Current Fungal Infection Reports (2019) 13:1–10
https://doi.org/10.1007/s12281-019-0334-4

CLINICAL PATHOLOGY (S CHALLA, SECTION EDITOR)

Epidemiology of Emerging Fungal Infections in ICU

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Published online: 15 January 2019

Abstract

Purpose of Review Globally, a change has been noticed in the epidemiology of fungal infections in the intensive care units (ICUs). The current review provides an insight into the current epidemiology of emerging fungal infections with special reference to their prevalence, spectrum of pathogen, outbreaks, and emergence of antifungal resistance reported from different ICUs of the world.

Recent Findings The ICUs across the world are witnessing multiple changes in the epidemiology of fungal infections including change in prevalence and spectrum of etiological agents, new susceptible risk groups, geographical variations, emergence of novel multi-drug resistant *Candida auris*, outbreak due to rare fungal species, emergence of antifungal resistance, etc. An understanding of the contemporary local epidemiology of fungal agents in ICU is essential for optimal patient management.

Summary Invasive candidiasis and invasive aspergillosis continue to haunt as major pathogens in the ICU, and several new risk factors associated with these infections have surfaced up. There is a contrasting picture for the species distribution of *Candida* among the different countries of the world. *C. auris*, the yeast behaving like bacteria, has emerged as a potential threat to ICUs across the five continents. Other mycelial agents like *Mucorales*, *Paecilomyces* spp., *Fusarium* spp., and *Cladosporium* spp., although encountered infrequently, continue to be reported as serious infections in ICU. The ICUs are also vulnerable sites for fungal infection outbreaks due to several fungi including rare ones like *Cryptococcus* spp., *Pichia anomala*, and *Kodamaea ohmeri*.

Keywords Epidemiology · Yeast · Mycelium · *Candida auris* · Antifungal resistance · Outbreaks

Introduction

Patients admitted to the intensive care units (ICU) are at increased risk of dying from systemic infections. A growing proportion of those cases are due to fungi, which have high mortality compared to bacterial infections and a considerable economic impact due to prolonged ICU stay [1–4]. With the advancement of medicine and supportive therapy in critically ill patients, increased number of elderly subjects is being admitted to the ICU, thereby substantially increasing the cumulative pool of patients at-risk for fungal infections over the past decade [3]. The severity of the acute illness, use of broad-spectrum antimicrobials, status of infection prevention, and control practices are few important factors that contribute to the emergence of fungal infections in ICU patients. Although diagnostic competency for fungal infections has improved, the critical status and the non-specific presentation of the invasive disease in ICU patients often delay confirmation of etiology and appropriate management [4]. It, thus, becomes imperative that the ICU team is well versed with the epidemiology of emerging fungal infections in their healthcare setting. Invasive candidiasis (IC) and invasive aspergillosis (IA) are the most important fungal diseases in terms of occurrence rates [5]; however, the spectrum of fungi causing infection is broadening over the years. The current review aims to present a comprehensive picture of the epidemiology of emerging fungal infections in the ICU. Specifically, the areas updated in this review are as follows:

a) Change in prevalence and spectrum of agent highlighting the importance of local epidemiology
b) Emergence of *Candida auris* in ICU
c) Change in host factor—new susceptible risk groups for fungal infections in ICU

This article is part of the Topical Collection on *Clinical Pathology*

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d) Emergence of rare fungal agents causing infections and outbreaks
e) Emergence of antifungal resistance

Change in Prevalence and Spectrum of Agent Highlighting the Importance of Local Epidemiology

Clinical presentations of fungal diseases in ICU

Recently, an early occurrence of invasive candidiasis (IC) has been noted where majority of the cases occur between five to 12 days of ICU admission [6]. The prevalent types of IC in ICU patients are candidemia and *Candida* peritonitis. The differentiation between candidemia originating from skin flora or gastrointestinal tract colonized with *Candida* species helps in planning intervention strategies, as vascular catheter related candidemia is of exogenous origin compared to endogenous origin of candidemia from gut [7, 8]. Though majority of ICU patients are mechanically ventilated and *Candida* spp. can be isolated from respiratory tract of every one out of four such patients [9], *Candida* pneumonia is extremely rare [7]. Other forms of IC, meningitis, endocarditis, and endophthalmitis are witnessed infrequently in ICU.

