Candida in COVID-19: Gut-Lung Axis, Dysbiosis, and Infections

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Abstract

Purpose of Review This review discusses the connections between the gut-lung axis, gut and respiratory tract dysbiosis, and *Candida* bloodstream, oral, and respiratory infections in COVID-19 patients.

Recent Findings COVID-19–related dysfunction in the intestinal barrier together with gut and lung dysbiosis played an important role in disease pathophysiology, which affected host immune homeostasis giving rise to prominent systemic and respiratory bacterial and fungal infections. Higher incidence of *Candida* bloodstream infections driven by accumulation of "classic" risk factors in severely ill COVID-19 patients was noted. Moreover, numerous *C. auris* outbreaks, characterized by high clonality of the strains, were reported from all around the world. Unlike other *Candida* species, *C. auris* colonization and infection cases most likely resulted from nosocomial transmission.

Summary Infections due to *Candida* species in severely ill COVID-19 patients reflected the overall immune dysregulation and were largely driven by gut and respiratory tract dysbiosis.

Keywords *Candida* · *Candida auris* · COVID-19 · COVID-19–associated candidiasis (CAC) · Dysbiosis · Gut-lung axis

Introduction

The COVID-19 pandemic has wreaked a devastating impact on global health with mortality approaching 7 million people [1]. People at the highest risk of severe COVID-19 were those of advanced age and those with comorbidities including hypertension, diabetes, chronic heart, and renal diseases [2]. Approximately 5–6% of symptomatic infected patients developed atypical pneumonia requiring hospitalization with many of them progressing to the intensive care unit (ICU) with respiratory failure and a further subset developing a more lethal cytokine storm resulting in an acute respiratory distress syndrome (ARDS) requiring mechanical ventilation [3]. A hallmark of severely ill COVID-19 patients was the development of a profound immune dysfunction [4] promoting the emergence of opportunistic bacterial, fungal, and viral infections [5–8]. Bacterial infections were often manifested as secondary pneumonias, urinary tract infections, and

sepsis and were closely associated with prolonged hospitalization, mechanical ventilation, and the presence of invasive medical devices [9–11]. Individuals with latent tuberculosis infection were at increased risk of developing active tuberculosis due to the immune system's compromised state caused by COVID-19 [5•]. The extensive use of antibiotics for treatment and prophylaxis, well known to disrupt the normal gut microbiota, increased the risk for developing *Clostridium difficile* infections within the gastrointestinal (GI) tract [12]. COVID-19 patients were also at heightened risk for developing viral infections due to herpes simplex virus (HSV), cytomegalovirus (CMV), and other respiratory co-infections [10, 13].

In recent years, it has been recognized that patients with certain severe viral and bacterial respiratory tract infections, including influenza, tuberculosis, and those with chronic diseases like chronic obstructive pulmonary disease (COPD), are prone to invasive fungal infections [6]. Seriously ill hospitalized patients with COVID-19 displayed an array of known risk factors for invasive fungal infections including lung damage resulting in a need for oxygen therapy, profound immunosuppression, and monoclonal antibody and corticosteroid therapy [14, 15•]. Such patients have impaired immune function of proinflammatory cytokines like interleukins IL-6, IL-1, IL-12, tumor necrosis factor (TNF), and

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interferon gamma (IFNγ), which promote opportunistic fungal infections [16]. Hence, patients with severe COVID-19 were also prone to develop invasive fungal infections [15•], particularly those caused by *Candida* [17••], *Mucorales*, and *Aspergillus* species [18] resulting in COVID-19–associated pulmonary aspergillosis (CAPA) [19, 20], COVID-19–associated mucormycosis (CAM) [21], and COVID-19–associated candidiasis (CAC) [22]. The high prevalence of CAC was not surprising given immune and barrier dysregulation in the gut and lung [22]. CAC carried a higher mortality than candidemia in non-COVID-19 patients during the same period [6, 23•]. It is the importance of gut-lung axis, gut, and respiratory tract dysbiosis and resulting bloodstream, oral and respiratory infections during COVID-19 that is discussed in this review.

Gut-Lung Axis in COVID-19

The lower gastrointestinal tract contains a complex microbiome of bacteria, fungi, and viruses, which are largely kept in-check in healthy individuals through host and microbial interactions [24]. The intestinal mucosa is a critical component that serves as a functional barrier. However, a breach in host containment can turn harmless commensal organisms into disease-causing pathogens that have life-threatening consequences for a patient resulting in sepsis, bloodstream infection, hyper inflammatory state, and multisystem failures [25]. The intestinal immune system harbors over 80% of the total body's lymphocyte population residing in intraepithelial, lamina propria, Peyer's patches, and mesenteric lymph nodes. Peyer's patches and mesenteric lymph form aggregates with the latter connected to lymphatic system via drainage channels. The Peyer's patches in concert with epithelial cells help induce local immune responses by mediating antigen presenting cell/T-cell interactions and release of cytokines [26]. Gut microbiota and their metabolites shape a healthy balance of Th17 and Treg cells [27]. Growing evidence supports strong crosstalk between the gut microbiota and lung, likely through the same interactions that maintain host health/disease balance [28], and the term "gut-lung axis" was created to describe this phenomenon.

