COVID-19–ASSOCIATED FUNGAL INFECTIONS
EDUCATIONAL INITIATIVE

Care Step Pathway for Managing a Suspected Pulmonary Invasive Fungal Infection in a Patient With COVID-19 in the ICU

COMPANION DOCUMENT

This is a companion document for the attached Care Step Pathway (CSP) to support the diagnosis and management of COVID-19–associated pulmonary aspergillosis (CAPA). Here we explain the rationale for creating this document, the reason for the selection of this format, and the process we used to create the content. We then walk through the individual sections, providing a discussion of the support behind the CSP recommendations.

After the discussion of the CSP, we include a brief overview of infection control and prevention strategies and antimicrobial stewardship recommendations that are tailored to the challenges of the pandemic. These overarching strategies are presented to assist decision makers as they develop their own institutional guidance materials.

This educational initiative was funded in part by a cooperative agreement with the Centers for Disease Control and Prevention (CFD-RFA-CK20-2003) to 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 Centers for Disease Control and Prevention 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.

DEVELOPMENT OF THE CSP

The CAPA CSP was developed as part of a collaborative agreement between the US Centers for Disease Control and Prevention; the University of Alabama at Birmingham; the Mycoses Study Group Education & Research Consortium (MSGERC); and Terranova Medica, LLC. Given the morbidity and mortality associated with CAPA, our collaboration has been guided by the urgent educational need to raise awareness of CAPA and illustrate appropriate screening, diagnosis, and management of this infection. However, with the rapid development of the COVID-19 pandemic and this emerging fungal infection, mycology researchers (including the MSGERC) are still working to characterize CAPA. Therefore, we are left with the challenge of providing much-needed guidance on managing a clinical entity in real time while it is still evolving.

For these reasons, we advise the users of this CSP to understand that these recommendations are made from a background of limited data. This is an emerging problem—the literature is scarce and variable, and the growing evidence base may change. Therefore, our soft consensus recommendations are made based on a review of the limited literature that is available, clinical experience with CAPA to date, and our collective experience in best practice managing invasive pulmonary aspergillosis (IPA) in the intensive care unit (ICU) setting. These recommendations are likely to develop as we learn more about CAPA in the near future. This is one of the reasons we have chosen the CSP format for these recommendations. This easily modified format has been used successfully in oncology to engage the entire healthcare team in assessing and managing specific clinical entities, including secondary complications.[Wood 2019] Developed for easy, in-clinic use, this format is less formal than a traditional clinical practice guideline and can be updated readily.

This CAPA CSP was developed by a panel of experts from the COVID-19–Associated Fungal Infections Educational Initiative (https://covidandfungus.org/steering-committee/; https://covidandfungus.org/content-committee/). The steering committee and content development faculty worked in subcommittees to develop the individual sections, which were then reviewed by the other content development members and the steering committee, with final review by the CDC collaborators.

Of note, this CSP has not been designed to address management of invasive candidiasis in patients with COVID-19. We anticipate creating a separate CSP on that topic in the future, although there are some general comments about preventing invasive candidiasis in the section on infection control and prevention. Other COVID-19–associated invasive fungal infections (CA-IFIs) that have a pulmonary component are also discussed for the purposes of supporting the differential diagnosis, so that these entities can be treated appropriately. We anticipate having more pathogen-specific guidance on these CA-IFIs in the near future.

ASSESSMENT

Suspected Pulmonary Invasive Fungal Infection (IFI) in a Patient with COVID-19 in the ICU
Care Step Pathway

ASSESS CLINICALLY

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 causal entity

LOOK AT TIMELINES FOR
- COVID-19 diagnosis
- ICU admission
- Mechanical ventilation
- Antibiotics, corticosteroids, tocilizumab, baricitinib

RECOGNIZE
- **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

The first step in managing CAPA is identifying at-risk patients for screening. Patients with severe COVID-19 who require mechanical ventilation are at increased risk for CAPA.[Salmanton-Garcia 2021; Koehler 2020a] In addition, non-ventilated patients with COVID-19 in the ICU who are experiencing clinical deterioration with no known causal entity should also be screened.[Van Biesen 2020; Armstrong-James 2020] Such clinical decline can take the form of pulmonary compromise or development of a sepsis-like syndrome, as illustrated in the CSP. Assessing the timeframe of the clinical course and specific therapeutic interventions can be helpful in evaluating the patient at risk for CA-IFIs as well as the fungal disease course.

