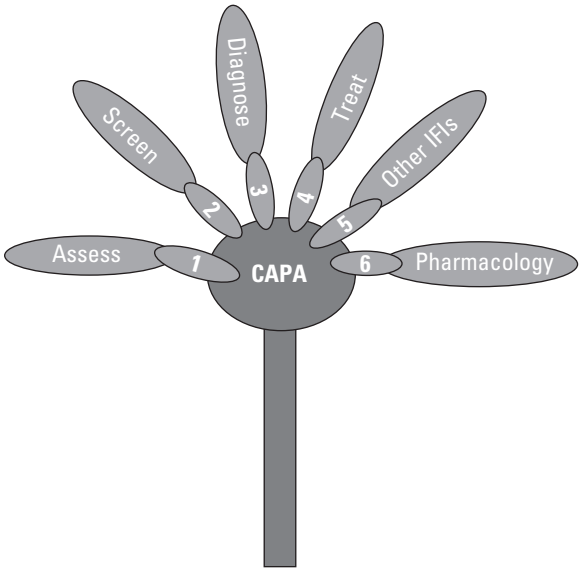

Figure 5 COVID-19–associated pulmonary aspergillosis Care Step Pathway approach.

Abbreviations: CAPA, COVID-19–associated pulmonary aspergillosis; IFI, invasive fungal infection.

publicly on the Covid-19–Associated Fungal Infections Educational Initiative website (covidandfungus.org) in the form of a CSP poster and a companion document. After its internet launch, the CSP was made available in printed form to one of the authors' COVID-19 ICUs for dissemination to the nurses and other health care team members as well as one of our faculty members who worked at an academic center and educated community affiliates.

We solicited feedback through an informal usability and user experience survey distributed using the VerticalResponse email marketing platform. We provided a direct link to the survey from the Covid-19–Associated Fungal Infections Educational Initiative website and distributed it directly to the centers who received printed forms. The survey included demographic questions for the responding health care team members (nurses, pharmacists, microbiologists, physicians). Also included were 4 objective questions about usability and experience: (1) How are you using the CSP? (2) What aspect of the CSP was most helpful? (3) What limited your ability to use the CSP? (4) What impact has the use of the CSP had for your patients?

The most helpful aspects of the Care Step Pathway are practical recommendations for CAPA screening, pharmacological considerations, treatment recommendations, and CAPA definitions.

Results

Using a checklist approach, we illustrated the application of the assessment, evaluation, and treatment sections of the CSP to the CAPA case reported above (Figure 6).

Clinical Assessment

Specific clinical issues for the ICU bedside registered nurse and other health care providers to consider in ICU patients infected with SARS-CoV-2 and receiving mechanical ventilation are shown in the checklist in Table 1. In this case, the patient showed pulmonary or clinical deterioration that was unexplained or unresponsive to antimicrobial therapies targeting bacterial sources. Moreover, the patient met clinical criteria for a COVID-19–associated invasive fungal infection. He required mechanical ventilation and remained in the ICU for more than 48 hours. Additionally, his imaging was consistent with ARDS or pulmonary invasive fungal infection, he showed clinical and hemodynamic deterioration, and he had recent corticosteroid and tocilizumab use.

With those clinical criteria met, the next step, evaluation, was undertaken (Table 2). Evaluation for probable CAPA was supported by an abnormal chest radiograph and a positive galactomannan airway specimen result.

Hospital formularies may determine available antifungal options at local hospitals. The patient in our study was initially treated with micafungin; however, owing to the presumptive CAPA diagnosis, he was switched to isavuconazonium sulfate in accordance with the CSP treatment checklist (Table 3).

The patient did not have evidence of other invasive fungal infections or travel to an endemic area. Criteria for the evaluation of other invasive fungal infections in the CSP include ruling out nonaspergillus pulmonary or rhinofacial/orbital molds such as mucormycosis or fusariosis, *Pneumocystis jirovecii, Cryptococcus* species, histoplasmosis, blastomycosis, coccidioidomycosis, or candidiasis. A diagnostic commentary is provided for each of these infections in the CSP.