During COVID-19, severely ill patients developed profound immune dysregulation and were often treated with broad-spectrum antibiotics and anti-inflammatory drugs, e.g., corticosteroids and cytokine antagonists. The resulting gut microbiome dysbiosis was associated with translocation of bacteria into the blood [29, 30]. The gut has been described as a main driver of critical illness [31], which induces dysfunction in the intestinal barrier and its hyperpermeability enabling luminal microbiota and metabolites to escape. Colonizing organisms can traverse the barrier either via a transcellular pathway involving epithelial cells or through a paracellular path involving tight junctions between adjacent epithelial cells. Impaired epithelial barrier function is often observed in inflammatory diseases, cancer, and transplantation and is impacted by factors such immune dysfunction and treatment with corticosteroid, cytokine antagonists, and antibiotics, as well as high fat diets [32, 33].

Fungi residing in the gastrointestinal tract (gut mycobiome) play important roles in host immune homeostasis, metabolism, and infection prevention [34, 35]. Fungal dysbiosis in the gut is associated with numerous diseases, including inflammatory bowel disease [36], colorectal cancer [37], and asthma [38, 39]. It is now apparent that there is a strong association between the gut and respiratory health, which surfaced prominently with COVID-19 [28, 38]. The gut-lung connection has been demonstrated in human and murine studies with some lung diseases influenced by gut microbiome changes and vice versa [39]. Thus, it is not surprising, given the ability of SARS-CoV-2 to replicate in both the respiratory and digestive tracts [40], that gut mycobiome in COVID-19 patients was a focus of several studies. Lv et al. compared the gut mycobiome of COVID-19- and H1N1-infected patients and healthy individuals. They discovered that in infected patients (in the comparison to healthy controls), the fungal burden in the gut was higher and that the relative abundances of some fungi with important functions were lower, but those of several opportunistic pathogenic fungi were higher [41]. Zuo et al. specifically identified *Candida albicans*, *Candida auris*, and *Aspergillus flavus* proportions to be increased in COVID-19 patients' gut [42••].

Similarly, lower respiratory tract dysbiosis with a shift to *Candida* species colonization and a decreased fungal diversity was noted in COVID-19 patients [43, 44••]. These data corroborate the notion of SARS-CoV-2–triggered disruption of lung immune homeostasis, leading to overgrowth of pathogenic bacteria and fungi, and inflammation.

Altogether, as summarized in Fig. 1, COVID-19-related dysfunction in the intestinal barrier together with gut and lung dysbiosis played an important role in disease pathophysiology, which affected host immune homeostasis giving rise to prominent systemic and respiratory bacterial and fungal infections [30, 45, 46].

Candida Respiratory Tract Colonization and *Candida* Pneumonia in COVID-19 Patients

Candida spp. are frequently isolated from respiratory specimens, especially from ICU patients receiving mechanical ventilation [47–49]. It was estimated that up to 20% of patients acquired tracheobronchial colonization with *Candida* spp. after 48 h of intubation and ventilation and that
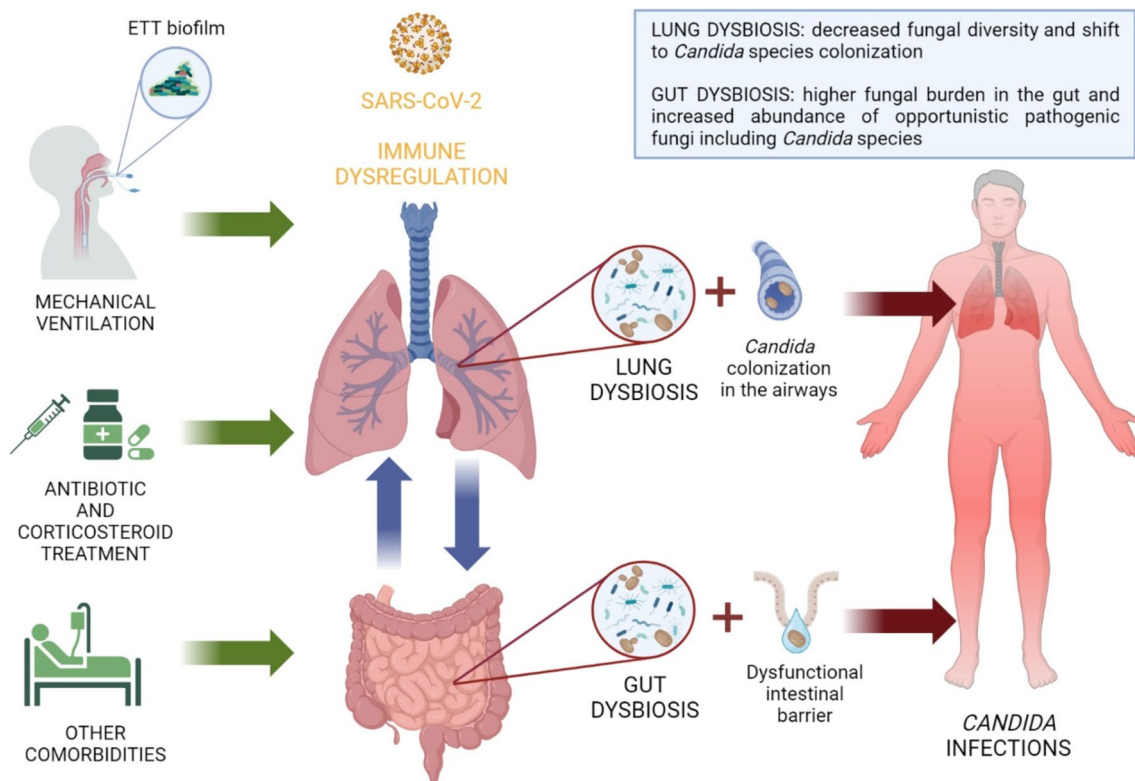
Fig. 1 Overview of factors involved in the development of *Candida* infections in COVID-19 patients. Created with BioRender.com