Of note, many patients with severe COVID-19 do not have the traditional host risk factors for IPA, including malignancy, solid organ transplantation, or hematopoietic cell transplantation (HCT).[Donnelly 2020; Chen 2020; Segrelles-Calvo 2021] Researchers are still teasing out the risk factors for CAPA. Although data are conflicting regarding an association between CAPA and immunosuppressants used in managing COVID-19 (eg, corticosteroids, tocilizumab, etc.) [Nasir 2020; Bartoletti 2020; Permpalung 2021; Segrelles-Calvo 2021; Armstrong-James 2020], our faculty suggests that clinicians should note the use of these immunosuppressants as part of the overall clinical picture, given their association with increased risk of IPA outside of the COVID-19 cohort.

ASSESSMENT (continued)

Healthcare providers also need to be aware of risk factors for other non-CAPA CA-IFIs affecting the respiratory system, including non-CAPA filamentous fungi (eg, the Mucorales), *Pneumocystis jirovecii* pneumonia, and endemic fungi. Some comorbidities render patients at increased risk for CAPA or other CA-IFIs. For example, uncontrolled diabetes mellitus and trauma are associated with increased risk for mucormycosis.[Hoenigl 2021] Moreover, corticosteroids used to treat COVID-19 may decrease the efficacy of insulin in diabetes mellitus, leading to diabetic ketoacidosis and increased free iron in the circulation. This may be part of the mechanism for the increased mucormycosis risk.[John 2021] Chronic obstructive pulmonary disease (COPD) is considered a risk factor for pulmonary CA-IFIs.[Armstrong-James 2020] Lymphopenia (as well as high-dose corticosteroid exposure) has been associated with a risk for pneumocystosis outside of the COVID-19 cohort. [Donnelly 2020] Human immunodeficiency syndrome (HIV) infection, solid organ transplantation (SOT), and hematologic malignancy are risk factors for invasive fungal infections, including cryptococcosis.[Donnelly 2020] Travel to an endemic region or prior infection could be a risk for infection or reactivation with an endemic mycosis during or after development of COVID-19. These factors should be noted when evaluating the patient and when performing the differential diagnosis.

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

Commentary on Prophylaxis

Currently, investigators estimate the incidence of CAPA in patients with severe COVID-19 who are receiving mechanical ventilation at around 10%.[Alanio 2020; Permpalung 2021; Bartoletti 2020; Chauvet 2020; White 2020] Targeted antifungal prophylaxis is considered appropriate in the settings of hematopoietic stem cell transplantation and solid organ transplant for select patients at a similar risk level (≥10% IFI risk).[Fleming 2014; Singh 2013] Therefore, given the high mortality associated with CAPA (>50% mortality vs approximately 31% in patients suffering from COVID-19 alone),[Salmanton-Garcia 2021; White 2020] the use of targeted antifungal prophylaxis for COVID-19 patients who are mechanically ventilated is currently being studied in several clinical trials, and we look forward to the results. However, at this point in time, we do not recommend antifungal prophylaxis or empirical antifungal therapy for patients with severe COVID-19 who are mechanically ventilated or experiencing clinical deterioration. This is partially driven by antifungal stewardship principles, as discussed below. We do, however, recommend routine screening for CAPA in these at-risk patients.

Rationale for Tests Recommended

In developing the recommendations for CAPA screening, we were cognizant of several considerations. First, we have recommended a variety of tests, with preference for lung/airway sampling over serology given the better performance characteristics of the former in the limited number of CAPA studies that have been published to date. Moreover, bronchoalveolar lavage (BAL) fluid is preferred over non-directed BAL (ND-BAL), over endotracheal aspirates (ETA), because BAL fluid has been validated in this setting and is more likely to recover host cellular material, which is more reflective of true infection vs colonization.[Koehler 2020a] However, because of the infectious concerns associated with obtaining BAL specimens, both ND-BAL and ETA specimens may be considered reasonable options, particularly in resource-limited settings. [Armstrong-James 2020; Wahidi 2020] In particular, ND-BAL using a closed suction apparatus appears to have performance characteristics (ie, diagnostic yield) comparable to BAL in CAPA. [Van Biesen 2020; White 2020]

CAPA DEFINITIONS

EVALUATE FOR CAPA (FOR TREATMENT DECISION MAKING)

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 one 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,* 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†, 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

*Consider initiation of treatment with a single sGM Index >0.7 while awaiting confirmatory tests in a patient who is experiencing clinical deterioration.
†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 increase the likelihood of the diagnosis, especially in the presence of radiology typical of pulmonary aspergillosis.