Awareness of pharmacological factors is important in the rapidly changing ICU setting. Medication levels can be affected by extracorporeal membrane oxygenation and

ASSESS CLINICALLY

Assessment

Clinical criteria
Assess and screen for IFIs in patients with COVID-19 who:
- Require mechanical ventilation OR
- Have been in the ICU >48 hours and are showing pulmonary and/or clinical (hemodynamic) deterioration with no established entity

Look at timelines for	Recognize
• COVID-19 diagnosis • ICU admission • Mechanical ventilation • Antibiotics, corticosteroids, tocilizumab, baricitinib	• **Imaging** (X-ray or CT) consistent with ARDS or with pulmonary IFI (diffuse infiltrates/consolidation or new cavitary or nodular lesions) • **Pulmonary deterioration**: worsening mechanical support requirement or need for rescue strategies, hemoptysis, pleural rub/chest pain • Other signs of **clinical (including hemodynamic) deterioration**: signs of sepsis, severe sepsis, or septic shock (fever, tachycardia, altered mental status, increased respiratory rate, hypotension, loss of consciousness) • **Comorbidities** and risk factors for IFIs (eg, COPD, uncontrolled DM [such as marked by concurrent or recent DKA], HIV, hematologic malignancy, neutropenia, allogeneic SCT, SOT, conditions such as rheumatologic disorders requiring biologics/high-dose corticosteroids), lymphopenia • Recent history of **corticosteroid** use • **Endemic mycoses**: travel to an area with endemic mycoses or prior endemic infection

SCREEN FOR COVID-19–ASSOCIATED PULMONARY ASPERGILLOSIS (CAPA) IN PATIENTS WHO MEET CLINICAL CRITERIA

- Obtain baseline CT; consider reimaging at clinical deterioration to look for changes
- Depending on available resources, plan for at least weekly testing while patient is in the ICU (in order of priority):
  - Culture, direct microscopy, cytology, or histopathology on respiratory samples (order of preference is BAL > ND-BAL > ETA)
  - Targeted biomarkers (GM [by EIA or LFA]) and/or molecular testing (*Aspergillus* PCR) on respiratory or serum samples
  - Consider BDG on serum samples

EVALUATE FOR CAPA (FOR TREATMENT DECISION-MAKING)

Evaluation

PROVEN CAPA (Clinical + Microbiologic Criteria Required)	PROBABLE CAPA (Clinical + Radiographic + Microbiologic Criteria Required)
Clinical criteria: As above	**Clinical criteria:** As above
Radiographic criteria: Not required	**Radiographic criteria**: Abnormal chest X-ray or CT Note: Radiologic signs consistent with pulmonary aspergillosis (nodules, halo sign, cavitation, wedge-shaped and segmented or lobar consolidation, infiltrates) can be, but are not always, present with CAPA.
Microbiologic criteria: Histopathologic or direct microscopic evidence of *Aspergillus* spp (dichotomous septate hyphae) in tissue (from lung biopsy) consistent with damage/invasion AND/OR *Aspergillus* spp recovered from culture of an appropriate clinical sample that is normally sterile	**Microbiologic criteria (at least 1 of the following diagnostic signals)**: 1. Culture positive BAL or ND-BAL *OR* Culture positive ETA (ideally confirmed with a GM or second culture result) 2. Presence of fungal hyphae/elements observed on **BAL or ND-BAL** by direct microscopy, cytology, Gram stain, or special fungal stains OR Presence of fungal hyphae/elements on **ETA** (confirmed with a GM) by direct microscopy, cytology, Gram stain, or other special fungal stains 3. Lung/airway specimen GMI ≥1.0 (for patient not on mold-active antifungals [eg, voriconazole, isavuconazole] for >3 days) 4. Two consecutive lung/airway specimen-positive *Aspergillus* PCR assays 5. sGMI >0.7,[a] confirm using one of the following second tests: • Lung/airway specimen GMI >0.8 OR • Second sGMI >0.7 OR • Positive PCR in serum or on lung/airway sample 6. sBDG positive (GM negative) • Repeat BDG,[b] sGM, and lung/airway specimen GM; confirm using one of the following second tests: - Lung/airway specimen GM Index >0.8 OR - sGMI >0.7 OR - Positive PCR in serum or on lung/airway sample

[a] Consider initiation of treatment with a single sGM Index >0.7 while awaiting confirmatory tests in a patient who is experiencing clinical deterioration.
[b] Repeat BDG positivity in the absence of additional diagnostic evidence is not sufficient to confirm CAPA, as it could also reflect other IFIs or BDG false positivity. However, it does increasethe likelihood of the diagnosis, especially in the presence of radiology typical of pulmonary aspergillosis.

Continued

Figure 6 Care Step Pathway for COVID-19–associated pulmonary aspergillosis.