their percent increases with extended ventilation [48]. However, an understanding of the significance of *Candida* spp. detection from respiratory samples is complicated, as it can represent one of the four scenarios: (1) contamination, an artifact introduced during sampling; (2) commensalism, member of the normal microbiome; (3) colonization, non-infectious resident that is not a member of a normal microbiome; and (4) infection, etiologic agent of infection. The diagnosis of *Candida* pneumonia should be confirmed by histopathology [47, 50]. Moreover, the presence of *Candida* spp. in any respiratory specimen always needs to be interpreted within its clinical and microbiological context, especially since there is a growing body of evidence of *Candida* spp. impact on human health even in noninfectious settings [51].

Candida pneumonia is rare, but colonization of the lower respiratory tract with *Candida* spp. has been associated with longer duration of mechanical ventilation, increased risk of ventilator-associated pneumonia (VAP), increased length of intensive care unit (ICU) and hospital stay, and higher mortality in mechanically ventilated patients [48, 52–56]. Major risk factors for *Candida* spp. acquisition in the respiratory tract include (1) host factors (STAT1 and dectin-1 defective mutations); (2) iatrogenic conditions (broad-spectrum antibiotics, mechanical ventilation, radiation therapy); (3) immunosuppression (neutropenia, systemic immunosuppression,

steroid use, HIV, diabetes mellitus, bone marrow or solid organ transplant); and (4) extraneous (prolonged hospital stay, ICU stay, burns) [51].

Patients with severe viral respiratory tract infections are well recognized to be at high risk for developing invasive fungal infections including pulmonary aspergillosis and mucormycosis [13, 21]. Influenza pneumonias often present with increased disease morbidity and mortality, and similar disease co-dependence was observed during COVID-19 [14]. In a population of 100 immunosuppressed COVID-19 patients, *Candida* species were recovered from 69% of bronchoalveolar lavage specimens. Indeed, *Candida* colonization with restricted species reflected dysbiosis of lung and gut microbiota, which correlated with acute respiratory distress syndrome among patients [57]. *Candida* colonization in such severely ill patients is typically not deemed to directly impact clinical outcomes and is more a reflection of generalized immune, barrier and microbiota dysfunction [14]. Yet, its contribution to the overall state of COVID-19, including ARDS and other clinically significant risk factors, needs to be better assessed [58].

In a 2018–2022 study from France, both the incidence and prevalence of detection of *Candida* spp. in respiratory specimens increased in COVID-19 pandemic. Moreover, the length of stay in the hospital, mechanical ventilation, diabetes, and the use of antibacterials were identified as

independent risk factors of *Candida* airway colonization [59••]. In Iran, *C. albicans* was found in the respiratory specimens of COVID-19 patients, especially those with diabetes, malignancies, and kidney disorders [57]. Similarly, we found virus- and drug-induced immunosuppression, together with prolonged hospital stay and mechanical ventilation, to increase the susceptibility to *Candida* colonization in the COVID-19 patients in New Jersey, USA [60]. Additionally, results of a Belgian study pointed to biofilms formed on endotracheal tubes (ETT), as a reservoir of microorganisms that can cause secondary infections in mechanically ventilated patients [43].

COVID-19–related epithelial damage of the airways gives way to fungal invasion in the respiratory tract. Although the most common agents of infection are molds of *Aspergillus* and *Mucor* genera, *Candida* lung infections, including *C. albicans* pneumonia with lung abscess [61], post-COVID-19 fungal empyema thoracis due to *C. glabrata* [62], and post-COVID-19 *C. glabrata* pneumonia [63], were presumptively reported, but histopathological evidence was provided only in one case [61].

Oral Candidiasis

The human commensal *Candida albicans* is a normal component of the oral cavity microbiota, and the development of oral and esophageal thrush is often a hallmark indication associated with immune dysfunction among patients with cancer and HIV/AIDS [64]. During COVID-19, the oral cavity was also impacted in patients resulting in typical oral clinical manifestations associated with systemic immune dysfunction including white and erythematous plaques, blisters, necrotizing gingivitis, ulcerations, salivary gland alterations, gustatory dysfunction, and coinfections [65]. Furthermore, overgrowth of *Candida* species was exacerbated by virus-infected salivary glands which compromised the production of histatin-5, a family of histidine-rich cationic antimicrobial proteins that help maintain a healthy balance of *Candida* in the oral biome [65]. *Candida* was frequently encountered in sputum samples, exceeding 53% in some studies, and due to the prolonged and chronic use of antifungal, high levels of mono- and multidrug resistance among *Candida* species isolates were reported [66].

Invasive *Candida* Infections in COVID-19 Patients

COVID-19–associated *Candida* spp. superinfections quickly became recognized as complications of the severe disease with the first four cases (*C. albicans*, $n = 3$; *C. glabrata*, $n = 1$) reported in 99 patients hospitalized in Wuhan

Jinyintan Hospital (China) from Jan 1 to Jan 20, 2020 [67]. Further studies reported an increased incidence of *Candida* bloodstream infections (candidemia) in COVID-19 patients (in comparison to patients without COVID-19), especially in the ICU settings (Table 1). However, results of *Candida* spp. clinical isolates genotyping revealed that such an increase was not characterized by an uncontrolled nosocomial transmission [60, 68, 69•], except for the spread of *Candida auris* (see the next section).