We recommend that a baseline computed tomography (CT) scan be obtained, if possible, so that changes can be assessed at clinical deterioration. Although serologic testing is less reliable in the setting of CAPA, it does have a role to play because of ease of sampling and the ability to follow patients easily over time. In terms of the specific tests to perform—culture, direct microscopy, and cytology or histology on a relevant respiratory sample—are considered the highest priority. Targeted biomarker assessment with GM (by either enzyme link immunoassay [EIA] or lateral flow assay [LFA]) is considered the next highest priority, along with molecular testing (*Aspergillus* PCR). Here again, lung/airway samples are considered higher priority than serologic testing because of performance characteristics of these tests in CAPA. Beta-D-glucan on serum only, a relative nonspecific fungal test, is next in the priority list.

Proven CAPA

The proven CAPA definition is partially drawn from that provided by the European Confederation for Medical Mycology (ECMM) and the International Society for Human and Animal Mycology (ISHAM): in a patient meeting the clinical criteria, this would include histopathological or direct microscopic detection from a tissue biopsy showing invasive growth or tissue damage consistent with *Aspergillus* spp or *Aspergillus* recovered from culture from a sterile aspiration or biopsy from a pulmonary site.[Koehler 2020a]

CAPA DEFINITIONS (continued)

Meeting radiographic criteria is not necessary for the proven CAPA category. Whereas many patients with CAPA have abnormal imaging because of the underlying acute respiratory distress syndrome (ARDS), multiple pulmonary nodules or lung cavitation is more consistent with CAPA than with COVID-19.[Koehler 2020a] Because the typical IPA radiology would be highly specific for CAPA, it can help firm up the diagnosis when present with other criteria.[White 2020]

Possible CAPA

Our group did not recommend a possible category for CAPA, given that this category would traditionally focus on clinical features without mycological evidence,[Donnelly 2020] which would support an empirical therapy approach. Since we are not supporting an empirical approach, the possible category is not helpful for our recommendations.

Probable CAPA

The definition of probable CAPA we have provided is relatively broad—requiring radiologic and clinical evidence in conjunction with a microbiologic signal that is defined by a wide range of test options. The rationale for having a permissive mycologic signal is to avoid missing cases and to accommodate the range of tests that are used in communty/resource-limited settings. This accommodation is a high priority, given that more stringent classification systems can be difficult to implement.[Permpalung 2021]

The highest priority diagnostic tests remain culture and cytology/histologic evidence. Our faculty suggest that, in the presence of radiology and clinical symptoms, a positive culture from BAL on ND-BAL or the presence of septate hyphae typical of *Aspergillus* spp. in the BAL or ND-BAL fluid (as determined by cytology/Gram stain, or Calcofluor white stain) would be sufficient for a definition of probable CAPA. A confirmatory BAL GM might be considered if the radiographic criteria are difficult to interpret.[Koehler 2020b] For ETA, given the greater risk for contamination, we recommend confimation of culture or cytology/histology results together with a GM, since the GM reflects release from actively growing hyphae (and thus is less likely to be positive in settings of contamination).

CAPA DEFINITIONS (continued)

GM and PCR are also high-priority tests. The cutoff point suggested for BAL GM (index >1) is based on the immunocompetent recommendations from the AspICU definitions.[Verweij 2020; Armstrong-James 2020] A BAL GM index of 0.5 or below is most likely not consistent with CAPA and could be useful for excluding it.[Meersseman 2008] The GM index cutoff of 1.0 for ND-BAL is also supported by a number of studies.[White 2020; Van Biesen 2020] While enzyme immunoassay (EIA) is more commonly used for GM testing, a GM lateral flow assay (LFA) might be helpful to use in resource-limited settings. The occurrence of 2 positive PCR tests is considered diagnostic for IPA in nonhematologic settings and therefore is considered at least similar to GM testing (while increasing sensitivity is a concern for colonization).[Koehler 2020a; Donnelly 2020]

The diagnostic yield of serum GM in CAPA is low, at approximately 20%; for this reason serum GM might be best used in concert with other diagnostic measures. We are recommending use of a serum GM index of 0.7 as a cutoff for CAPA. This is higher than manufacturer's recommendation (0.5) and thus is likely to provide higher specificity for CAPA. 1,3-beta-D-glucan, which is a global fungal marker, can be used in screening by detection in serum, but would require a secondary signal that is specific for CAPA, as illustrated in the CSP.

NON-CAPA PULMONARY IFI DIAGNOSIS

EVALUATE FOR OTHER IFIs, AS APPROPRIATE*

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.
Non-pulmonary 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 <24h) Probable: T2 Candida™ positive or sequential BDG positives in the presence of *Candida* colonization index/score

*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.