Treatments

TREATMENT FOR PROBABLE OR PROVEN CAPA

For patients with a CAPA diagnosis, first-line options include:

- Voriconazole 6 mg/kg IV every 12 h x 1 day, then 4 mg/kg every 12 h for 6-12 weeks OR
- Isavuconazole 200 mg every 8 h x 6 doses, then 200 mg IV or oral daily for 6-12 weeks OR
- Posaconazole (if available, IV 300 mg twice daily, then 300 mg once daily for 6-12 weeks; alternatively use delayed-release tablets at the same dosage)
- Consider LAmB (3-5 mg/kg/day) or azole combined with an echinocandin in suspected azole resistance (persisting or rising GMI, breakthrough during treatment), proven azole-resistant aspergillosis, or in areas with high environmental azole resistance. See pharmacological considerations for discussion of DDI and TDM

EVALUATE FOR OTHER IFIs, AS APPROPRIATE[a]

Pathogen(s)	Diagnostic commentary
Non-Aspergillus pulmonary molds (eg, mucormycosis and fusariosis)	Similar to CAPA, but GM generally unhelpful; consider panfungal PCR or Mucor PCR. Blood culture may be positive for cases of hyalohyphomycosis and phaeohyphomycosis
Nonpulmonary molds (eg, rhinofacial/orbital mucormycosis)	Recovery of molds from normally sterile sites in the presence of known risk factors and clinical scenario (eg, uncontrolled DM, DKA, sinusitis/recovery of Mucorales spp). Evaluate cytology/histopathology; consider Mucor PCR.
PCP	BDG positivity in serum and PCP qRT-PCR positivity in BAL, ND-BAL, or ETA and no evidence of other IFI, particularly in the presence of PCP risk factors. Radiographically, may exhibit extensive, mostly GGO on CT scans with an upper lobe and perihilar predominance with peripheral sparing or a mosaic pattern (however, differentiation from typical COVID-19 chest radiology may be difficult)
***Cryptococcus* spp**	Cryptococcal antigen testing on lung/airway sample, blood, or CSF
Other endemics	*Histoplasma* or *Blastomyces* antigens in urine, serum, or body fluid; *Coccidioides:* positive antibody testing
Candidiasis	Proven: Positive *Candida* spp blood culture, sterile site culture, or peritoneal catheter culture (in place < 24 h) Probable: T2 Candida™ positive or sequential BDG positives in the presence of *Candida* colonization index/score

[a] As mentioned, other fungal diagnoses can be considered in settings where clinical criteria are met, the BDG test is positive, but the *Aspergillus* tests are negative.

NON-CAPA PULMONARY IFI COMMENTARY

Clinicians need to pursue a specific diagnosis, because non-CAPA pulmonary IFIs, including PCP, non-*Aspergillus* molds, *Cryptococcus* spp, and endemic mycoses, require different management schemes from CAPA. Consult pathogen-specific guidelines for management.

CONSIDER PHARMACOLOGIC FACTORS

- PK can be altered in seriously ill COVID-19 patients because of inflammation/metabolic changes, organ dysfunction, and augmented renal clearance
  - ECMO may increase antifungal drug dosage requirements by up to twofold to overcome drug loss from the ECMO circuit sequestration
  - Renal toxicity and electrolyte disturbances associated with LAmB may be challenging in the context of SARS-CoV-2 and other COVID-19 therapeutics; monitor BUN/sCr, potassium and magnesium and replace electrolytes as needed, as well as avoid concomitant medications with overlapping toxicities when possible
  - Liver toxicity and QTc prolongation associated with some azoles may be challenging in the context of SARS-CoV-2 and other COVID-19 therapeutics; monitor LFTs and EKGs as well as avoid concomitant medications with overlapping toxicities when possible
- Evaluate for DDIs: at initiation/stopping of antifungal therapy or when modifying concomitant medications or doses
  - Voriconazole: CYP450 CYP2C19, 2C9, 3A4 substrate and inhibitor
  - Isavuconazole: CYP3A4 and 3A5 substrate and moderate 3A4 inhibitor
  - Posaconazole: strong CYP3A4 inhibitor, PgP substrate and inhibitor
  - Dexamethasone induces 2C9, may decrease voriconazole levels; 3A4 inhibitors may increase dexamethasone levels
  - Remdesivir: CYP3A4, CYP2C8, 2D6, OATP1B1 and P-glycoprotein substrate and weak inhibitor of CYP3A4/some transport proteins
- Strongly consider TDM (based on your institutional guidance) for patients receiving mold-active azoles. Note there is no standard target trough range for isavuconazole.