IA can have several manifestations in the ICU and vary with the host–pathogen interactions from mere colonization and chronic colonization in pre-existing cavity to acute invasive disease. Majority of such infections involve the lungs and sinuses. The aggressive angio-invasive form is seen in neutropenic patients while chronic lesions are frequent in patients of chronic obstructive pulmonary disease (COPD) and those receiving steroids. Other manifestations include endocarditis, mediastinitis, infection of vascular graft, and osteomyelitis, which occur as sporadic cases or in outbreak settings. Involvement of central nervous system may occur by hematogenous seeding from the lungs, direct spread from sinuses or during neurosurgery [8].

Global trends in yeast and mycelial infections in ICU

a. Changes in prevalence rates: *Candida* spp. ranked fourth (15.5%) among bloodstream infections in Australian ICUs [10] while 3.2% patients had microbiologically proven fungal blood infections in French ICUs [11]. A positive impact has been observed in 3474 ICUs of the United States of America (USA) where, the incidence of catheter-related candidemia decreased from 0.5 to $0.3/10^3$ catheter days. This favorable decline was largely due to the empiric use of fluconazole in high-risk patients especially of surgical ICUs [12]. The rates of IC in ICU during contemporary times are depicted in Table 1. The disparity in the results of different studies is not surprising as they differ in their demographical features, healthcare practices, presence of co-morbidities, and other ICU-related interventions. Nevertheless, the true incidence of IC is expected to be much higher, as only 30–50% cases are diagnosed by a positive blood culture [32].

The recognition of IA in new susceptible groups admitted in ICU is of recent occurrence. In an Italian study covering 18 ICUs, incidence of IA was 0.2% (12 cases in 5561 patients) [33]. In another multi-centric study involving 30 ICUs from 8 countries, proven IA was seen in 17% patients (94 of 563 cohort) and another 36% had putative IA [34]. Baddley et al. [35] in their retrospective compilation of ICUs from > 600 USA hospitals over 4 years (2005–2008) reported 412/6424 (6.4%) ICU patients with IA. Among 1850 hospitalized patients in Belgium ICU, incidence of IA was 6.9% [36]. Prior studies based on autopsy findings suggest that IA is the most common missed diagnosis in ICU patients [37]. Among patients of severe hospital-acquired pneumonia admitted in Spanish ICU, the incidence of proven IA was 19% over 7 years [38]. Uncommon yet devastating, mucormycosis has been increasingly reported from ICU patients especially in India over the past half a decade [39•]. Epidemiological data specific for mucormycosis in ICU settings is largely inadequate and is derived from individual case reports or small case series [40–42]. Taj-Aldeen et al. [14] in their analysis of fungal disease burden in Qatar reported an incidence of 0.37 per 10^5 populations for mucormycosis in their ICUs. Tortorano et al. [30] reported four cases of mucormycosis in their 38-ICU study. There were two cases of *Lichtheimia* spp. in poly-trauma patients: one case of *Rhizopus oryzae* in diabetic ketoacidosis patient, and another case was diagnosed as mucormycosis after post-mortem examination of a lymphoma patient. Three cases of cutaneous mucormycosis by *Lichtheimia* spp. were reported as possible cross-contamination in French ICU [40]. Goncalves et al. [43] recently analyzed the fungal spores present in the ICU air of their Brazilian hospital. They isolated *Penicillium* spp. (15.2%) followed by *Aspergillus* spp., *Cladosporium* spp., *Fusarium* spp., *Paecilomyces* spp., *Curvularia* spp., *Alternaria* spp., Zygomycetes, and sterile mycelium. The most common species isolated in morning hours was *Aspergillus* spp. (14%) and in the afternoon was *Cladosporium* spp. (14%). Rudramurthy et al. also reported high fungal spore burden in Indian ICUs, with predominance of *A. flavus* and *A. fumigatus* [44]. The fact that these fungi are present in the ICU environment, they are potential etiologies for emerging fungal infections in the ICU given the vulnerabilities of critically ill ICU patients. Though Cryptococcal meningitis is primarily a disease of AIDS patients, such patients when admitted to ICU are

