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# COVID-19-associated fungal infections

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**Coronavirus disease 2019 (COVID-19)-associated invasive fungal infections are an important complication in a substantial number of critically ill, hospitalized patients with COVID-19. Three groups of fungal pathogens cause co-infections in COVID-19: *Aspergillus*, *Mucorales* and *Candida* species, including *Candida auris*. Here we review the incidence of COVID-19-associated invasive fungal infections caused by these fungi in low-, middle- and high-income countries. By evaluating the epidemiology, clinical risk factors, predisposing features of the host environment and immunological mechanisms that underlie the pathogenesis of these co-infections, we set the scene for future research and development of clinical guidance.**

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has rapidly spread across the globe, accounting for almost 300 million cases of coronavirus disease 2019 (COVID-19) so far (Fig. 1). The first cases of COVID-19-associated pulmonary aspergillosis (CAPA) were reported from China in early 2020<sup>1</sup> (Fig. 1). Since then, multiple case series and cohort studies have highlighted the importance of this potentially life-threatening secondary infection, sometimes caused by azole-resistant *Aspergillus* spp.<sup>2</sup>. The most commonly affected patients are those with acute respiratory failure due to COVID-19, particularly patients receiving systemic corticosteroids or tocilizumab therapies<sup>3–10</sup>. The outcomes of CAPA have been devastating, with reports on the independent contribution of CAPA estimating mortality rates of more than 40% (refs. <sup>4,6,9,11</sup>) (Fig. 2).

COVID-19-associated mucormycosis (CAM) gained worldwide attention in early 2021, during the second wave of the COVID-19 pandemic in India (Fig. 1). An unprecedented surge of cases of mucormycosis, a fungal infection caused by moulds belonging to the order Mucorales, posed a major healthcare problem with >47,500 cases reported by the Indian government between May and August 2021 (<https://governmentstats.com/mucormycosis/index.html>). This was covered in the lay press wrongly as a ‘black fungus’ pandemic, referring to the colour of the necrotic tissue as a result of the destructive nature of the fungal pathogen, but failing to consider that the term black fungus actually refers to a different category of fungal pathogens that is not associated with CAM<sup>12,13</sup> (Fig. 2 and Supplementary Table 1). Uncontrolled diabetes, and systemic corticosteroid (over)treatment, are two risk factors for the development of CAM in India and other countries<sup>14</sup>. While disease manifestation and incidence vary considerably between different geographical regions<sup>15</sup>, rhino-orbital-cerebral and pulmonary diseases are the most frequent clinical presentations of CAM in patients with COVID-19. Mucormycosis adds particular insult to injury in a substantial proportion of critically ill patients with COVID-19 due

to high mortality rates and because this disease is necrotizing and often requires aggressive surgical debridement, which results in disfigurement in those who survive<sup>16</sup>.

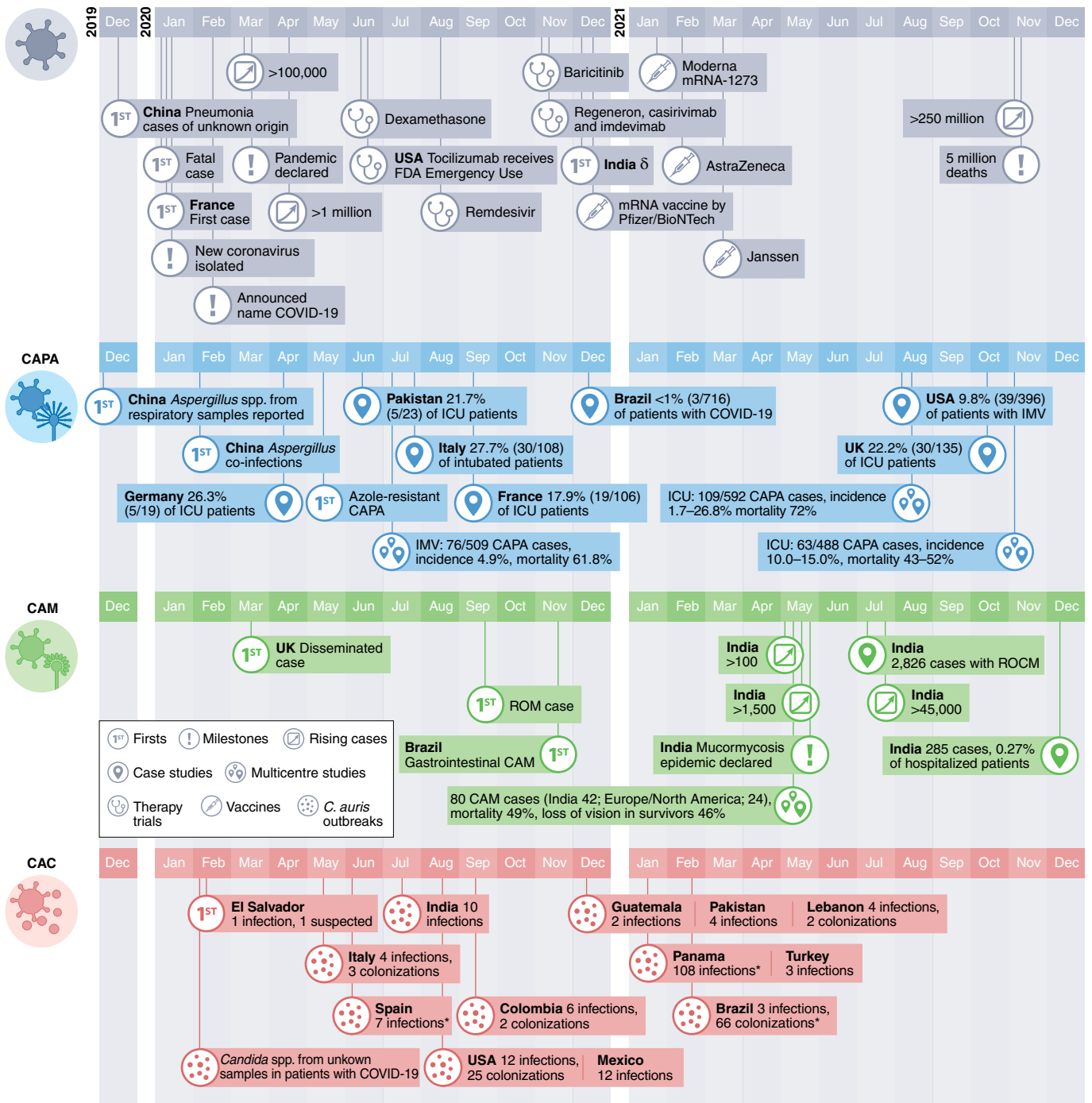
Invasive *Candida* infections in patients with COVID-19 in the intensive care unit (ICU) were first described shortly after the emergence of SARS-CoV-2<sup>17</sup> (Fig. 1). Common risk factors in patients in the ICU include the use of antibiotics, central venous catheters and corticosteroids; invasive *Candida* infections impose considerable comorbidity. Of particular concern are outbreaks of severe *Candida auris* infections in patients with COVID-19 in the ICU<sup>18,19</sup> (Fig. 2). *C. auris* is difficult to distinguish from other *Candida* species and is often resistant to many or all antifungal drugs<sup>20</sup>. It can persist on surfaces; unlike other invasive fungal infections (IFIs), it can be transmitted in healthcare facilities.

SARS-CoV-2 infection alters immune and metabolic responses in patients, which together produce an inflammatory environment that is highly permissive to fungal infections; however, the underlying mechanisms are complex. In this Review, we discuss the epidemiology, risk factors, predisposing features of the host environment and immunological mechanisms that are involved in the pathogenesis of COVID-19 fungal co-infections.