Figure 6 *Continued*

Abbreviations: ARDS, acute respiratory distress syndrome; BAL, bronchoalveolar lavage; BDG, (1,3) β-D-glucan; BUN, blood urea nitrogen; CA-IFI, COVID-19–associated invasive fungal infection; COPD, chronic obstructive pulmonary disease; CSF, cerebrospinal fluid; CT, computed tomography; DDI, drug-drug interaction; DKA, diabetic ketoacidosis; DM, diabetes mellitus; ECMO, extracorporeal membrane oxygenation; EIA, enzyme immunoassay; EKG, electrocardiogram, ETA, endotracheal aspirate; GGO, ground-glass opacity; GM, galactomannan; GMI, galactomannan index; HCT, hematopoietic cell transplant; HIV, human immunodeficiency virus; ICU, intensive care unit; IFI, invasive fungal infection; IV, intravenously; LAmB, lipid amphotericin B; LFA, lateral flow assay; LFT, liver function test; ND-BAL, nondirected bronchoalveolar lavage (deep inline suction, aka "mini-BAL"); PCP, *Pneumocystis jirovecii* pneumonia; PCR, polymerase chain reaction; PK, pharmacokinetics; qRT-PCR, real-time polymerase chain reaction; s, serum; sCR, serum creatinine; SCT, stem cell transplant; SOT, solid organ transplant; TDM, therapeutic dose monitoring.

The development of the Care Step Pathway was funded in part by a cooperative agreement between the Centers for Disease Control and Prevention (CDC; CFD-RFA-CK20-2003) and the University of Alabama at Birmingham. The University of Alabama at Birmingham is collaborating with the Mycoses Study Group Education & Research Consortium and Terranova Medica, LLC, on this initiative. The CDC is an agency within the Department of Health and Human Services (HHS). The contents of this resource center do not necessarily represent the policy of CDC or HHS and should not be considered an endorsement by the Federal Government.

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the presence of renal and liver failure. In a patient with COVID-19, QTc prolongation can affect the myocardium and the potential for drug-drug interactions; thus, serial electrocardiograms are warranted during treatment. Indeed, many antifungal drugs can alter pharmacodynamic pathways, leading to drug-drug interactions and pharmacokinetic issues such as increasing or decreasing drug levels. Monitoring for therapeutic drug levels may be indicated. Moreover, transition of antifungal therapy from an IV to an oral route of administration requires planning. Koehler et al[2] recommended 6 to 12 weeks of azole therapy, although the optimal duration of treatment for CAPA is still unknown. Continuity of care is an important factor in improving patient outcomes. The course of treatment should be clearly communicated during the transition of care to step-down units and outside facilities. Owing to the high bioavailability of voriconazole and isavuconazonium sulfate oral formulations, the need for IV access should be reassessed on transfer or discharge to avoid additional complications and high costs associated with IV drug formulations and home health care.[13,14]

Finally, the length of ventilation, including ventilator weaning, highlights the severe nature of CAPA. In our case, the patient survived his CAPA and was able to describe his case publicly in video interviews. The full CSP poster, CSP companion document with references, and patient case interview are available at the Covid-19–Associated Fungal Infections Educational Initiative website (covidandfungus.org).

Care Step Pathway Usability and Experience Survey

Eleven individuals evaluated the CSP via survey. Of those individuals, 55% evaluated hard copies of the CSP that were directly distributed to specific institutions, and 44% downloaded the CSP directly from the website. In terms of specialties, 44% of respondents were from critical care and pulmonary medicine, 33% were from infectious diseases, and the remainder were from other specialties (laboratory medicine). Regarding the most common uses of the CSP, 24% of respondents were using it for clinical assessment, 24% for CAPA treatment guidance, 19% for screening, 15% for diagnosis of CAPA, 10% to evaluate for non-CAPA invasive fungal infections, and 10% to assess pharmacological factors. Respondents indicated that the most helpful aspects of the CSP were practical recommendations for

Table 1 Clinical assessment checklist using CAPA criteria

Present	Clinical assessment criteria
☒	COVID-19, ICU, and mechanical ventilation
☒	Imaging consistent with ARDS or pulmonary IFI
☒	Clinical and hemodynamic deterioration
☒	Recent corticosteroid use
☒	Recent antibiotic use
☒	Recent use of tocilizumab or baricitinib
☐	Recent travel to an area known as a fungal endemic area (Ohio River Valley/Southeast: histoplasmosis; Southwest/California: coccidioidomycosis)

Abbreviations: ARDS, acute respiratory distress syndrome; CAPA, COVID-19–associated pulmonary aspergillosis; ICU, intensive care unit; IFI, invasive fungal infection.