Table 1 Prevalence of invasive candidiasis among ICUs of different countries

S. no	Country	Author	Year	Rate of candidemia (/10^5 population)	Rate of *Candida* peritonitis (/10^5 population)
1	Belgium	Lagrou et al. [13]	2015	8.4	0.75
2	Qatar	Taj et al. [14]	2015	8.2	3.4
3	Spain	Rodriguez et al. [15]	2015	8.1	1.42
4	Serbia	Arsenijevic et al. [16]	2018	6.6	2.7
5	Dominican Republic	Gugnani et al. [17]	2015	5.5	0.75
6	Ukraine	Osmanov et al. [18]	2015	5	0.82
7	Denmark	Mortensen et al. [19]	2015	4.8	3.1
8	Germany	Ruhnke et al. [20]	2015	4.6	4.6
9	Hungary	Sinko et al. [21]	2015	3.7	Not evaluated
10	Vietnam	Beardsley et al. [22]	2015	3.5	Not evaluated
11	Argentina	Riera et al. [23]	2018	2.5	1.25
12	Trinidad	Denning et al. [24]	2015	1.5	0.8
13	Czech Republic	Chrdle et al. [25]	2015	1.5	0.75
14	Malaysia	Velayuthan et al. [26]	2018	1.5	0.8
15	Jamaica	Gugnani et al. [27]	2015	1.5	0.8
16	Jordan	Wadi et al. [28]	2018	1.5	0.75
17	France	Gangneux et al. [29]	2016	0.9	0.74
18	Italy	Tortorano et al. [30]	2011	7.3/10^3 ICU admission	Not evaluated
19	India	Chakrabarti et al. [31•]	2015	6.5/10^3 ICU admission	Not evaluated
20	USA	Fagan et al. [12]	2013	0.3/10^3 catheter days	Not evaluated

prone to develop Cryptococcal bloodstream infection. In a multi-centric study involving 38 Italian ICUs [30] out of 384 fungal infections over 2 years, three were due to cryptococcosis. The clinical profile of these patients was agranulocytopenia in first, AIDS in second, and chronic renal failure in the third patient. All three succumbed to death. Owing to lack of ICU-specific data, the incidence of other fungal infections in ICU settings is difficult to estimate.

b. Changes in species distribution: The last two decades have witnessed a shift from *C. albicans* to non-*albicans Candida* species (NAC). Predominant species of *Candida* causing candidemia in ICU are depicted in Table 2. The International Surveillance Program, ARTEMIS DISK, reported a 10% fall in incidence of *C. albicans* over 6 years, though it was still the most commonly isolated species [50]. Broadly, in all multi-centric European studies pertaining to ICU candidemia, more than 50% cases (range 54–84%) are attributable to *C. albicans*, followed by *C. glabrata* as the second most common species in Northern Europe and *C. parapsilosis* in Southern Europe [30, 39•]. Prevalence of *C. glabrata* was double in USA as compared to Europe, predominantly at the cost of *C. albicans* [51]. Colombia recently reported a *C. albicans* to NAC ratio of 48:52 with *C. tropicalis* being the second most common species (38.6%) followed by *C. parapsilosis* (28.5%) [52]. Among other Latin American countries, *C. albicans* ranged from 19 to 66%, *C. parapsilosis* from 5 to 49%, and

Table 2 *Candida* species distribution among ICUs of different countries

S. no.	Country	Author	Year	Most common *Candida* species	2nd most common species	3rd most common species
1	Italy	Tortorano et al. [30]	2011	*C. albicans* (60%)	*C. glabrata* (13.4%)	*C. parapsilosis* (13%)
2	India	Chakrabarti et al. [31•]	2015	*C. tropicalis* (41.6%)	*C. albicans* (20.9%)	*C. parapsilosis* (10.9%)
3	Australia	Chapman et al. [45]	2017	*C. albicans* (44.4%)	*C. glabrata* (26.7%)	*C. parapsilosis* (16.5%)
4	Brazil	Colombo et al. [46]	2013	*C. albicans* (34%)	*C. parapsilosis* (26%)	*C. tropicalis* (20%)
5	Belgium	Goemaere et al. [47]	2018	*C. albicans* (63.5%)	*C. glabrata* (21%)	*C. parapsilosis* (6%)
6	China	Lin et al. [48]	2018	*C. albicans* (36%)	*C. parapsilosis* (24%)	*C. tropicalis* (22.8%)
7	S. Africa	Kreusch et al. [49]	2013	*C. albicans* (46%)	*C. parapsilosis* (25%)	*C. glabrata* (23%)