## Epidemiology and risk factors

**CAPA.** Cases of CAPA emerged during the first months of the pandemic. However, incidence rates varied widely, probably because CAPA is difficult to diagnose in patients with COVID-19-associated acute respiratory distress syndrome (ARDS). Specifically, clinical features and radiological findings of CAPA resemble those of severe COVID-19<sup>2</sup> and blood tests lack sensitivity<sup>6,21–23</sup> due to the invasive growth of *Aspergillus* in the airway and the clearance of *Aspergillus* galactomannan (GM) from systemic circulation by neutrophils in non-neutropenic patients<sup>24–26</sup>. This results in a clinical picture of CAPA that is different from primarily angioinvasive invasive pulmonary aspergillosis (IPA) observed in patients with neutropenia;

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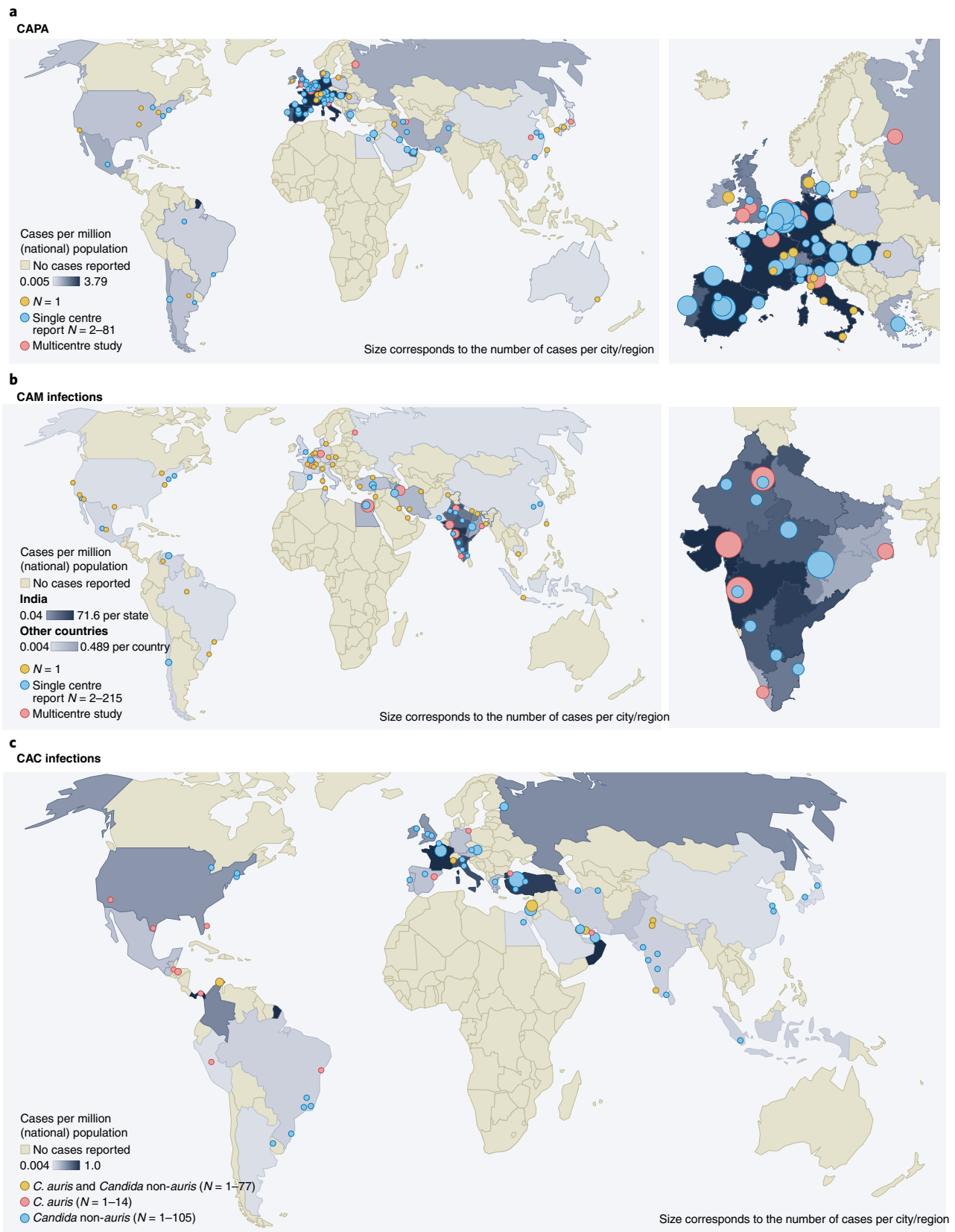


**Fig. 1 | Timeline of key events of COVID-19, CAPA, CAM and CAC.** \*Not specified if in patients with COVID-19/unclear reported numbers. IMV, invasive mechanical ventilation.

CAPA is often limited to airway invasive growth for several days before it becomes angioinvasive<sup>27</sup>. However, once CAPA becomes angioinvasive and produces positive serum GM, mortality is more than 80%, even if systemic antifungal therapy is provided<sup>28,29</sup>. Testing of bronchoalveolar lavage (BAL) for CAPA enables earlier detection<sup>21–23</sup>, but due to the risk of COVID-19 transmission, bronchoscopies were rarely performed, particularly during the early phase of the pandemic<sup>30</sup>. Lack of autopsies may also have resulted in an underestimation of CAPA prevalence in some hospitals<sup>31,32</sup>.

In the absence of consensus definitions for CAPA, classification criteria were modified<sup>33,34</sup>; these modifications varied widely between

studies and often included non-specific mycological evidence such as culture results or even GM testing of tracheal aspirates. Using these variable criteria, a median incidence of 20.1% (range 1.6–38%) was reported in patients with COVID-19 acute respiratory failure requiring invasive ventilation<sup>35–38</sup>. Implementation of more conservative European Confederation of Medical Mycology/International Society for Human and Animal Mycoses consensus criteria to detect CAPA in late 2020 (requires culture, GM enzyme-linked immunosorbent assay, lateral flow assay or *Aspergillus* PCR from either BAL or blood for classification of probable CAPA)<sup>25</sup> together with non-bronchoscopic lavage for possible CAPA, has resulted



**Fig. 2 | Distribution of CAPA, CAM and CAC.** The CAPA (**a**), CAM (**b**) and CAC (**c**) distributions, including *C. auris* infections for countries that reported respective cases. References can be found in Supplementary Table 1. **a,b**, The dots represent cities where cases occurred (yellow, single case; blue, at least two cases at one site; red, multicentre studies/multiple sites per city/national reports). The colour of countries and the size of the dots are proportional to the number of cases per million population of the respective country. **c**, The dots represent cities where cases occurred (red, *C. auris*; yellow, *C. auris* and *Candida non-auris* cases; blue, *Candida non-auris* cases). The colour of countries and size of the dots are proportional to the number of cases per million population of the respective country (cut-off at 10 million population: El Salvador, Lebanon, Panama, Qatar and United Arab Emirates).