Reasons for the higher frequency of candidemia in COVID-19 patients are still not fully understood. Unlike COVID-19–associated pulmonary aspergillosis (CAPA), where hyperinflammation is thought to be the main predisposing mechanism [15•], COVID-19–associated candidemia (CAC) most likely results from a combination of concomitant "classic" risk factors, such as prolonged hospital stay, ICU stay, (poorly controlled) diabetes mellitus, use of broad-spectrum antibiotics, use of corticosteroids, presence and duration of CVC, mechanical ventilation, and parenteral nutrition (Table 1). Also, as already discussed, a path to infection most likely resulted from dysbiosis of the fungal gut microbiome, decreased fungal diversity, and a shift toward *Candida* colonization in SARS-CoV-2–infected patients. Additionally, pandemic-related issues in overwhelmed healthcare facilities (crowded hospital rooms, decreased staff-to-patient ratios, limited availability of personal protective equipment (PPE)), leading to breaches in infection control practices (deviations from catheter management policies, inappropriate use of PPE), were possible contributors to the increased number of *Candida* infections in COVID-19 patients [50, 68, 77].

In most reports, the predominant identified species was *C. albicans* (Table 1), but some healthcare institutions noticed a trend of increasing non-*albicans* clinical isolates over the years. For example, in Gregorio Marañón Hospital in Madrid, Spain, the proportion of isolates between 2020 and 2022 decreased in *C. albicans* (60.3% vs. 36.7%) and increased in *C. parapsilosis* (10.3% vs. 28.6%) and *C. tropicalis* (8.8% vs. 16.3%) [69•]. Uniquely in India, *C. auris* was found to be the most predominant agent of CAC [96, 97].

Since the beginning of the COVID-19 pandemic, experts debated whether it would result in increased prevalence of antimicrobial resistance, with Clancy, Buehrle, and Nguyen saying "yes" and Collignon and Beggs saying "no." However, they did not make any specific predictions regarding antifungal resistance [98–100]. Regrettably, antifungal drug susceptibility of the CAC isolates was determined rarely (Table 1), complicating comprehensive assessment of the situation and trend analysis. Posteraro et al. reported development of echinocandin resistance upon caspofungin treatment in a fatal case of COVID-19–associated *C. glabrata* infection [101].

Mortality in CAC patients was in the 28 to 100% range, with some healthcare institutions reporting significantly

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Table 1 Reported *Candida* bloodstream infections (except *C. auris*) in COVID-19 patients (in alphabetical order by country)

Location	Time period	Type of study	Number of cases and *Candida* species	Incidence	Risk factors	Mortality	Antifungal drug susceptibility	Reference
Vienna, Austria	January to June 2021	Retrospective analysis	6 CA 1 CP	5.9% rate (cohort of COVID-19 ICU patients with at least one superinfection)	Higher age, preexisting DM	57.1%	N/A	[70]
Rio De Janeiro, Brazil	Comparison: (1) January 2019 to February 2020; (2) March to September 2020	Retrospective analysis	41 episodes of candidemia, 16 in period 1, and 25 in period 2 (9 COVID-19 patients)	Increased incidence Period 2: 4.76 per 1000 admissions (candidemia in non-COVID-19 patients) 2.68 per 1000 admissions (candidemia in COVID-19 patients) 14.80 per 1000 admissions (admissions of patients with COVID-19)	MV	30-day: −66.7% (6/9) COVID-19 −56.3% (9/16) non-COVID-19, period 1 −62.5% (10/16) non-COVID-19, period 2	N/A	[71]
Brazil	February to December 2020	Retrospective case series analysis	1 CA 1 CK 1 CL 1 CO (with endocarditis)	N/A	N/A	100%	N/A	[72]
Porto Alegre, Brazil	16 March to 31 August 2020	Retrospective case series analysis	8 CA 2 CG 1 CT	Tenfold increased incidence COVID-19 patients: 11.83 (hospital 1) and 10.23 (hospital 2) per 1000 patients-day; non-COVID-19 patients: 1.43 (hospital 1) and 1.15 (hospital 2)	CORT	72.7% (8/11)	N/A	[73]
Assiut, Egypt	3 May to 30 June 2020	Prospective analysis	3 CA 2 CG	N/A	N/A	N/A	CA-FLC and VRC resistant but echinocandin- and polyene-susceptible	[74]
Zagazig, Egypt	May to August 2021	Prospective analysis	ICU: 24	N/A	Poor DM control, CORT, multiple comorbidities	87.5% (21/24)	N/A	[75]

Table 1 (continued)