C. tropicalis from 9 to 39% [52]. In Argentina, Brazil, and Colombia, an increase in frequency of *C. glabrata* candidemia was observed in recent years [53]. In Australia, *C. glabrata* increased from 16% in 2004 to 26.7% in 2014 [45]. There is some fluctuation and no drastic change in the species distribution on a long-term global scale, though individual centers may experience vast variations in their *Candida* spectrum. Davis et al. [51], in their non-neutropenic ICU patients, observed an increase in *C. glabrata* from 0 to 30% over 3 years with *C. tropicalis* nearly disappearing during the same time in Detroit, USA.

c. Range of mortality—According to Extended Prevalence of Infection in the ICU study (EPIC-II), candidemia had the highest crude ICU mortality (42.6%) compared to gram-negative (29.1%) and gram-positive (25.3%) bacteremia [54]. Two Italian studies have reported crude mortality at 30 days ranging from 39.3% [54] to 46.2% [30] for IC in their ICUs. The same was 44.7% among Indian ICUs [31•]. Attributable mortality is considered a better index though it is difficult to calculate as the demarcation between mortality due to candidemia and that due to severe underlying disease is difficult to establish. Nonetheless, Indian ICUs have reported an attributable mortality of 19.6% [31•] to candidemia while Falagas et al. [55], in their review of six studies, have reported the attributable mortality to range from 5 to 71%. With respect to different species, Dimopoulos et al. [56] documented a multivariate odds ratio of 6.7 for lethal outcome in NAC as compared to *C. albicans* candidemia. USA-based survey reported higher mortality (> 50%) associated with *C. glabrata* and *C. krusei* and lower mortality (28%) associated with *C. parapsilosis*, in comparison to *C. albicans* [57].

In Italian ICUs, the crude mortality rate of IA was 63% [30]. The mortality was significantly higher in medical ICUs (56%) than surgical ones (23%) ($p = 0.008$). In one of the earliest studies by Janssen et al. in 1996, the reported mortality rate of proven or probable IA in ICU was as high as 92% in the Netherlands despite antifungal therapy and adequate supportive care [58]. Similar high mortality of 90% was reported by Meersseman et al. in 2004 from Belgian ICUs [56]. Other studies reported crude mortalities of 80% in Spanish [59] and 76% in Belgian ICUs for IA [60]. Blot et al. [61], in their international multi-centric evaluation of European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) guidelines on 524 ICU patients with IA, reported a non-significant difference in mortality among proven (77%), probable (72%) and putative (67%) cases ($p = 0.3$). Trof et al. [62] reported that isolation of *Aspergillus* spp. was associated with increased mortality in critically ill patients, irrespective of invasion or colonization.

Emergence of *C. auris* in ICU

C. auris infection has emerged as a serious problem in ICUs of many countries, as the organism is developing antifungal resistance very fast, is easily transmitted among patients in ICU, is not easily identified by phenotypic identification system practiced in majority of the clinical laboratories, and causes severe infection with high mortality. Ever since its debut in 2009 [53], *C. auris* has spread to over 25 countries of five continents [63•]. In one of the largest ICU-acquired candidemia study from India, a total of 5.3% cases from 19 of 27 ICUs were due to *C. auris*. Significant risk factors associated with *C. auris* infection were admission in public-sector hospitals, longer duration of ICU stay and central venous catheter, and prior antifungal exposure. Thirty-day crude mortality of *C. auris* infection was 42%, and attributable mortality was 27% [64•]. Whole genome sequencing of 47 isolates identified four clades of the organism with little variation of organisms in a single clade [65].