**Table 1 | Main characteristics of CAPA, CAM and CAC**

	CAPA	CAM	CAC
Prevalence	Prevalence about 10% among invasively ventilated patients with COVID-19 <sup>4</sup>	Prevalence of 0.27% among hospitalized patients with COVID-19 in India <sup>15</sup> ; limited evidence from Europe suggests prevalence about 1–2% among invasively ventilated patients with COVID-19 (ref. <sup>14</sup> )	Unknown; outbreaks reported from 12 countries in the Americas, Europe and Middle East <sup>18,52</sup>
Infectious agents (!, of particular concern)	<i>A. fumigatus</i> predominant <sup>4!</sup> Azole-resistant <i>A. fumigatus</i>	<i>Rhizopus</i> spp. predominant <sup>14,16</sup>	<i>C. albicans</i> predominant <sup>53!</sup> <i>C. auris</i>
Sites of infection	Lungs <sup>21</sup>	ROM, ROCM <sup>14,16</sup> Pulmonary <sup>14</sup> Gastrointestinal <sup>14</sup> Disseminated <sup>14</sup>	Bloodstream <sup>52</sup> Abdomen
Therapy	Voriconazole or isavuconazole as first-line treatment for possible, probable and proven CAPA <sup>21</sup> Liposomal amphotericin B, posaconazole or echinocandins as second line <sup>21</sup>	Surgical debridement <sup>14</sup> Liposomal amphotericin B <sup>14</sup> If renal compromise, intravenous isavuconazole or intravenous posaconazole <sup>48</sup>	Caspofungin or micafungin as first line <sup>52,53</sup> Liposomal amphotericin B as second line <sup>53</sup>
Challenges	Reluctance to perform aerosol-generating procedures, such as autopsies and bronchoscopies Azole-resistant aspergillosis awareness (not tested if not suspected)	Diagnostics in ICU setting (BAL, gut biopsy) <sup>14</sup> Reluctance to perform aerosol-generating procedures, such as autopsies and bronchoscopies, awareness (not tested if not suspected)	High rate of multidrug resistance for <i>C. auris</i> <sup>18</sup> Misleading identifications, ability to form biofilms, reluctance to perform autopsies

in a substantial reduction of the mean incidence of probable/proven CAPA cases<sup>4,7,31</sup>, bringing the prevalence of CAPA down to about 10% among invasively ventilated patients with COVID-19. However, incidence continues to vary widely between ICUs, due to non-uniform approaches to COVID-19 treatments, different burdens of *Aspergillus* exposure and differing diagnostic algorithms as well as genetic predisposing risk factors<sup>39,40</sup>. The combination of dexamethasone and tocilizumab, invasive ventilation and older age, have been reported as risk factors for developing CAPA<sup>4</sup> (Table 1, Fig. 3 and Supplementary Table 2). Unlike influenza-associated pulmonary aspergillosis, CAPA develops later and is diagnosed a median of 8 days after ICU admission<sup>4,6,7</sup>. CAPA has been consistently associated with COVID-19 mortality rates of more than 50% (ref. <sup>6–9</sup>); the combination of *Aspergillus* growth from BAL fluid culture and positive BAL fluid GM can predict 90-day mortality (hazard ratio 2.53), even in the absence of a positive serum GM<sup>41</sup>. In the largest multicentre studies, CAPA is an independent prognostic factor for mortality, with hazard ratios between 1.45 and 1.97 (refs. <sup>4,11</sup>).

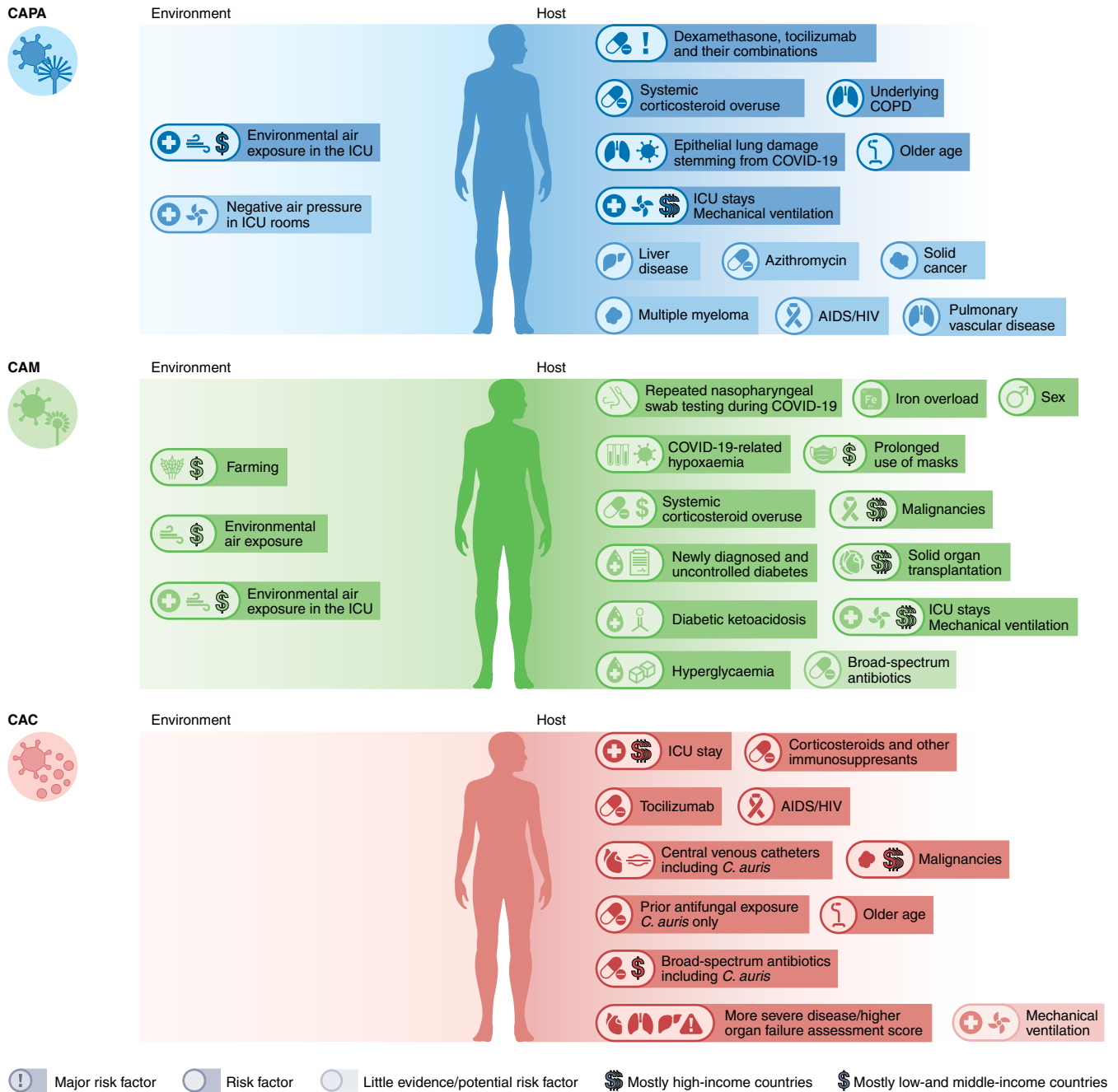
**COVID-19-associated mucormycosis.** Before the COVID-19 pandemic, India and Pakistan had the highest burden of invasive mucormycosis, predominantly occurring in men<sup>42</sup>. Indian population-based case rates of mucormycosis estimate the burden of CAM to be 70-times higher than the global rate, with predicted annual cases of >200,000 before the pandemic<sup>43,44</sup>. The high incidence of CAM has been linked to environmental factors, such as exposure to fungal spores<sup>43,45</sup> and chronic illness, such as poorly controlled diabetes mellitus<sup>46</sup>. In high-income countries, common underlying conditions are haematological malignancies and organ transplants. Further predisposing factors include use of immunosuppressants, such as corticosteroids, and neutropenia (Table 1 and Fig. 3)<sup>45</sup>.

These known risk factors, combined with the changes in metabolism and immune function owing to COVID-19 and COVID-19 treatment modalities, resulted in a surge of CAM cases particularly in low- and middle-income countries. While CAM cases in patients

with classical risk factors, such as underlying haematological malignancies, occurred during the first months of the pandemic, the number of reported cases of CAM increased dramatically in the second wave of the pandemic, possibly driven by the use (sometimes overuse) of systemic corticosteroids, by the increasing case numbers in low- and middle-income countries with high environmental Mucorales exposure and by an increase in patients with uncontrolled or undiagnosed diabetes. Globally, the highest number of cases was reported from India, with such dramatic increases compared with pre-COVID-19 rates that the Central Government of India declared a mucormycosis epidemic on 10 May 2021. Prevalence of CAM in India was 0.27% in hospitalized patients with COVID-19 and 1.6% in patients managed in the ICU<sup>15</sup> (Fig. 2). Estimates on incidence rates in other countries are scarce, although CAM cases have been described in countries in Asia, Africa, Europe and South, Middle and North America<sup>14,47</sup> (Fig. 2).