Given the possibility of non-CAPA IFIs causing pulmonary symptoms, clinicians need to be able to diagnose these as well. For non-*Aspergillus* molds, the most frequent occurring has been the Mucorales, and this would require additional mycological culture and non-culture-based analyses, which may include Mucorales-specific PCR testing.[Gangneux 2020; Hoenigl 2021] This might be suspected in patients with poorly controlled diabetes mellitus, hematologic malignancy, and allogeneic HSCT, particularly in the setting of high-dose corticosteroids. [Cornely 2019; Hoenigl 2021] Of note, the endemic mycoses may be reactivated in patients with COVID-19, and so tracking prior history as well as travel history may be helpful. Culture and histology play a key role here in addition to serologic testing.[Donnelly 2020]

Pneumocystis jirovecii pneumonia is also diagnosed based on clinical findings and radiographic imaging, including the finding of ground glass opacities.[Roux 2014] This can be difficult to differentiate from the radiographic findings of COVID-19–associated ARDS. Therefore, in patients who are at increased risk for *P jirovecii* pneumonia (such as those who are HIV positive), testing is recommended. Definitive *P jirovecii* diagnosis traditionally involves microscopic visualization of the organism in respiratory tract specimens by various stains, of which immunofluorescence is preferred due to its high sensitivity, as well as real-time polymerase chain reaction (rt-PCR) testing of respiratory samples.[Alanio 2016]

CAPA TREATMENT

TREATMENT FOR PROBABLE OR PROVEN CAPA

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

- Voriconazole 6 mg/kg IV q12 hrs x 1 day, then 4 mg/kg q12 hours for 6-12 weeks OR
- Isavuconazole 200 mg q8 hrs 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 pharmacologic considerations for discussion of DDI and TDM

CAPA treatment is relatively standardized per the IPA guidelines, with some modifications to address COVID-19. Of note, the IV formulations of drugs are preferred due to possible malabsorption and gastropareses.[Koehler 2020a] Options include voriconazole and isavuconazole, although isavuconazole has less hepatotoxicity, neurotoxicity, and risk of QT-interval prolongation.[Koehler 2020a; Patterson 2016] Posaconazole is also considered an appropriate option and is further supported by recent data vs voriconazole for IPA in the non-COVID–19 setting.[Koehler 2020a; Patterson 2016; Maertens 2021] Lipid formulations of amphotericin B (LAmB) can be considered in settings in which azole-resistant strains are an issue,[Koehler 2020a] especially when an azole cannot be used. Treatment should continue for 6 to 12 weeks.[Koehler 2020a] Echinocandins are not recommended as primary treatment but can be considered in combination with an azole in areas of azole resistance.[Koehler 2020a]

Note that non-CAPA IFIs should be treated per pathogen-specific guidelines. [Hoenigl 2021] We anticipate providing additional guidance on these pathogens in the near future.

PHARMACOLOGIC CONSIDERATIONS

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 2-fold 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 therapeutics; monitor BUN/sCr, potassium & 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 & inhibitor
  - Isavuconazole: CYP3A4 and 3A5 substrate & 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 & 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.

Several pharmacologic factors need to be considered during treatment for CAPA. Patients with COVID-19 may have inflammatory/metabolic changes, organ dysfunction, and augmented renal clearance.[Le Daré 2021] For example, extracorporeal membrane oxygenation (ECMO) may increase drug dosage requirements up to 2-fold.[Zhao 2020] Renal toxicity and electrolyte disturbances associated with LAmB may be difficult to manage. In addition, drug-drug interactions (DDIs) are challenging. For example, both dexamethasone and remdesivir may alter antifungal drug levels, and need to be considered with antifungal agents.

Impaired renal or hepatic function, dialysis, or ECMO may alter drug concentrations and protein binding in patients with COVID-19. Given the range of pharmacologic perturbations and DDIs possible, patients with COVID-19 who are receiving antifungals need therapeutic drug monitoring (TDM) at least weekly.[Koehler 2020a] It is important to address the target levels within your own institution. However, it is also important to note that isavuconazole does not have a defined target trough concentration; nevertheless, isavuconazole TDM may be considered for patients who are on dialysis, receiving ECMO, or who are obese.[Zurl 2020]

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Infection Control and Antifungal Stewardship and Infection Control/ Prevention Commentary

(not part of the CSP)

The following sections relate to overarching principles for addressing antifungal stewardship and infection control and prevention principles related to CA-IFIs.