It is not clear where from *C. auris* has emerged. In a hospital of the UK, only one patient was found to be colonized with *C. auris* while screening 2246 patients at admission [66]. In a prospective study, it was observed that after the entry of a *C. auris* infected patient in ICU, the organism rapidly (within 4 days) colonizes all patients. It was difficult to get rid of the colonized organism without twice daily chlorhexidine body wash. The organism can persist even on dry linen for 7 days [67]. In a systematic study from the UK, reusable skin-attached thermometers and systemic fluconazole exposure were found to be significantly associated with *C. auris* infection [68]. The guidelines provided by the Centre for Disease Control and Prevention (CDC), Atlanta, USA for the control of *C. auris* recommend (a) speciation of all *Candida* isolates obtained from sterile body sites like blood and cerebrospinal fluid to initiate appropriate therapy and (b) speciation of all *Candida* isolates obtained from non-sterile sites so as to initiate infection control practices while handling colonized patients and continue the same for at least 1 month till no evidence of transmission of *C. auris* exists.

Change in Host Factor—New Susceptible Risk Groups for Fungal Infections in ICU

Among the host factors, critical physiology like higher age, high Acute Physiology and Chronic Health Evaluation (APACHE-II) score, neutropenia (> 10 days), *Candida* colonization index (> 0.5), and critical pathology like

gastrointestinal perforation, necrotizing pancreatitis, severe bacterial sepsis, and diabetes mellitus are associated with an increased risk of IC. Among the iatrogenic factors, administration of corticosteroids, broad-spectrum antimicrobials, and total parenteral nutrition; invasive procedures like central venous catheters, mechanical ventilation, and hemodialysis; and major surgeries like those of gastrointestinal system contribute to increased risk of IC [69]. Several authors have tried to elucidate the individual risk factors for IC caused by *C. albicans* vs NAC in the ICU. While few observed no differences in risk factors [70], majority have documented certain differences. Montagna et al. [54], in their review, have analyzed several risk factors and reported that abdominal surgery and diabetes mellitus present increased risk of *C. albicans* infections while antifungal prophylaxis with fluconazole decreases it. Increased age, female gender, use of corticosteroids, parenteral nutrition, neutropenia, and central venous catheters increased the risk of NAC infections. *C. parapsilosis* was significantly associated with parenteral nutrition as the yeast has selective growth advantage at higher glucose concentrations [71]. Use of antimicrobial agents like piperacillin–tazobactam and vancomycin increased risk of *C. glabrata* and *C. krusei* candidemia [6], and use of prior caspofungin increased breakthrough *C. parapsilosis* candidemia [41] while no increased risk was observed for *C. glabrata* on fluconazole-treated patients [72].

Any patient in ICU may acquire IC as the risk factors are commonly present in those patients. However, the IA story in ICU is still evolving. It is challenging to delineate colonization from infection in cultures growing *Aspergillus* spp. from non-sterile site. The diagnosis of IA is difficult as the patients do not have specific clinical features, imaging seldom help in non-neutropenic patients, and invasive sample collection is difficult in critically ill patient [73]. The clinical guideline proposed by EORTC/MSG does not help in majority of the patients due to different host factors in ICU patients [74]. In recent years, non-cancer, non-transplant patients admitted in the ICU are forming a discrete pool of population vulnerable to IA [60, 75]. Among non-neutropenic, apparently immunocompetent patients admitted in the ICU, the risk of IA is attributed to the biphasic response in sepsis wherein the initial hyper-inflammation phase is followed by the phase of immune-paralysis. The neutrophil deactivation during this latter phase puts those patients at increased risk of IA [76]. Another subset of non-neutropenic patients at particular risk of IA in ICU are those of COPD. Structural and functional alterations in the lung, frequent hospitalizations and exposure to invasive procedures, rampant administration of broad-spectrum antimicrobials, and steroid therapy contribute in predisposing a COPD lung to IA [77]. Cirrhosis, both compensated and decompensated, puts these patients at heightened risk of IA due to impaired phagocytosis [68, 78]. Environmental factors, especially the concentration of *Aspergillus* spores in the air, have been implicated in sporadic cases and outbreaks of IA in ICUs [79].