Location	Time period	Type of study	Number of cases and Candida species	Incidence	Risk factors	Mortality	Antifungal drug susceptibility	Reference
Paris, France	March 2020 to January 2021	Retrospective analysis	6 CA 5 CP 1 CK 1 CT	4.9% for ICU patients with severe COVID-19	CORT, other immunosuppressive drugs	41.7% (5/12)	N/A	[76]
Patras, Greece	2010 to August 2021 (pandemic period: April 2020 to August 2021)	Retrospective analysis	76	Increased incidence during the pandemic period in patients with and without COVID-19 38.8 candidemia episodes per 100 admissions 19.1 candidemia episodes per 1000 patient-days	CORT; majority of candidemias in both periods were catheter-related	58.2%	N/A	[77]
Budapest, Hungary	March to July 2020	Retrospective observational case-series analysis	2 CA 1 CA+CG 1 CA+CP 2 CG 1 CM	N/A	N/A	85.7% (6/7)	N/A	[78]
Jaipur, Rajasthan, India	June 2021 to November 2021	Single-center matched case control observational study	22 CT 8 CAU 7 CA 4 CP 2 CF 2 CG 1 CL	5.7%	Immunosuppressants	28%	CA: all susceptible but 1 5FC-R isolate; non-CA: 28% FLC-R; 23% VRC-R voriconazole, 23% 5FC-R	[79]
Shiraz, Iran	September to November 2021	Observational single-center study	2 CA	N/A	Heart failure, HTN, COPD, bacterial infections, CVC, MV, and ICU admission	N/A	N/A	[80]
Parma, Italy	27 February to 10 May 2020	Prospective analysis	17 CA 4 CG 3 CT 1 CD	N/A	N/A	N/A	N.A	[81]
Milan, Italy	10 to 18 March 2020	N/A	1 CA (also endophthalmitis and endocarditis) 1 CP 1 CT	6.9% (3 out of 43 patients with severe COVID-19 treated with tocilizumab)	Tocilizumab	N/A	N/A	[82]

Table 1 (continued)

Location	Time period	Type of study	Number of cases and Candida species	Incidence	Risk factors	Mortality	Antifungal drug susceptibility	Reference
Milan, Italy	Comparison: (1) 15 February to 30 June 2020; (2) 2 January to 31 December 2017	(1) Prospective cohort (2) Historical cohort	21 (CA most frequent)	Increased incidence COVID-19 patients vs. non-COVID-19 patients: 10.97 vs. 1.48 cases per 10,000-PDFU COVID-19 ICU patients vs. non-COVID-19 ICU patients: 81.68 vs. 14.46 cases per 10,000 PDFU	ICU stay, immunosuppressive agents	57.1% vs. 58.8%	N/A	[83••]
Rome, Italy	1 March to 15 April 2020	Retrospective analysis	2 CA 2 CP 1 CG+CP	N/A	Immune dysregulation in severe COVID-19, BSABT; less adherence to the infection control and prevention measures	N/A	All echinocandin-susceptible All but 1 CP were FLC-susceptible	[84]
Afula, Israel	15 June to 20 September 2020	Retrospective study	CA CG CP	Increased incidence in comparison to historical non-COVID-19 cohort 0.679 episodes per 1000 hospital days	MV, CVC, lymphopenia and hypoalbuminemia, BSABT, CORT	100%	N/A	[85]
Mexico	27 March 2020 to 21 September 2021	Case–control study	22 candidemias CP (12/27 isolates) CA (11/27) CG (3/27)	N/A	Invasive procedures, BSABT	28% vs. 44% (controls)	N/A	[86]
Oman (single center)	N/A	Retrospective study	ICU: 3 CA 1 CG 1 CA+CT	N/A	Prolonged hospital stay, CVC, surgical procedure, BSABT	3/5 died	Pan-susceptible	[87•]
Madrid, Spain	28 February to 28 June 2020	Retrospective study	ICU: 9 CA 4 CP 2 CG	Increased incidence at the ICU 10.8% vs. 1.07–2.19/1000 patients (non-COVID-19)	MV, vasopressor therapy, CVC, PN, BSABT, CORT	40%	N/A	[88]

Table 1 (continued)

Location	Time period	Type of study	Number of cases and Candida species	Incidence	Risk factors	Mortality	Antifungal drug susceptibility	Reference
Madrid, Spain	1 February to 30 April 2020	Observational prospective study	1 CA 2 CP	N/A	Tocilizumab alone or in combination with systemic corticosteroids, interferon type 1β or lopinavir-ritonavir	N/A	N/A	[89]
Madrid, Spain	January 2019 to December 2020	Retrospective analysis	22 CA 4 CT 3 CG 2 CP 1 CKEF	Increased incidence 4.73 per 1000 admissions in COVID-19 patients vs. 0.85 in non-COVID-19 patients	ICU admission, CVC, PN, CORT	62.5% in COVID-19 patients vs. 46.5% in non-COVID-19 patients	Most resistant isolates ($n=7$) came from patients without COVID-19, including multiresistant CG	[68]
Madrid, Spain	January 2020 to December 2022	Retrospective analysis	27 in 2020 10 in 2021 6 in 2022 The proportion of isolates between 2020 and 2022 decreased in CA (60.3% vs. 36.7%) and increased in CP (10.3% vs. 28.6%) and CT (8.8% vs. 16.3%)	Fungemia incidence (episodes per 1000 admissions) tended to decrease over time (2020=1.60, 2021=1.36, 2022=1.16)	N/A	N/A	Antifungal resistance remained very low, and FLC-resistant CP was not detected	[69●]
Barcelona, Spain	28 February to 22 April 2020	Observational cohort study	ICU: 2 CA	0.2% (2/989 patients)	PN, urinary catheters	N/A	N/A	[90]
Ankara, Turkey	1 March 2019 to 1 March 2021	Retrospective analysis	42 CA 20 CP 19 CG 13 CT 11 other species Species distribution not different than in non-COVID-19	Increased incidence 2.16 (COVID-19) vs. 1.06 (non-COVID-19)	CORT, BSABT	92.5% (significantly higher in COVID-19 patients than non-COVID-19 patients)	Susceptible: FLC 69.5% VRC 71.4% CAS 77.1% MCF 95.2% AmB 91.6% Susceptibility not different than in non-COVID-19	[23●]
UK	N/A	National, multi-center, prospective cohort analysis	11 CA 1 CP 1 CA+CP	9.6% (12/135)	N/A	38.5% (5/13)	N/A	[91]
London, UK	20 February to 30 April 2020	Retrospective case series analysis	3 CA	N/A	Central line-associated infections	N/A	N/A	[11]