Antimicrobial Stewardship

- Data suggest bacterial co-infections are present on hospital admission in 4.9% [95% CI 2.6-7.1] of COVID-19–infected patients, with secondary bacterial infections developing in 16% [95% CI 12.4-9.6] after presentation (https://www.tarrn.org/covid)
- Many COVID-19–infected patients receive antibiotics during hospital admission (https://www.cambridge.org/core/journals/infection-control-and-hospital-epidemiology/article/antibiotic-prescription-during-the-covid19-pandemic-a-biphasic-pattern/6C746A25685EAD0B44D3E33EC7A24594#r3)
- Use of broad-spectrum antibiotics may contribute to *Candida* colonization and infections; antifungal exposure may also lead to antifungal resistance and breakthrough of resistant fungi, so antimicrobial stewardship is important to optimize use of these agents
- While antifungal prophylaxis is currently not recommended in COVID-19 patients, it is important to assess risk factors for fungal infection in these patients and use diagnostic-driven modalities in decision making regarding use of antifungal therapy, as illustrated in the CSP
- When treating Covid-19–associated IFIs, antifungal therapy should be optimized for target pathogens, using evidence-based data when available. For example, azoles would be preferred for CAPA, while treatment of *C auris* and other *Candida* spp. infections should be based on local resistance patterns and susceptibility data
- Patients initiating/receiving antifungal therapy should be carefully evaluated for organ function, electrolyte balance, and the presence of drug-drug interactions. TDM should be performed as appropriate to guide treatment. This is discussed in more detail in the CSP under CONSIDER PHARMACOLOGIC CONSIDERATIONS

INFECTION CONTROL AND ANTIFUNGAL STEWARDSHIP AND INFECTION CONTROL/ PREVENTION COMMENTARY (continued)

(not part of the CSP)

Infection Control and Prevention

Invasive aspergillosis and other filamentous fungal infections

- The risk of invasive aspergillosis and other filamentous fungal infections may be related to intrinsic factors associated with the pathogenesis or treatment of COVID-19, but most often healthcare-associated aspergillosis and other filamentous fungal infections have been associated with the use of negative pressure; use of contaminated drugs or materials; inadequate heating, ventilation, and air conditioning (HVAC) system maintenance; and with construction or remodeling activities
- Clustering of cases of invasive aspergillosis or other filamentous fungal infections in a hospital or unit caring for COVID-19 patients should trigger a stewardship examination of the management protocols, particularly targeting the use of systemic corticosteroids and immunomodulators, and a search for environmental factors or commonalities in drugs or materials used for patient care

Risk factors	Examples	Mitigation
Intrinsic	• Lymphopenia • Steroids • Immunomodulators	• Protocol review and medication stewardship activities (eg, positive pressure rooms, neutropenic precautions)
Environmental	• Rooming in negative pressure • Contaminated linens • Contaminated compounded medications • Contaminated materials such as gauze or Band-Aids • New construction in or outside the unit • Uncontained remodeling activities, inadequate maintenance of HVAC systems	• Surveillance and cluster investigation • Airflow engineering controls • Strict containment of construction or remodeling activities • USP best practices for medication compounding • Appropriate storage of medical materials

INFECTION CONTROL AND ANTIFUNGAL STEWARDSHIP AND INFECTION CONTROL/ PREVENTION COMMENTARY (continued)

(not part of the CSP)

Invasive candidiasis

- Patients with COVID-19 have multiple risk factors for invasive candidiasis; therefore, a high incidence of this co-infection can be expected. However, studies have shown significant variation in invasive candidiasis rates in different units
- Aside from endogenous risk factors and those related to interventions targeted at the management of COVID-19, some investigators have hypothesized that increases in rates of candidemia and other bloodstream infections may be related to a breakdown of the CLABSI-prevention bundles and deterioration of line care.[Stifter 2020] These may be in turn be related to high patient volumes, crisis standards of care, and less frequent patient contact due to high risk to the healthcare worker/PPE use
- There have been multiple outbreaks of *Candida auris* and resistant *Candida* infections in COVID-19 units, emphasizing the nosocomial transmission capabilities of this *Candida* species and others.[Arastehfar 2021; de Almeida 2021; Di Pilato 2021; Macauley 2021; Prestel 2021] Detection of an outbreak of *C auris* should prompt unit-wide screening and strict infection prevention measures such as transmission-based precautions (often contact precautions, depending on the setting) , enhanced hand hygiene, and use of disinfectants that are effective against *C auris*
- Routine antifungal prophylaxis against invasive candidiasis is not recommended and may result in the development of antifungal resistance. Targeted prophylaxis in high-risk patients or units with a high incidence has not been studied in the context of COVID-19 and may result in overuse of antifungals as the risk predictor models in current use have not been validated in patients with such high frequency of risk factors

Further Reading

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INFECTION CONTROL AND ANTIFUNGAL STEWARDSHIP AND INFECTION CONTROL/ PREVENTION COMMENTARY (continued)

(not part of the CSP)

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