Among the risk factors for mucormycosis, immune-deficient patients especially those with hematological or solid organ malignancy are at increased risk. With respect to other ICU patients, increased risk is seen with patients of diabetic ketoacidosis and use of contaminated dressings in trauma patients [39•].

Emergence of Rare Fungal Agents Causing Infections and Outbreaks

Fungal agents have been threatening the already critical environment of the ICUs by appearing as outbreaks caused by uncommon species. The 1996–1998 outbreak of *Pichia anomala* (*C. pelliculosa*) at a leading tertiary care center in India involved patients of three ICUs (neonatal, neurosurgical and pediatric) with a mortality of 42%. The possible source were the contaminated hands of the healthcare workers, and the outbreak could be controlled only after improved handwashing practices and nystatin–fluconazole prophylaxis to all ICU admitted patients [80]. Another outbreak involving a rare fungus, *Kodamaea ohmeri*, was reported from the same center involving 38 patients of pediatric surgery ICU in the year 2007–2008. The risk factors significantly associated with fungemia were prematurity and use of piperacillin–tazobactam and endotracheal tube, and the mortality was 50% [81]. An outbreak of *C. tropicalis*, involving 16 neonates between 28 and 36 weeks of gestation, was reported from North India, the fungus being isolated from the blankets and mattresses of the neonates [82]. A cluster of six cases of Cryptococcal bloodstream infection and respiratory infection was reported from USA-based ICU in 2013. No environmental source could be identified, and short-term steroid course was the only identified risk factor [83]. An outbreak consisting of five cases of gastrointestinal mucormycosis due to *Rhizopus microsporus* was reported in 2004 in Spanish ICU subsequent to use of contaminated wooden tongue depressors and had an attributable mortality of 40% [84]. Similarly, outbreaks and pseudo-outbreaks by contaminated bronchoscopes and other devices have been reported for *Fusarium solani*, *Penicillium* spp. and *Sporothrix cyanescens* [85]. Outbreaks, implicating bronchoscopes used in the ICU, have been reported for other yeast infections like *Trichosporon cutaneum*, *Rhodotorula rubra*, and *Trichosporon mucoides* as well [86, 87].

There are several challenges unique to emergence of such rare species in the ICU. Their epidemiology, with respect to reservoirs and modes of transmission, is not well understood, making their detection difficult. The identification of these rare agents is challenging for the microbiology laboratory as

Table 3 Relative susceptibilities to common antifungal agents of predominant *Candida* spp. from ICUs of different countries of the world

No.	Study characteristics			*C. albicans* (% resistance)					*C. glabrata* (% resistance)					*C. parapsilosis* (% resistance)					*C. tropicalis* (% resistance)				
	Country	Year	*n*	F	V	AB	C	A	F	V	AB	C	A	F	V	AB	C	A	F	V	AB	C	A
1	Slovakia [88]	2017	295	2	4	0	–	0	32	11	0	–	0	20	2.5	0	–	0	–	–	–	–	–
2	Iran [89]	2015	67	–	0	0	0	–	–	6	9.4	0	–	–	–	–	–	–	–	0	0	0	–
3	France [90]	2017	244	4	0	0	0	–	50	40	0	7	–	0	0	0	0	–	0	0	0	0	–
4	SENTRY [91]	2011	745	0	0	–	0.3	0.3	6	6	–	2.2	2.2	7	0	–	0	0	5	5	–	0	0
5	India [31•]	2014	918	5.2	7.8	0.5	3.6	1	1.5	0	3.1	23	6.2	4	3	2	0	0	2.6	8.1	1	4.2	2.1
6	Brazil [92]	2016	47	0	0	0	–	0	36	0	0	–	0	0	0	0	–	0	0	0	0	–	0
7	Europe [54]	2014	92	0	0	0	0	5	33	55	0	0	33	0	0	0	5.8	5.8	–	–	–	–	–
8	Serbia [16]	2018	43	4	4	0	0	0	–	–	–	–	–	0	0	0	0	0	–	–	–	–	–
9	Italy [93•]	2018	1091	0	–	–	0	0	33	–	–	2	0	0	–	–	0	0	–	–	–	–	–
10	China [94]	2013	389	9.6	0	0	0	–	4	6	0	0	–	19	3.6	0	0	–	6	0	0	0	–

N number of *Candida* isolates tested for antifungal susceptibility, *F* fluconazole, *V* voriconazole, *AB* amphotericin B, *C* caspofungin, *A* anidulafungin

they require molecular expertise and even the specific guidelines for performing and interpreting their antifungal susceptibility are lacking. Finally, the facilities of reference laboratories are not available in all regions and countries.

