















1 **Supplemental Table 2:** Characteristics and risk factors of COVID-associated pulmonary aspergillosis (CAPA), COVID-associated mucormycosis
 2 (CAM), and COVID-associated candidiasis (CAC).

3  = particularly relevant for low- and middle-income countries (LMICs)

4  = relevant also for *C. auris*

	CAPA	CAM	CAC
Prevalence	Prevalence about 10% among invasive ventilated COVID-19 patients ¹⁻³	Prevalence of 0.27% among hospitalized COVID-19 patients in India ⁴	Unknown, outbreaks reported from 12 countries in the Americas, Europe and Middle East
Infectious agents	<i>A. fumigatus</i> predominant ! Azole resistant <i>A. fumigatus</i>	<i>Rhizopus</i> spp. predominant ⁴	<i>C. albicans</i> predominant ! <i>C. auris</i>
Shared risk factors	Male sex ⁴⁻⁹ Older age ^{1,4,10-14} Systemic corticosteroids Severe COVID-19, ARDS ICU treatment		
Risk factors	Dexamethasone, Tocilizumab and their combination ^{1,2,13-19} (Major!) (Prolonged) mechanical ventilation ²⁰ Environmental exposure/hospital air exposure/ventilation systems/building renovation work ^{16,21}  Chronic obstructive pulmonary disease ^{2,12,13,16,17} Greater extent of lung damage caused by COVID-19 ¹²	Uncontrolled Diabetes Mellitus ^{4,6,7,10,23-27}  Newly diagnosed Diabetes Mellitus ¹⁰ Diabetic ketoacidosis ²⁷ Hyperglycaemia ²⁷ Systemic Corticosteroids ^{4,6,7,10,23,25,27-31} ( overuse) COVID-19 related hypoxemia ^{4,7}	Indwelling devices (CVC, urinary catheter, prosthetic device) Prolonged ICU stay ^{20,35-37}  11,38,39 CVCs ^{36,40,41}  11,38 More severe disease/higher organ failure assessment score ^{20,42} Corticosteroids and immunosuppressants ^{20,35,40,41,43} other

	<p>Potential Minor Risk factors</p> <p>Negative air pressure in ICU rooms²²</p> <p>Azithromycin¹⁵</p> <p>HIV/AIDS²</p> <p>Solid cancer^{17,19}</p> <p>Pulmonary vascular disease¹⁹</p> <p>Liver disease¹⁹</p> <p>Multiple myeloma¹⁹</p> <p>Diabetes⁹</p>	<p>Iron overload^{10,32}</p> <p>Environmental exposure/hospital air exposure^{10,32} </p> <p>Prolonged use of masks³³ </p> <p>Occupation farmer⁶ </p> <p>ICU admission and mechanical ventilation^{27,30}</p> <p>Underlying malignancies or SOT^{27,30}</p> <p>Repeated nasopharyngeal swab testing³³ </p> <p>Exocrine damage</p> <p>Endothelial damage</p> <p>Overexpression of glucose regulated protein (GRP78)⁴</p> <p>Potential Minor Risk factors</p> <p>Broad-spectrum antibiotics^{25,34} </p>	<p>Tocilizumab^{20,37,44}</p> <p>Prior antifungal exposure³⁹  including <i>C. auris</i></p> <p>Lack of hygiene plans/ABS program </p> <p>Broad spectrum antibiotics^{36,41,45}  including <i>C. auris</i></p> <p>Malignancies²⁰</p> <p>Potential Minor Risk factors</p> <p>Mechanical ventilation^{38,40,41,46}</p>
Sites of infection	Lungs	<p>ROM, ROCM^{4,47,48} </p> <p>Pulmonary^{27,30,49}</p> <p>Gastrointestinal²⁷</p> <p>Disseminated</p>	Bloodstream
Diagnostics	<p>Imaging: halo sign, multiple pulmonary nodules or lung cavitation (alone not sufficient)⁵⁰</p> <p>Bronchoscopy, including tracheobronchial inspection and BAL sampling</p>	<p>RO(C)M: Nasal endoscopy²⁹</p> <p>Sinus debridement²⁹</p> <p>Cranial CT/MRI²⁹</p>	<p>Blood cultures⁵¹</p> <p>Imaging (abdomen)⁵²</p>

	<p>Culture, microscopy and PCR from BAL and lung biopsy samples⁵⁰</p> <p>Galactomannan from BAL⁵⁰</p> <p>Biopsy</p>	<p>Pulmonary:</p> <p>Imaging: Halo sign or reversed halo sign, vascular occlusion sign²⁹</p> <p>Culture</p> <p>Direct microscopy using fluorescent brightener²⁹</p> <p>Histopathology</p>	
Therapy	<p>Voriconazole or isavuconazole as first line for possible, probable, and proven CAPA⁵⁰</p> <p>Amphotericin B, posaconazole or echinocandins as second line⁵⁰</p>	<p>Surgical debridement²⁹</p> <p>Liposomal amphotericin B²⁹</p> <p>If renal compromise isavuconazole iv or posaconazole iv⁵³</p>	<p>Caspofungin or micafungin as first line^{51,54,55}</p> <p>Liposomal amphotericin B as second line⁵⁵</p>
Follow up	<p>Repeated susceptibility testing for resistance⁵⁰</p>		<p>Repeated blood cultures until clearance⁵¹</p>
Clinical outcome	<p>About 50% mortality rate at 12 weeks, 17.2% attributed^{2,9,13,56}</p>	<p>Case-fatality rate at 12 weeks 45.7%⁴</p> <p>Age, rhino-orbital-cerebral involvement, and intensive care unit admission were associated with increased mortality rates⁴</p> <p>Mortality lower for RO(C)M 37.3% (22/59) versus 81% (17/21) for pulmonary, gastrointestinal and disseminated mucormycosis (P<0.001)²⁷</p>	
Challenges in LMICs	<p>Countries with lower socioeconomic status are likely to have inadequate resources available to diagnose and treat patients with CAPA</p>	<p>Disfiguring surgeries may be the first option for RO(C)M before considering expensive antifungals</p>	<p>Resource-limitation to run and repeat susceptibility tests</p>

6 References

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