In contrast to the large case series from India, with patients suffering from either rhino-orbital mucormycosis (ROM) or rhino-orbital cerebral mucormycosis (ROCM), which have a distinct clinical presentation that is rarely missed, in high-income countries the site of involvement is primarily pulmonary or disseminated. Lack of diagnosis of CAM might arise because the clinical and radiological presentation of pulmonary and disseminated mucormycosis overlaps with the clinical features of COVID-19<sup>16,48</sup>. In fact, CAM is sometimes only diagnosed if invasive diagnostics, including histology and autopsies, are used<sup>48</sup>. Together this means that it is likely that the true burden of CAM in high-income countries is underestimated. In addition, the geographical distribution of caseloads with independent risk factors for ROM/ROCM, such as diabetes mellitus, may contribute to the observed epidemiology of COVID-19-associated CAM<sup>46</sup>.

*Rhizopus* spp. are the predominant pathogen causing CAM in case series from India and other countries<sup>14,15,47,49</sup>. Most ROM/ROCM CAM cases are diagnosed about 10 days after SARS-CoV-2 detection; however, delayed diagnosis up to three months post-COVID-19 has been reported<sup>14,49</sup>. Depending on the clinical



**Fig. 3 | Risk factors for CAPA, CAM and CAC.** References can be found in Supplementary Table 2.

manifestation, mortality rates differ<sup>14</sup>. COVID-19-associated ROM has mortality rates of 14% and higher<sup>49</sup>, whereas pulmonary or disseminated mucormycosis has mortality rates in excess of 80%<sup>14</sup>.

**COVID-19-associated candidiasis including *C. auris*.** A substantial proportion of patients with COVID-19 require ICU treatment, parenteral nutrition and mechanical ventilation, which together with systemic corticosteroid therapy, predisposes them to infections with *Candida* spp. In some studies, a two- to tenfold higher incidence of candidemia has been reported in patients with COVID-19 compared with patients without COVID-19<sup>50,51</sup>. *Candida albicans* is the most frequently reported yeast species in critically ill patients with COVID-19 (44% of candidemia cases in one US multicentre

study<sup>52</sup>) but in some geographical areas the emerging pathogen *C. auris* was predominant<sup>53</sup>.

Since *C. auris* was first identified in Japan in 2009, case numbers of infection have increased globally. It can colonize the skin and environmental surfaces and can be transmitted as a nosocomial pathogen<sup>54</sup>. These features have made *C. auris* a global fungal public health threat. Infection with *C. auris* and other *Candida* species is associated with prolonged stay in the ICU, administration of broad-spectrum antibiotics and systemic steroids, central lines, diabetes mellitus, kidney disease and mechanical ventilation (Fig. 3 and Table 1)<sup>55,56</sup>. Prior exposure to antifungals is a major risk factor for *C. auris* bloodstream infection<sup>57</sup>. Tocilizumab use has also been linked to *C. auris* fungemia in patients with COVID-19<sup>58,59</sup>.

Under-resourced public health systems, increased workload of healthcare workers and over-occupancy of beds during the COVID-19 pandemic are negatively impacting infection control measures<sup>60</sup>. The first reported cases of *C. auris* bloodstream infections in patients with COVID-19 were in February 2020<sup>61</sup>. Since then, 13 outbreaks have been reported worldwide, ranging from 2 to 12 infections each and multiple colonized patients in addition (Figs. 1 and 2). Commercially available biochemical-based tests may misidentify *C. auris*, making management in resource-limited countries another challenge. Consequently, the true scale of infections may be underestimated. Currently, no reliable data on incidence in patients with COVID-19 globally can be extrapolated. COVID-19-associated *C. auris* outbreaks have resulted in mortality rates ranging from 30% (ref. <sup>62</sup>) to 83% (ref. <sup>19</sup>) in those with candidemia. Corticosteroid use, sepsis and older age have been identified as independent risk factors for mortality in patients with COVID-19-associated candidiasis (CAC)<sup>50</sup>.

### Pathogenesis of COVID-19-associated IFIs

**COVID-19-associated immune dysfunction.** The immunopathogenesis of COVID-19-associated IFIs is not completely understood but involves multiple factors caused by the viral infection, fungus and host immune response<sup>63</sup>. SARS-CoV-2 targets cells expressing angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2), including airway epithelial cells, type 2 pneumocytes, vascular endothelial cells and alveolar macrophages<sup>64</sup>. The infection causes airway epithelial damage, characterized by disrupted epithelial junctions, impaired ciliary clearance and functional defects, such as the release of antimicrobial proteins<sup>65</sup>. During fungal infection, airway fibrinolysis and disruption of epithelial tight junctions by fungal proteases during germination, such as alkaline protease 1 from *Aspergillus* spp., can promote allergic inflammation and further sustain lung pathology<sup>66</sup>. The obstruction of the airways due to the release of fibrinous material from the tissue and dying cells decrease oxygen and carbon dioxide diffusion; this hypoxic milieu can influence both fungal virulence and the host immune response<sup>67</sup>. This results in a vicious circle, in which secondary fungal metabolites such as gliotoxin and mucoricin can further increase both local and systemic hypoxia by damaging host tissues, restraining angiogenesis and tissue repair<sup>68,69</sup>.

On viral infection, injured epithelial cells may also express apical receptors, such as integrins<sup>70</sup>, which in turn mediate the interaction with proteins on the surface of the *Aspergillus*, Mucorales or *Candida* cell wall, namely the thaumatin-like protein CalA, spore-coating (CotH) proteins and mannoproteins, respectively, to promote fungal adherence and invasion<sup>71–73</sup>. Fungal adhesion can be further enhanced by the expression of fungal cell wall components, such as galactosaminogalactan in *Aspergillus*, which also mediates biofilm formation<sup>74</sup>. On the other hand, the influenza virus can hijack the cytoskeletal system to allow viral entry and replication<sup>75</sup>, a feature that may, to an extent, also facilitate fungal invasion. In this regard, gliotoxin can promote actin cytoskeleton rearrangements in epithelial cells to favour conidia internalization<sup>76</sup>. Moreover, gliotoxin and other secondary metabolites, such as fumagillin, also contribute to immune evasion by inhibiting immune cell function<sup>77</sup>.

Virus-infected cells release danger-associated molecular patterns (DAMPs), which act as danger signals on adjacent epithelial cells and resident alveolar macrophages to promote the release of proinflammatory cytokines and chemokines, and elicit the influx of macrophages and neutrophils, exacerbating the local inflammatory response<sup>78</sup>. DAMPs have been implicated in the regulation of inflammation in fungal diseases<sup>79</sup>; in particular, the DAMP/receptor for advanced glycation end products (AGEs) axis was found to integrate signals derived from Toll-like receptors (TLRs) and amplify inflammatory responses in experimental aspergillosis<sup>79</sup>.

