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 *OR*
- Are immunocompromised

LOOK AT TIMELINES FOR

- COVID-19 diagnosis
- ICU admission
- Mechanical ventilation
- Antibiotics, corticosteroids, tocilizumab, baricitinib, or other immunomodulatory agents

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

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 for non-tissue samples: 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)

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.

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 (isavuconazole 200 mg = 372 mg isavuconazonium sulfate) 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

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 or panfungal 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
Invasive Candidiasis/Candidemia	Positive *Candida* spp blood culture, sterile-site culture, or peritoneal catheter culture (in place <24h) *OR* T2 Candida™ positive or sequential positive serum BDGs in the presence of qualifying *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.

Non-CAPA PULMONARY IFI COMMENTARY

Clinicians need to pursue a specific diagnosis, because non-CAPA pulmonary IFIs, including PCP, non-*Aspergillus* molds, *Cryptococcus* spp, endemic mycoses, and invasive candidiasis 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 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.

ARDS = acute respiratory distress syndrome; BAL = bronchoalveolar lavage; BDG = 1-3 beta-D-glucan; BUN = blood urea nitrogen; CA-IFI = COVID-19-associated invasive fungal infection; CAPA = COVID-19-associated pulmonary aspergillosis; 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 transplantation; HIV = human immunodeficiency virus; ICU = intensive care unit; IFI = invasive fungal infection; LAmB = lipid amphotericin B; LFA = lateral flow assay; LFT = liver function test; ND-BAL = non-directed bronchoalveolar lavage (deep inline suction, aka “mini-BAL”); PCR = polymerase chain reaction; PK= pharmacokinetics; qRT-PCR = real-time polymerase chain reaction; PCP = *Pneumocystis jirovecii* pneumonia; s = serum; sCR = serum creatinine; SOT = solid organ transplantation; TDM = therapeutic dose monitoring

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