Table 1 (continued)

Location	Time period	Type of study	Number of cases and Candida species	Incidence	Risk factors	Mortality	Antifungal drug susceptibility	Reference
Valhalla, NY, USA	1 May 2014 to 31 October 2020	Retrospective analysis	ICU: 4 CA, 2 CG, 3 CP, 2 CT, 1 CD, 1 other non-CA	Increased incidence 51/1000 admissions (COVID-19) vs. 11/1000 (non-COVID-19)	Lower ICU admission SOFA score, longer ICU stay, CVC	75% (9/12)	N/A	[92]
New Jersey, USA	Patients admitted between 10 March and 10 April 2020, with follow-up through June 10, 2020	Retrospective cohort analysis with matched case-controls	2 CA, 2 CG, 2 CP, 2 CT	8.9% ($n=8$) over a median ICU stay of 25 days	MV	38%	N/A	[93]
New York, USA	1 March to 18 April 2020	Retrospective observational analysis	8	N/A	MV, CVC, CORT, biologics, prolonged hospitalization, BSABT	N/A	N/A	[94]
USA	April to August 2020	Case-level analysis of population-based candidemia surveillance data	64	N/A	ICU, MV, CVC, CORT and immunosuppressants	62.5% (COVID-19) vs. 32.1% (non-COVID-19)	N/A	[17••]
USA	1 March 2020 to 5 March 2022	Multicenter retrospective cohort analysis	393 CA, 380 non-CA, 14 CAU, 19 Candida spp. (not speciated)	Increased incidence 3.18/1000 admissions (COVID-19) vs. 0.99/1000 admissions (non-COVID-19)	ICU, length of stay, MV	59.6% (COVID-19) vs. 30.8% (non-COVID-19)	N/A	[95]

BSABT broad-spectrum antibiotics, *BSI* bloodstream infection, *CORT* corticosteroids, *DM* diabetes mellitus, *HTN* hypertension, *MV* mechanical ventilation, *N/A* not available, *PDFU* person-day of follow-up, *PN* parenteral nutrition, *CA* Candida albicans, *CAU* Candida auris, *CD* Candida dubliniensis, *CF* Candida famata, *CG* Candida glabrata, *CKEF* Candida kefyr, *CK* Candida krusei, *CL* Candida lusitaniae, *CM* Candida metapsilosis, *CO* Candida orthopsilosis, *CP* Candida parapsilosis, *CTR* Candida tropicalis, *5FC* 5-flucytosine, *FLC* fluconazole, *VRC* voriconazole

Table 2 Published reports of *Candida auris* colonizations and/or infections in COVID-19 patients

Location	Time period	ID method	Number of *C. auris* cases	Clade	Antifungal drug susceptibility				Major findings	Reference
					Method	FLC	MCF	AmB		
Salvador, Brazil	December 2020	MALDI-TOF and rDNA sequencing	1 CVC tip 1 BSI	I	BM	S	S	S	Pan-susceptible isolates of clade I	[114]
Salvador, Brazil	December 2020 to February 2021	VITEK 2, MALDI-TOF and rDNA sequencing	8 colonized axillae 1 BSI	I	BM (CLSI)	S	S	S	Risk factor for colonization: *C. auris*-contaminated digital thermometer	[115]
Colombia (nationwide study)	March 2016 to December 2020	MALDI-TOF	122 (113 (93%) were clinical cases, and 66% of those were BSIs (n=75))	N/A	BM (CLSI and/or Sensititre)	N/A^a	N/A^a	N/A^a	Overstretched resources resulted in an underestimation of cases in 2020	[116]
Colombia (4 institutions in the North)	June to September 2020	MALDI-TOF	6 BSIs	N/A	N/A	N/A	N/A	N/A	Despite the strict control measures due to COVID-19, persistent presence of *C. auris* infections	[117]
Germany	N/A	MALDI-TOF	1 colonized patient 1 BSI	I	VITEK 2 and BM (EUCAST)	R	S	S	1st documented transmission of *C. auris* in Germany (two critically ill COVID-19 patients) Most likely vehicle of transmission: reusable blades used in intubation	[118●]
Athens, Greece	October 2020 to January 2022	MALDI-TOF	5 ICU patients (*C. auris* isolated from urine, ulcer, blood, bronchial secretions)	I	BM (EUCAST)	R	S	R 60% S 40%	Horizontal transmission of clade I *C. auris* for the first time in Greece	[110]
New Delhi, India	April to July 2020	MALDI-TOF and rDNA sequencing	10 BSIs	I	BM (CLSI)	R	S	R 40% S 60%	*C. auris* was the predominant agent of candidemia; hospital-acquired BSIs	[96]
Northwestern India	August 2020 to January 2021	MALDI-TOF and rDNA sequencing	14 BSIs	I	BM (CLSI)	R	S	R 21% S 79%	*C. auris* was the predominant identified *Candida* species	[97]
Israel (nationwide study)	May 2014 to May 2022	CHROMagar Candida, VITEK 2, and rDNA sequencing	41	I, II, III, IV	BM (CLSI)	N/A^a	N/A^a	N/A^a	*C. auris* incidence rates corresponded in time with COVID-19–related surges in hospitalization	[107]
Genoa, Italy	July 2019 to May 2020	MALDI-TOF and *C. auris*-specific PCR	10	I	BM (Sensititre)	R	S	R	All but one isolate were part of a cluster likely stemming from the index case	[119]
Genoa, Italy	28 February to 31 May 2020	MALDI-TOF	6 total; *C. auris* cultured from BAL (2), swab (3), blood (1) 4 patients diagnosed with *C. auris* candidemia	N/A	BM (Sensititre)	R	S	R	Significant spread of resistant pathogens among critically ill COVID-19 patients	[120]