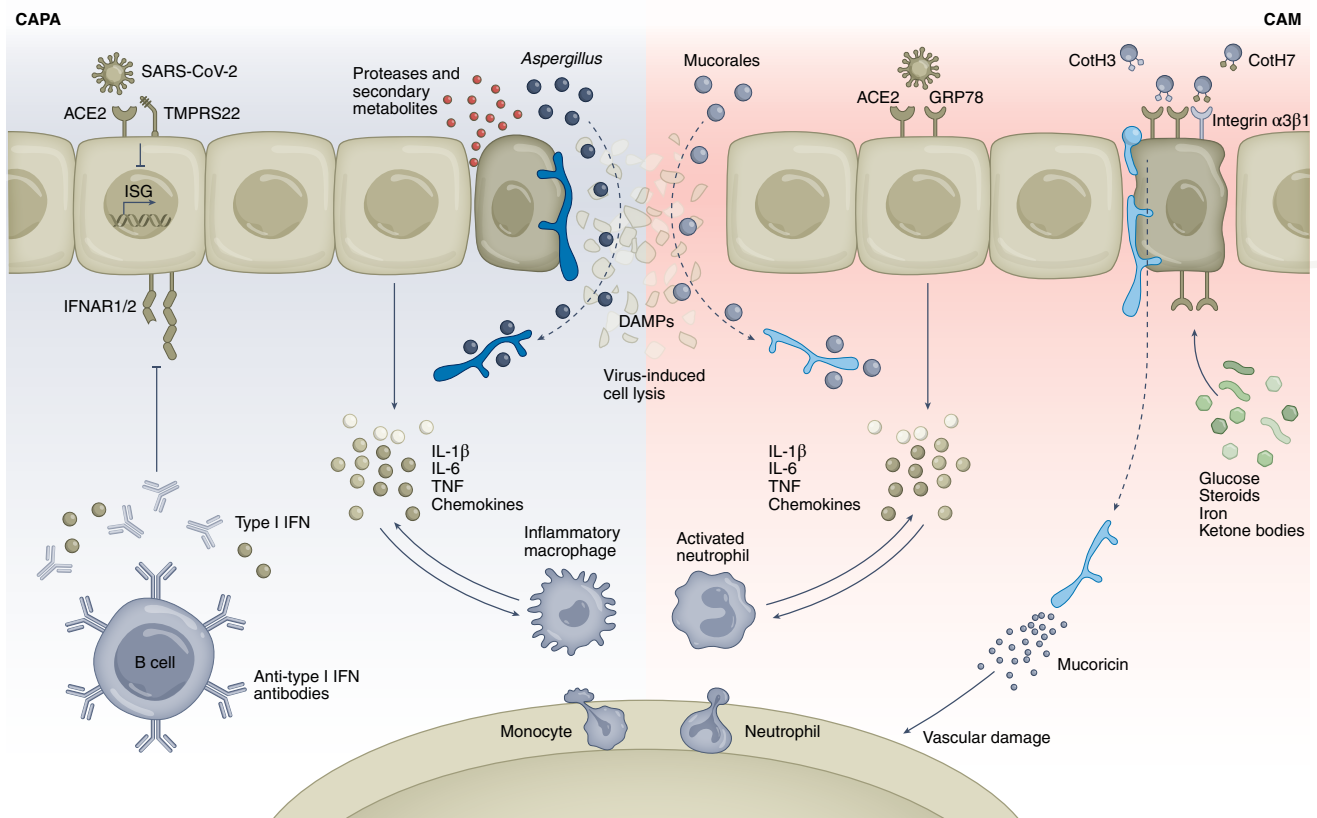
In this regard, genetic variants causing the hyperactivation of danger signalling were identified as risk factors for the development of invasive aspergillosis in immunocompromised hosts<sup>80</sup>. Chronic hyperglycaemia also promotes the irreversible glycation and oxidation of proteins and lipids leading to the formation of AGEs<sup>81</sup> and these could be presumably implicated in the pathogenesis of mucormycosis.

Hyperinflammation is a hallmark of COVID-19, characterized by high levels of circulating proinflammatory cytokines, including interleukin-6 (IL-6), interferon- $\gamma$  (IFN- $\gamma$ ), IL-1 $\beta$  and tumour necrosis factor (TNF), and acute phase reactants and ferritin<sup>82</sup> (Fig. 4). The activation of antiviral immunity after viral recognition by innate immune cells might also paradoxically promote systemic inflammatory reactions and establish a highly permissive environment to the development of fungal co-infections by potentiating the expression of specific virulence factors and damage to the host. While these cytokines are essential for the innate control of fungal infection, an exacerbated production instead disrupts immune homeostasis and drives a pathogenic activation of the immune system that leads to tissue damage and fungal invasion<sup>83</sup>. In this regard, single-cell RNA sequencing and proteomics applied to blood samples from patients with severe COVID-19 have revealed defective monocyte activation and dysregulated myelopoiesis with release of immature dysfunctional neutrophils and monocytes into the circulation<sup>84</sup>. High-dimensional flow cytometry analyses also revealed an expansion of intermediate monocytes that exhibit a proinflammatory phenotype<sup>85,86</sup>.

The severe lymphopenia and lymphocyte dysfunction typically observed in COVID-19<sup>86</sup> may also influence the development of fungal co-infections. Severe lymphocytopenia was among the factors included in a prognostic model that predicted the development of invasive mould disease in haematological patients<sup>87</sup>. Moreover, Mucorales-specific T cells are detected in patients with mucormycosis<sup>88</sup> and impairments in T cell responses during COVID-19 are aggravated in patients with diabetes<sup>89</sup> at high risk of CAM. These observations suggest that the severely impaired cellular immunity in COVID-19 may increase susceptibility to secondary fungal infections.

In contrast to the general hyperinflammation phenotype, patients with COVID-19 display a remarkably decreased type I IFN (IFN- $\alpha$  and IFN- $\beta$ ) response<sup>90</sup>, resulting in part from the ability of SARS-CoV-2 to inhibit protein translation and abolish the type I IFN-dependent induction of IFN-stimulated genes<sup>91</sup> (Fig. 4). Impaired IFN response was also associated with the presence of neutralizing autoantibodies against type I IFNs, which could negate their antiviral activity, in approximately 10% of patients with severe disease<sup>92</sup>. Importantly, type I IFNs can prime human dendritic cells in promoting type 1 T helper responses against *Aspergillus*<sup>93</sup> and are key drivers of type III IFNs (IFN- $\lambda$ ), which are critical instructors of neutrophil-mediated antifungal responses<sup>94</sup>. In fact, high levels of IFN- $\lambda$ , and to a lesser extent of type I IFN, were detected in the upper airways of patients with mild COVID-19 compared with those with severe disease<sup>95</sup>; this might help explain the increased susceptibility of the latter patients to fungal co-infections. In contrast, excessive or prolonged production of IFN- $\lambda$  can hamper tissue repair during influenza or SARS-CoV-2 infection and ultimately increase susceptibility to secondary infections<sup>96,97</sup>.

Recognition of the influenza virus by TLR7 promotes type I IFN production by dendritic cells<sup>98</sup>; genetic variants in TLR7 that underlie the transcriptional downregulation of type I IFN signalling were found to predispose to COVID-19 in young males<sup>99</sup>. Strikingly, TLR7 expression was found to suppress the effector functions of macrophages against *Aspergillus* and aggravate pulmonary disease<sup>100</sup>, suggesting that, despite the essential role of type I IFNs in antifungal immunity, TLR7 signalling may be largely dispensable for protection from CAPA<sup>101</sup>.



**Fig. 4 | Immunological pathways and factors involved in CAPA and CAM.** SARS-CoV-2 infects alveolar epithelial cells by binding to the ACE2 receptor with the help of TMPRSS2. The virus represses type I IFN responses by blocking the transcription of IFN-stimulated genes and pre-existing genetic variants; type I IFN autoantibodies add further to this effect, preventing signalling through the IFNAR1/2 receptor complex. Delayed type I IFN responses favour the release of proinflammatory cytokines and chemokines, leading to the recruitment of monocyte-derived macrophages and neutrophils into the lungs that further contribute to cytokine and chemokine production. This general dysregulation of the immune response underlies a hyperinflammatory state that results in a 'cytokine storm' and ARDS that ultimately favours the development of fungal co-infections. During COVID-19, virus-induced cell lysis favours the invasion of the tissue by fungi; the release of DAMPs from damaged or dying cells further potentiates the hyperinflammatory phenotype. Conditions such as hyperglycaemia, steroid overuse and high levels of iron and ketone bodies upregulate the expression of GRP78, which, besides acting as a cofactor in viral entry, binds to spore-coating CotH3 to favour invasion of nasal epithelial cells by Mucorales. Similarly, the interaction of CotH7 with integrin  $\alpha 3\beta 1$  in alveolar epithelial cells contributes to the progression of pulmonary mucormycosis. The production of mucorin by Mucorales hyphae promotes vascular damage that allows the enhanced recruitment of leucocytes from the bloodstream into the tissue, thereby favouring the hyperinflammatory state.

