COVID-19-Associated Fungal Disease

Since the global spread of COVID-19, reports of secondary infections with fungal organisms, particularly *Aspergillus* spp., have emerged. Diagnostic criteria have been proposed for COVID-19-associated pulmonary aspergillosis (CAPA).

**COVID diagnosis can be 2 weeks prior to CAPA or within 96 hours after SARS-CoV-2 + ICU**

### CAPA Diagnostic Criteria

Unlike invasive pulmonary aspergillosis (IPA), no additional immune-suppressing event beyond COVID-19 and associated therapies is required.

#### PROVEN CAPA

- Histopathology with tissue invasion
- OR
  - Detection from sterile site by any of the following means:
    - Culture
    - Histology
    - PCR

#### PROBABLE CAPA

**TRACHEOBRONCHITIS**

- Tracheobronchitis (eschar, pseudomembrane, ulceration)
- AND
  - BAL with fungal elements OR
  - Positive fungal culture
  - Positive BAL PCR OR
  - BAL GM >1.0 index OR
  - Serum GM >0.5 index

**PULMONARY DISEASE**

- Unexplained pulmonary infiltrate or cavitating lesion
- AND
  - BAL with fungal elements
  - Positive fungal culture
  - Positive BAL PCR
  - BAL GM >1.0 index OR
  - Serum GM >0.5 index

### Risk Factors for CAPA

- Solid organ transplant recipients
- Prolonged corticosteroids (>3 weeks at any dose)

### Traditional Risk Factors for IPA

- Neutropenia (<500/mm³) for >10 days
- Hematologic malignancy
- Allogeneic stem cell transplant recipients
- Treatment with T- or B-cell inhibitors
- Inherited immune deficiency syndromes

### Treatment of CAPA

**First line:** Voriconazole or isavuconazole

**Salvage therapy:** Echinocandin plus voriconazole

**Duration:** Unknown, but most recommend 6-12 weeks

**When to start therapy:** At time of suspected diagnosis. *Do not wait* for confirmatory microbiologic, radiographic, or histopathologic evidence. Antifungal therapy can be stopped if diagnostic criteria not met.

**When to suspect CAPA:** Refractory fever for ≥3 days, fever after >48 hours of defervescence, hemoptysis or worsening pleuritic chest pain

### Incidence of CAPA

- 5%-35% of ICU patients with COVID-19 ARDS have been reported to have CAPA
- This may be an overestimation of the true incidence, as it is likely that cases of colonization have been counted as true infection
- Using stringent diagnostic criteria, the true incidence is believed to be around 5%—similar to the incidence of non-COVID ARDS
- Immune-modulating therapies such as corticosteroids and IL-6 inhibitors may increase the risk

### Other Fungal Disease Related to COVID-19

- **Mucormycosis**
  - <10 cases of associated mucormycosis reported
  - Risk factors: Diabetes, renal disease, immune suppression

- **Invasive candidiasis (IC)**
  - Unclear if the incidence of IC has been impacted
  - No unique risk for IC secondary to COVID

- **Endemic fungi**
  - Reports of increased incidence of endemic fungal infections, particularly coccidioidomycosis
  - Unknown if increased risk secondary to COVID or COVID therapies

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