Table 2 (continued)

Location	Time period	ID method	Number of C. auris cases	Clade	Antifungal drug susceptibility				Major findings	Reference
					Method	FLC	MCF	AmB		
Genoa, Italy	February 20, 2020, to May 31, 2021	MALDI-TOF	92 colonized patients, 27 developed BSI	N/A	BM (Sensititre)	R	S	R 56% S 44%	C. auris candidemia in up to 1/4 of colonized critically ill patients; multisite colonization-independent risk factor for candidemia	[121]
Turin, Italy	July 2021 to March 2022	MALDI-TOF	8 colonized patients; 2 invasive infections; C. auris cultured from the skin (7), urine (2), respiratory tract (1), blood (1)	N/A	BM (MICRO-NAUT-AM)	R	N/A	N/A	C. auris colonization after a long hospital stay in patients transferred from different hospital	[122]
Beirut, Lebanon	October to December 2020	MALDI-TOF	14	N/A	Etest	R	S	R	Rapid transmission of C. auris in healthcare settings. Urgent need for surveillance programs	[111]
Beirut, Lebanon	1 October 2020 to 15 June 2021	MALDI-TOF and VITEK 2	32 patients; C. auris cultured from urine, deep tracheal aspirates (DTA), blood, and wounds	I	VITEK 2 and Etest	R	S	R	CVC, urinary catheter, high qSOFA score, prolonged LOS associated with increased C. auris isolation rates	[123, 124]
Monterrey, Nuevo León, Mexico	April to October 2020	MALDI-TOF and MLST	12 patients and 3 environmental isolates	IV	BM (CLSI)	R 53.3% S 46.7%	S	R	Exceedingly high mortality in patients with COVID-19–associated C. auris BSI	[125]
Karachi, Pakistan	April to December 2020	Biochemical[c]	4 BSIs	N/A	BM (Sensititre)	R	N/A (CAS-S)	S	High number of critically ill COVID-19 patients developed candidemia with a high mortality	[126]
Qatar	March 2020 to June 2021	MALDI-TOF	65 (screening specimens, blood, urinary, respiratory, and wound)	I	BM (Sensititre) or VITEK 2	N/A[a]	N/A[a]	N/A[a]	Highly clonal isolates	[127]
Valencia, Spain	April 2019 to March 2021	MALDI-TOF or C. auris-specific PCR	56 candidemia cases	N/A	BM (Sensititre) or VITEK 2	R	2 R isolates	S	71.4% of the C. auris candidemia cases in patients admitted to the ICU	[128]
Valencia, Spain	27 February 2020 to 26 February 2021	MALDI-TOF	29 infections and 53 colonization cases	N/A	BM (Sensititre)	N/A	N/A	R	The factors associated with a higher risk of death were those with coinfection, especially with C. auris	[129]
United Arab Emirates	February 1 to July 31, 2020	N/A	C. auris among top 20 organisms but the exact number of infections not provided	N/A	N/A	N/A[b]	N/A[b]	N/A[b]	Poor clinical outcomes in co-infected patients	[130]

Table 2 (continued)

Location	Time period	ID method	Number of C. auris cases	Clade	Antifungal drug susceptibility				Major findings	Reference
					Method	FLC	MCF	AmB		
Southern California, USA	Late 2019 to early 2022	C. auris-specific PCR and MALDI-TOF	8 patients	III (dominant clade)	BM	R	S	N/A	Robust C. auris surveillance program-active and passive surveillance, multidisciplinary efforts (microbiology laboratory and the hospital epidemiology team)	[131]
Miami, Florida, USA	N/A	MALDI-TOF	12 patients	III	VITEK 2	R	R 8% (1/12) S 92% (11/12)	S	Prolonged hospitalization due to critical illness from COVID-19 and use of antimicrobials may have contributed to clinical infections	[132]
Florida, USA	August 4 to 18, 2020	N/A	35 screening cases, 6 of which had positive clinical cultures later	N/A	N/A	N/A	N/A	N/A	Candida auris outbreak in a COVID-19 specialty care unit	[133]

[a]Susceptibility data available for the entire collection of C. auris, no extractable data for COVID-19 patients

[b]Cumulative susceptibility data available for all Candida spp., no extractable data for C. auris

[c]Germ tube test, chromogenic medium BiGGY morphology (Oxoid), cycloheximide tolerance, microscopic morphology on Cornmeal Agar (Dalmau method), and API 20C AUX (bioMérieux, France)

FLC fluconazole, MCF micafungin, CAS caspofungin, AmB amphotericin B, S susceptible, R resistant, BM broth microdilution, BSI bloodstream infection, CVC central venous catheter, ID identification, N/A not available

higher mortality in COVID-19 patients than non-COVID-19 patients [17, 23, 95].