While the sustained innate immune function leading to overt hyperinflammation is probably the main mechanism predisposing to CAPA, Mucorales species are instead endowed with specific virulence factors that may explain their preferential incidence among patients with COVID-19. Recent advances in genomics and transcriptomics coupled with the ability for gene manipulation technologies<sup>102–106</sup> have enhanced our understanding of the pathogenesis of mucormycosis as it relates to angio-invasion and tissue necrosis and can provide an explanation for the development of CAM. Specifically, Mucorales universally express CotH invasins<sup>104,107</sup> that allow inhaled spores to bind to the glucose-regulated protein 78 (GRP78) host receptor of nasal epithelial<sup>72</sup> and endothelial cells<sup>108</sup>. It is also noted that both CotH proteins and GRP78 are highly upregulated during hyperglycaemia and ketoacidosis, which also increase the growth of the fungus via acquiring elevated available serum iron while reducing the host immune response<sup>109</sup> (Fig. 4). The increased expression of the fungal CotH and host GRP78 in nasal epithelial cells leads to the inhaled spores being deposited in the sinus, causing ROM or ROCM rather than causing pulmonary infection via CotH/integrin  $\alpha 3\beta 1$  interactions<sup>72</sup> (Fig. 4).

It is noteworthy that GRP78 synthesis is upregulated in patients with COVID-19 as a result of the virus-induced endoplasmic reticulum stress cascade<sup>110</sup>. Biochemical analyses have shown that GRP78 can form a complex with SARS-CoV-2 spike protein and ACE2 to act as a host auxiliary factor for SARS-CoV-2 entry and infection of host cells<sup>111</sup>. Importantly, treatment of lung epithelial cells with a humanized monoclonal antibody (hMAb159) that blocks the activity of endoplasmic reticulum chaperones was found to deplete GRP78 and reduce ACE2 expression on the cell surface, as well as viral entry and infection in vitro<sup>111</sup>. In a murine model of pulmonary mucormycosis, the interaction of CotH7 with the integrin  $\beta 1$  receptor on alveolar epithelial cells promoted the activation of the epidermal growth factor receptor (EGFR) and mediates host cell invasion<sup>72</sup> (Fig. 4). This process may be of particular relevance to the pathogenesis of CAM since upregulation of the EGFR pathway in experimental SARS-CoV infection drives enhanced lung disease and fibrosis<sup>112</sup>. Infection of colonic epithelial cells by SARS-CoV-2 also demonstrated that the activation of EGFR promotes viral replication<sup>113</sup>. On the other hand, the toxin mucorin inhibits protein synthesis and induces inflammation, vascular permeability and hypovolaemic shock and organ necrosis in mouse models of



mucormycosis<sup>69</sup>. Therefore, vascular endothelial injury, further driven by COVID-19-associated inflammation, may also represent an important susceptibility feature of CAM.

The activation of a nutritional immunity programme in macrophages to restrict intracellular iron availability and inhibit fungal growth is an essential mechanism required to counter infection with Mucorales<sup>114</sup>. IL-6 production during COVID-19-associated hyperinflammation and in poorly controlled diabetes stimulates ferritin production, which results in increased levels of free iron in patients with COVID-19<sup>17</sup>. As Mucorales species require free iron for their biological processes, iron availability might therefore represent a critical mechanism involved in the pathogenesis of CAM<sup>115</sup>. This is illustrated in patients with COVID-19 and ketoacidosis or renal failure undergoing deferoxamine chelation<sup>116</sup>, where the circulating levels of free iron are further augmented. In addition, the impairment of neutrophil migration, ingestion and phagolysosome fusion caused by corticosteroids<sup>117</sup>, and the dysbiosis exerted by the intensive use of antibiotic treatment may also amplify the risk for CAM. SARS-CoV-2 can also infect human pancreatic  $\beta$  cells<sup>118</sup> and promote morphological, transcriptional and functional alterations that result in reduced numbers of insulin-secreting granules and impaired glucose-stimulated insulin secretion<sup>119</sup>. Although it is currently not known whether the ability to infect  $\beta$  cells is a feature specific of the D614G variant of SARS-CoV-2 used in these studies, it is tempting to speculate that the escalating incidence of CAM cases during the second wave of the pandemic could be attributed, at least in part, to this viral pathogenic mechanism of induction of hyperglycaemia and ketoacidosis<sup>120</sup>.

Circulating monocytes from patients with COVID-19 with severe respiratory failure show a decreased expression of human leucocyte antigen DR<sup>121</sup>, which is considered a marker of immune paralysis, a feature often associated with *Candida* sepsis. This is in line with the observation that monocytes from patients with severe COVID-19 exhibit a decreased expression of the co-stimulatory CD80 molecule and a blunted cytokine response after whole-blood stimulation with *C. albicans*, but not *Aspergillus fumigatus*<sup>122</sup>. Moreover, it is worth noting that recognition of *Candida* RNA by TLR7 and the downstream production of type I IFN—both often compromised in patients with severe COVID-19—has been reported to play an essential role in host defence against experimental candidiasis<sup>123,124</sup>. Although these results suggest a possibly disturbed immune response towards *C. albicans*, the relevance of these mechanisms to susceptibility to CAC is unclear. Moreover, the lymphopenia typical of COVID-19 is probably not the cause for enhanced susceptibility to CAC, as patients with HIV experiencing low lymphocyte counts are also not more prone to develop invasive candidiasis. Therefore, while the generally altered numbers and activation profiles of immune cells may contribute to tissue damage and the severity of COVID-19 favouring the progression of fungal disease, available evidence suggests that classical clinical risk factors, rather than overt immune dysfunction, are the major drivers of susceptibility to CAC.

### Immunomodulation

Due to the need to counter the hyperinflammation that characterizes severe COVID-19, most of the available options to treat severe COVID-19 are immunomodulatory drugs, including corticosteroids and cytokine blockers such as tocilizumab. Despite their relevance to COVID-19 management, these drugs hamper the activation of innate and adaptive antimicrobial responses and therefore represent important predisposing factors to secondary fungal infections. Corticosteroids promote functional impairments of several immune cells, including neutrophils and monocytes/macrophages, and also T cells<sup>117</sup>. For this reason, the use of high-dose systemic corticosteroids is a relevant risk factor for developing aspergillosis, also in the context of COVID-19<sup>125</sup>, even though a contribution

of additional underlying risk factors such as chronic respiratory diseases might confound these associations<sup>8</sup>. Moreover, treating patients with diabetes and COVID-19 with high doses of corticosteroids exacerbates hyperglycaemia, which results in augmented fungal invasion and impaired immune responses, thus generating the 'perfect storm' for increased CAM pathogenesis<sup>126</sup>.

In a large randomized controlled trial in critically ill patients with COVID-19, treatment with IL-6 receptor antagonists resulted in improved outcomes, including survival<sup>127</sup>. However, several reports have identified a link between the blockade of signals mediated by this critical cytokine in antifungal immunity and the risk of secondary fungal infections in critically ill patients with COVID-19<sup>4,128,129</sup>. The reasons for this may be many in view of the pleiotropic effects of IL-6; however, in fungal sepsis, loss of IL-6 signals was recently found to impair the activation of LC3-associated phagocytosis, a molecular process that is essential for fungal killing by monocytes and macrophages<sup>130</sup>. For this reason, clinical trials are required to address the benefit of the combined use of IL-6 receptor antagonists and antifungal prophylaxis in patients with severe COVID-19.