Table 2 Clinical evaluation checklist using CAPA criteria

Present	Clinical evaluation criteria
☒	Meets clinical criteria
☒	Radiographic: abnormal chest radiograph or CT
☐	BAL culture positive
☐	BAL direct microscopy, cytology, Gram stain, or fungal stains positive
☒	Airway specimen has a positive galactomannan result
☐	Two consecutive airway specimen *Aspergillus* PCR assays positive
☐	Serum (1,3) β-D-glucan assay positive

Abbreviations: BAL, bronchoscopy alveolar lavage; CAPA, COVID-19–associated pulmonary aspergillosis; CT, computed tomography; PCR, polymerase chain reaction.

Table 3 Treatment checklist using CAPA criteria

Present	CAPA treatments
☐	Voriconazole 6 mg/kg IV every 12 hours x 1 day, then 4 mg/kg every 12 hours for 6-12 weeks
☒	Isavuconazonium sulfate 372 mg every 8 hours x 6 doses; then 372 mg IV or orally daily for 6-12 weeks (equivalent to isavuconazole 200-mg dosing)
☐	Posaconazole 300 mg IV twice daily, then 300 mg once daily for 6-12 weeks, may use delayed-release tablets at the same dosage
☐	Liposomal amphotericin B (3-5 mg/kg/day) or azole combined with an echinocandin in suspected azole resistance based on rising galactomannan tests

Abbreviations: CAPA, COVID-19–associated pulmonary aspergillosis; IV, intravenously.

CAPA screening, pharmacological considerations, treatment recommendations, and CAPA definitions. Respondents indicated the following limitations of CSP use: inadequate time to implement the CSP (18%), lack of institutional support for recommended testing (27%), and colleagues' lack of understanding of fungal diseases (55%). At this early stage of use, 70% of respondents reported that they did not know what impact use of the CSP has had on patient outcomes; nevertheless, 20% reported that its use could be associated with decreased mortality, and 10% reported that its use could be associated with decreased length of stay.

Discussion

In the initial phases of the COVID-19 pandemic, many patients experienced prolonged hospitalizations, and those who received mechanical ventilation had increased morbidity and mortality. Despite the use of evidence-based practice with ventilation involving prone positioning and lung protection,[15] many patients did not recover as would be expected with ARDS from another viral illness. Given the recommendation to use glucocorticosteroids for the treatment of severe COVID-19, fungal infections should be considered as the cause of pyrexia and leukocytosis in patients with severe illness despite adequate and appropriate antimicrobial therapy. Observation of these clinical scenarios led to the search for and identification of atypical types of pneumonia in COVID-19 patients, including CAPA in ICU patients receiving mechanical ventilation.

The CSP for CAPA constitutes a vital educational tool for health care providers, including bedside nurses, who care for patients infected with SARS-CoV-2, particularly in the ICU. This tool's ability to promote early identification of CAPA among ICU patients has the potential to raise awareness of CAPA among clinical nursing staff members and medical providers, shorten ICU stays, reduce ventilator days, and improve mortality. As discussed in the case report, prompt recognition and antifungal treatment of CAPA resulted in both improvement in clinical condition and reduced ventilator needs.

Our usability and experience survey regarding the CSP was limited by the informal nature of the survey and the small number of respondents. Although the results are informative, the responses could be biased by an increased willingness to complete the survey among those with interest in the topic.

Conclusion

The CSP described in this article was developed to increase awareness of the potential association of SARS-CoV-2 infection with invasive fungal infections, particularly pulmonary aspergillosis. The case study demonstrates the utility of application of the CSP for diagnosing and treating CAPA in the ICU setting. This educational tool can improve understanding of potential invasive fungal infections in COVID-19 patients receiving mechanical ventilation and facilitate an evidence-based approach to assessment, diagnosis, and treatment, leading to earlier intervention and fewer missed opportunities for improved patient outcomes. CCN

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See also

To learn more about caring for patients with COVID-19, read "Cutaneous Manifestations of COVID-19 in Critical Care" by Swoboda in *AACN Advanced Critical Care,* 2022;33(2):186-195. Available at **www.aacnacconline.org.**

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