Candida auris in COVID-19 Patients

Even before the COVID-19 pandemic, *Candida auris* had already established itself as one of the hot topics among infectious diseases experts. In 2019, it was named an urgent threat in the CDC's Antibiotic Resistance (AR) Threats Report due to its antifungal drug resistance and easy transmission, often leading to nosocomial outbreaks [102]. In the initial months of the pandemic, it was speculated that COVID-19 patients, especially the ones receiving critical care, would establish a population highly vulnerable to colonization and infection by *C. auris* [103]. These predictions proved correct, and numerous *C. auris* outbreaks occurred in countries all around the world (Table 2), as well as single cases in Japan [104], Qatar [105], and Turkey [106] were reported. Moreover, broader temporal analyses performed in India [79], Israel [107], and the USA [108, 109] informed of a growing number of *C. auris* cases during pandemic years. New *C. auris* introductions into previously unaffected healthcare facilities were also described [107, 110, 111]. The pooled mortality rate of *C. auris* candidiasis from published studies was estimated to exceed 60% (64.7% [112], 67.849% [113]).

The outbreaks were characterized by high clonality of the strains [107, 110, 114, 115, 118–120, 125, 127, 132] supporting the notion of intrahospital transmission of *C. auris*. Prolonged hospital stays, high burden of severely sick patients, and challenges in the implementation of infection control practices (e.g., extended or incorrect use of personal protective equipment) during the COVID-19 pandemic are thought to be the main drivers of patients' colonization with *C. auris* [96, 112, 127]. Lengthy lockdowns and travel restrictions most likely also contributed to the local spread pattern [114, 127].

Following the CDC guidance [134], echinocandins were used as first-line therapy in invasive *C. auris* cases [96, 97, 107, 110, 112, 114, 115, 118, 125, 126, 131], followed by amphotericin B [96, 112, 118, 125, 126, 131] and azoles [107, 110, 118, 125, 126]. Antifungal drug susceptibility (if determined) was clade-dependent with isolates of clade I (South Asian) showing almost uniform fluconazole resistance and high rates of amphotericin B resistance (Table 2). However, in Brazil, the researchers found unexpected low antifungal minimal inhibitory concentration (MIC) values and the absence of any resistance-conferring mutations in clade I isolates [114, 115]. Only a few studies identified molecular determinants of antifungal drug resistance in recovered *C. auris* clinical isolates. Well-known azole resistance-conferring mutations included Erg11 Y132F and K143R from India [97], Erg11 K143R and Tac1b A640V

from Italy (120), Erg11 Y132F from Lebanon [123] and Qatar [127], and Erg11 V125A/F126L from the USA [131]. Moreover, previously reported echinocandin resistance-conferring Fks1 mutations S639F and S639Y were detected Qatari isolates [127].

COVID-19 patients who developed *C. auris* infection were often severely ill with the most prevalent comorbidities being hypertension, diabetes mellitus, and cardiovascular diseases [96, 97, 113, 114, 121, 122, 124, 125, 130, 131, 133]. Other risk factors, including mechanical ventilation, extensive antibiotic use, steroid treatment, and placement of indwelling devices, also contributed to the *C. auris* infection acquisition [79, 96, 97, 107, 111, 114, 115, 117, 118, 121, 122, 124–126, 131–133]. In some cases, *C. auris* infection occurred concurrently with bacterial superinfection, further complicating patient management [107, 114, 118, 120, 124–126, 129, 133].

Public health professionals have speculated on the role of COVID-19 pandemic-related logistical issues, including low PPE compliance due to anticipated/existing PPE shortages and relaxation of the measures to control *C. auris* due to the higher workload of healthcare workers, which would promote nosocomial transmission of *C. auris*. Recent experience has highlighted the urgent need for uninterrupted *C. auris* surveillance and containment efforts.

Conclusion

COVID-19 patients who progressed to severe disease with acute respiratory distress were notable for their associated immune dysfunction and increased risk for developing opportunistic invasive fungal infections, including the ones caused by *Candida* species. Additionally, many of severely ill COVID-19 patients were treated with broad-spectrum antibiotics disrupting the normal intestinal flora composition [135] and corticosteroids enhancing *Candida* cells adhesion to the epithelial cells [136]. The resulting dysbiosis with promotion of *Candida* growth in the gastrointestinal and respiratory tracts with eventual translocation of *Candida* to the bloodstream system led to an increased number of *Candida* infections in COVID-19 patients. For commensal organisms like *C. albicans* and *C. glabrata*, which form a prominent reservoir in the gut, COVID-19 highlighted the importance of the gut-lung axis. While *Candida* in respiratory fluids of patients with pneumonia was associated with high mortality, it did not rise to the level of attributable mortality. Yet, such organisms almost certainly increased the body's overall inflammatory state contributing to patient decline. Early and appropriate management of lung and gut dysbiosis should become a part of routine standard-of-care for such patients with the aim of preventing the progression toward invasive *Candida* infections.

Finally, the steady rise of *C. auris* colonization and infection cases among hospitalized COVID-19 patients is a cautionary tale, as this environmentally hearty and drug-resistant organism continues to prey on the chronically ill immunocompromised hosts. Active surveillance of patient body sites (axilla, groin, nares) and healthcare environment is critical for limiting transmission and preventing infections. Here, molecular diagnostics methods offer rapid and accurate detection of patient and surface colonization and can aid in implementation of infection prevention and control measures especially in case of patient transfers.

Declarations

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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