Besides IL-6, another major inflammatory pathway in COVID-19 involves inflammasome activation and the consequent release of IL-1 $\beta$ <sup>131</sup>. Although inflammasome activation is generally required for protective responses to fungal pathogens<sup>132,133</sup>, inflammasome-dependent inflammation may become pathogenic if uncontrolled<sup>134,135</sup>. Type I IFNs can act as negative regulators of inflammasome activation and IL-1 $\beta$  production in response to fungal pathogens<sup>136</sup>, which suggests that the impaired type I responses in COVID-19 may facilitate aberrant inflammasome activation and the development of fungal co-infections. A recent phase III trial demonstrated that the early treatment of COVID-19 with the IL-1 receptor antagonist anakinra decreased mortality and shortened hospital stay<sup>137</sup>. Whether this therapeutic strategy could prevent the development of co-infections or instead potentiate susceptibility to them requires further investigation but IL-1 receptor blockade has been shown to ameliorate inflammation and restrain susceptibility to experimental aspergillosis in both chronic granulomatous disease<sup>135</sup> and cystic fibrosis<sup>134</sup>.

Although the clinical benefit of immunomodulatory therapies in the treatment of COVID-19 is well established nowadays, recent evidence suggests collateral effects on susceptibility to fungal infections. Although in-depth clinical studies are required, these observations suggest that immunomodulation in critically ill patients with COVID-19 should be carefully tailored to the disease stage, for example, early immunosuppression in the ARDS stage and immune-enhancing strategies to rescue late-stage immunodepression, to minimize the risk of secondary infections.

### Immunomodulatory treatment

Besides systemic antifungal treatment<sup>21,48,138</sup>, the management of COVID-19-associated IFIs should ideally also consider adjunctive host-directed therapies aimed at resolving immunopathology, while maintaining a balanced immune response required to adequately eliminate the invading fungus. Therefore, although several immune-dampening therapies have been explored in COVID-19 to reduce systemic inflammation, administration of immune boosting agents should also be considered. The most important clinical trials of immunotherapy in COVID-19 are discussed in detail in van de Veerdonk et al.<sup>139</sup>.

In the later disease stages where immune paralysis is often present, administration of recombinant IFN- $\gamma$  or type I IFNs could prove beneficial<sup>140</sup>. IFN- $\gamma$  has been shown to restore immune function, including antigen presentation and the capacity of immune cells to produce proinflammatory cytokines, in a case series of patients with fungal sepsis<sup>141</sup>. More recently, two case series reported a potentially beneficial effect of IFN- $\gamma$  in patients with severe COVID-19, using positive-to-negative viral culture conversion and monocyte

**Box 1 | Unique challenges and characteristics of COVID-19-associated fungal infections in low- and middle-income countries**

The environmental exposure to Mucorales<sup>45</sup>, but also *Aspergillus* spp., combined with susceptible hosts owing to uncontrolled underlying diseases such as diabetes (major risk factor for CAM<sup>16</sup>) further worsened by overuse of antibiotics in the absence of stewardship programmes (major risk factor for CAC) and particularly overuse of dexamethasone predisposes for opportunistic fungal infections in low- and middle-income countries (LMICs; Fig. 3 and Supplementary Table 2). AIDS and chronic obstructive pulmonary disease (COPD) are also more frequently observed in LMICs<sup>161</sup>, where they may predispose patients to COVID-19-associated IFIs. Prolonged wearing of masks has also been described as a risk factor for CAM in LMICs (Fig. 3 and Supplementary Table 2). Overall, implementation of infection control measures during the SARS-CoV-2 pandemic is further complicated due to limited resources. This is particularly problematic for *C. auris* as a nosocomial pathogen with intrahospital transmissions. While CAM and CAC have a high predominance in LMICs, CAPA is rarely reported, probably due to a diagnostic bias resulting from unobtainable indirect/molecular testing reluctance and inadequate resources to perform bronchoscopies and limited ICU capacities. In the rare cases where CAPA manifests as cerebral infections, it is more likely to be diagnosed in LMICs. For CAM, ROM and ROCM are reported in >95% of cases in LMICs<sup>15</sup>. By contrast, cases of pulmonary, disseminated and gastrointestinal mucormycosis, which are much harder to diagnose, represent about half of CAM cases in high-income countries<sup>14</sup>. CAM cases are probably underreported in LMICs due to lack of diagnostics. Diagnosis of CAPA mostly relies on culture and microscopy of biopsy specimens, but biopsies are rarely performed. Similarly, bronchoscopies are rarely performed, and while serum GM testing is often available with the *Aspergillus* GM lateral flow assay<sup>162</sup>, serum GM testing has only very limited sensitivity for CAPA (<20%, ref. <sup>23</sup>). Diagnosis of CAM in LMICs is usually achieved with nasal endoscopy and sinus debridement followed by culture and microscopy, as well as cranial computed tomography; therefore, pulmonary or disseminated disease is mostly undiagnosed. For CAC, blood culture and cultures from swabs from normally sterile sites are usually performed; cases of intra-abdominal invasive candidiasis may sometimes be missed.

The resource-limited setting also influences treatment options. For example, the costs and lack of availability of lipid formulations of amphotericin B and isavuconazole may require disfiguring surgeries as first option for ROM/ROCM before considering antifungals; conventional amphotericin B deoxycholate is used much more frequently despite its renal toxicity<sup>16</sup>. Even itraconazole, which does not have a place in the treatment of CAM in high-resource countries, is sometimes used for treatment due to lack of availability of alternative options. If posaconazole is available, it is mostly as an oral solution, which has inferior efficacy and pharmacokinetics as compared to tablet or parenteral formulations used predominantly in high-income countries. For CAPA, voriconazole is often available as an oral formulation, but the alternatives are often second-line treatments, including itraconazole, amphotericin B or posaconazole oral solution. Echinocandins as the treatment of choice for *Candida* infections are also rarely available, and fluconazole is used for most CAC cases. Mortality is high at more than 40–50% for all invasive fungal disease entities. In addition, in many survivors, CAM is a life-changing event due to extensive surgery.

In summary, major challenges in LMICs include the lack of diagnostics for CAPA and CAM disease manifestations other than ROM or ROCM. In particular, the fact that bronchoscopies and BAL are rarely performed impacts the diagnosis of other disease manifestations. Dexamethasone overuse together with uncontrolled underlying diseases puts large numbers at risk for IFIs; environmental exposures, which often are ubiquitous, add fuel to the fire, resulting in large outbreaks affecting many thousands, as observed for CAM in India. Finally, higher rates of intrahospital transmission of *C. auris*, as well as misleading species identification and lack of susceptibility testing, are challenges that drive the incidence and mortality of CAC. Limited availability of antifungals, in particular liposomal amphotericin B, and echinocandins (the latter is particularly challenging in LMICs, where higher rates of multidrug-resistant *Candida* spp. are observed) further challenge successful management of COVID-19-associated IFIs in LMICs.

human leukocyte antigen-DR isotype (HLA-DR) expression and total lymphocyte counts as primary end points<sup>142,143</sup>. Given the well-established positive effects of IFN- $\gamma$  on antifungal immunity, these observations support the possibility that, besides a direct effect on COVID-19, IFN- $\gamma$  therapy may also have clinical value in preventing or treating fungal co-infections. Of note, large prospective trials in the context of influenza-associated aspergillosis are ongoing not only to assess the therapeutic potential of IFN- $\gamma$  but also to identify biomarkers that could allow the identification of patients who would benefit the most from this immunotherapy. Such efforts are thus expected to pave the way towards a new generation of adjunct host-directed medicine approaches to manage fungal infections more efficiently.

Other preclinical investigational therapies include fungus-directed immunotherapies aiming to boost the host immune response to infections. These include antibodies targeting components of the cell wall or toxins. For example,  $\beta$ -1,3-glucans are major components of many pathogenic fungi including *A. fumigatus* and *Candida*. A murine monoclonal antibody specific for  $\beta$ -1,3-glucans, 2G8 (an IgG2b), was shown to be protective in rodent models of *C. albicans* infections<sup>144</sup>. Recently, a humanized version of 2G8 monoclonal antibody (H5K1) was shown to inhibit the growth of *C. auris* and acted synergistically with either

casposfungin or amphotericin B in time-kill curves and enhanced opsonophagocytosis by macrophages in vitro<sup>145</sup>. Although it is currently unknown whether H5K1 protects against experimental fungal infections, this humanized monoclonal antibody has the potential to protect against several infections since it binds to *C. albicans*, *C. auris*, *Candida glabrata*, *A. fumigatus* and *Fusarium solani*<sup>145</sup>. Also, a fully human antibody-targeting *C. albicans* cell surface Hyr1p was shown to bind to *C. auris* and enhance its phagocytosis by J774.1 macrophage cells. This antibody protects mice from *C. albicans* disseminated infection<sup>146</sup>.

Another passive immunization approach was shown to enhance treatment outcome against mucormycosis. A murine monoclonal antibody (C2, an IgG1) targeting the cell-surface invasin CotH3 was shown to be protective in mouse models of severe mucormycosis especially when combined with antifungal drugs<sup>147</sup>. A humanized version of C2, VX01, had a tenfold increase in binding affinity to recombinant CotH3p and was equally protective against murine mucormycosis when compared with the mouse C2 monoclonal antibody and had safe profiles in human tissue cross-reactivity studies<sup>148</sup>. VX01 is currently in manufacturing. Similarly, polyclonal antibodies targeting mucorin toxin enhanced median survival time and prolonged overall survival of mice with mucormycosis through reduction of tissue damage<sup>69</sup>.

**Table 2 | Current and future antifungal treatment of CAPA, CAM and CAC**

Invasive fungal disease/antifungal therapy	First line	Second line	Future treatment first line	Future treatment 1 advantages/disadvantages	Future treatment second line	Future treatment 2 advantages/disadvantages
<b>CAPA</b>	Voriconazole or isavuconazole <sup>25</sup>	Liposomal amphotericin B <sup>25</sup> or posaconazole <sup>25</sup>	Opelconazole <sup>158</sup>	Inhaled antifungal, limited systemic toxicity or drug–drug interactions, used for early treatment or prophylaxis	Fosmanogepix <sup>158</sup> or olorofim <sup>158</sup>	New mechanism of action, fewer drug–drug interactions, activity against azole-resistant CAPA, oral formulation only for olorofim
<b>CAM</b>	Liposomal amphotericin B <sup>48</sup>	Isavuconazole <sup>48</sup> or posaconazole <sup>48</sup>	Fosmanogepix <sup>158</sup>	New mechanism of action, oral and intravenous formulation, variable activity against Mucorales, potential use in combination with liposomal amphotericin B (synergism in animal model)	Ibrexafungerp <sup>158</sup>	New mechanism of action, oral formulation, variable activity against Mucorales, potential use in combination with liposomal amphotericin B (synergism in animal model)
<b>CAC</b>	Caspofungin or anidulafungin or micafungin	Fluconazole or liposomal amphotericin B or voriconazole	Ibrexafungerp <sup>158</sup> or rezafungin <sup>158</sup>	Oral formulation (ibrexafungerp), echinocandin with very long half-life allowing for once weekly intravenous therapy (rezafungin), activity against resistant <i>Candida</i> spp.	Fosmanogepix <sup>158</sup>	Good activity against resistant species, no activity against <i>Candida krusei</i>

Finally, monoclonal antibodies against Als3p from *C. albicans* blocked the interaction of the fungus with host cells<sup>149</sup>; vaccination with rAls3-N was shown to protect from lethal disseminated candidiasis<sup>150</sup>. Likewise, bioinformatic and immune-profiling studies identified three orthologues on the *C. auris* cell wall with three-dimensional structural and functional similarity with *C. albicans* Als3p. Anti-Als3p antibodies bound to *C. auris* prevented biofilm formation and enhanced the opsonophagocytic activity of macrophages. Importantly, the experimental vaccine NDV-3A (recombinant Als3p-N formulated with alum) significantly improved overall survival of mice infected with haematogenously disseminated *C. auris* and acted synergistically with micafungin<sup>151</sup>.

### Conclusion and future perspectives

Despite the broad importance and socio-economic impact of medical mycology, research on fungal infections has lagged behind compared to other pathogens. The recent SARS-CoV-2 pandemic has highlighted the importance of fungal infections for morbidity and mortality, even in previously immunocompetent populations who suffer from viral disease. IPA in patients in the ICU had been frequently overlooked before, as shown in a pre-COVID-19 autopsy study, where 2.8% of autopsies in patients in the ICU revealed IPA; only 40% of those autopsy cases had been diagnosed pre-mortem<sup>152</sup>.

To estimate incidence and set a standard for epidemiological studies and future clinical trials, it will be important to define consensus criteria that are used homogeneously for the classification of IFIs. As a breakthrough, global efforts by mycologists have resulted in the development of broadly accepted consensus criteria for CAPA in late 2020<sup>21</sup>. To reduce morbidity and mortality from opportunistic IFIs, a general awareness of the relevance of fungal co-infection is critical to avoid delays in diagnosis and treatment. In the absence of antifungal prophylaxis, screening of COVID-19

patients for fungal diseases is essential, which optimally—at least for CAPA and CAM—involves repeated testing of samples from the lower respiratory tract in case of clinical suspicion<sup>22</sup>, while blood cultures remain the criterion standard for CAC. The difficulties to diagnose pulmonary or gastrointestinal CAM may contribute to the overwhelming proportion of ROM/ROCM in CAM cases reported from India and other low- and middle-income countries (Box 1), while in high-income countries, pulmonary CAM is reported in about 50% of cases<sup>14</sup>. Culture and histology remain central for diagnosing CAM and CAC<sup>48,53</sup>, but new diagnostics including Mucorales PCR from blood<sup>153,154</sup> and T2 *Candida* MR for diagnosing CAC<sup>155</sup> may become more broadly used in the near future. In the absence of biopsies with histological evidence, bronchoscopies are central for diagnosing CAPA and pulmonary CAM; BAL should be tested for culture, GM and *Aspergillus* and Mucorales PCR. Given that these diagnostics are not always available in house with fast turnaround times<sup>156,157</sup>, rapid diagnostics such as the *Aspergillus* GM lateral flow assay, have proven to be reliable alternatives for testing respiratory specimens<sup>22</sup> that could also be used for diagnosing CAPA in resource-limited settings (Box 1). These tools may allow earlier diagnosis and quicker initiation of appropriate treatment, directly improving survival rates.

The costs, route of administration and toxicity of currently available antifungal drugs make their use difficult, particularly in low- and middle-income countries, where limited supplies and choice are available for treating the high burden of CAM and CAC caused by multidrug-resistant *Candida* species. Safer and more effective drugs are needed. New antifungal agents are in the advanced stages of development (Table 2)<sup>158</sup> but their role in daily clinical practice, particularly in low- and middle-income countries, is undetermined.

Our expanding knowledge of the host–fungus interaction may foster the development of new fungus- and host-directed therapies.

Such approaches aimed at modulating the immune system may become invaluable in treating fungal disease in the context of exuberant inflammation associated with COVID-19. Also, randomized controlled trials are needed to validate the potential benefit shown in smaller observational studies of mould-directed antifungal prophylaxis in settings with high CAPA rates<sup>159</sup>. Given that CAPA develops on median in 8 days after ICU submission<sup>4,11</sup>, which is later than influenza-associated aspergillosis for which a recent trial failed to show a significant benefit of antifungal prophylaxis<sup>160</sup>, prophylaxis for CAPA may indeed be promising<sup>159</sup>.

In conclusion, several steps are necessary to reduce the negative impact of fungal infections in COVID-19. Increased awareness and more routine diagnostic strategies are needed for early diagnosis of these infections, which is vital for improving survival. Given that these infections disproportionately affect low- and middle-income countries, it is also key to provide low- and middle-income countries with the necessary resources to diagnose and treat these infections effectively. Lastly, we need increased focus on prevention, which could start with restricting access to dexamethasone over the counter to prevent overuse, and improved, broadly accessible care for diabetes.

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## Competing interests

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