Emergence of Antifungal Resistance

The ICUs bear the dual brunt of antifungal resistance. On one hand, the colonization of patients with multiple fungal agents along with administration of several antifungal agents as empiric therapy favors emergence of acquired resistance among fungal pathogens. On the other, the critically ill patient along with any breach in infection control practices causes emergence of intrinsically resistant species to outgrow others, often leading to an outbreak.

The antifungal susceptibility data for candidemia from various ICUs of the world is summarized in Table 3. Globally, *C. albicans* has maintained good susceptibility to nearly all antifungal agents in the ICU with the highest resistance being shown to azole group (fluconazole and voriconazole) being less than 10%, followed by echinocandins (being less than 5%). Resistance to antifungals is a major concern in *C. glabrata*-associated candidemia in nearly all ICUs across the world. While resistance rates range from 4% to over 50% for fluconazole and voriconazole, rates for echinocandins vary from 0% to over 30%. Resistance to amphotericin B lies within 10% in contemporary times. *C. parapsilosis* has shown resistance up to 20% for fluconazole in countries like China [94] and Slovakia (69) and up to 6% for echinocandins in Europe [54]. *C. tropicalis* has maintained high susceptibility to antifungal agents in most countries except a resistance of 6% to fluconazole reported from China [94] and 5% reported from SENTRY surveillance study (encompassing Europe, Latin America and North America) [91]. The Indian ICUs [31•], wherein *C. tropicalis* is the predominant species, have reported resistance to all antifungal agents ranging from 1 to 8%. Among the *C. auris* isolates reported from two ICU-based studies, contrasting susceptibilities have been reported. While the resistance rates to fluconazole, voriconazole, amphotericin B, and echinocandins were reported as 31%, 4%, 13.5%, and 7.7% (for caspofungin), respectively from Indian ICUs (2012, $n = 52$) [31•], those reported from British ICUs (2017, $n = 79$) [95] were 100%, 98%, 18%, and 0% (for micafungin), respectively.

Among the mycelial fungi, the susceptibility data from ICU-based studies is limited to *A. fumigatus*. Montagna et al. [33] isolated 12 cases of *A. fumigatus* infection from 18 ICUs of Italy over one and a half year. The susceptibility of five of them was performed, and all were susceptible to amphotericin B, voriconazole, posaconazole, caspofungin, and anidulafungin. In another study from ICU in the Netherlands [96], 5 out of 20 *A. fumigatus* strains isolated were resistant to azoles antifungals. Other studies, though not dedicated to ICU settings, have reported a prevalence of 3.2% for azole resistance in *A. fumigatus* isolates across 19 European countries [97] and a 100% 90-day mortality for IA by azole-resistant *A. fumigatus* [98].

Conclusions

The prevalence of invasive fungal infections in ICUs is on the rise especially in developing countries. Not only neutropenic patients but also non-neutropenic hosts are found to be susceptible to invasive mold infections. The spectrum of fungal agents causing those infections has broadened across the world, and the spectrum varies with geographical location of ICU. It is important to have surveillance study to know local epidemiology of invasive fungal infections. Outbreaks due to fungi have

been reported in many ICUs even due to rare fungal species. Identification of those agents is a challenge in routine clinical mycology laboratory with the standard phenotypic methods. The globally emerging agent, *C. auris*, thrives in ICU environment, but the source of agent is still not clearly known. Recent emergence of antifungal resistance in both yeast and mycelial fungi has complicated the management of these patients. Routine antifungal susceptibility testing of fungi causing invasive infections may be important, but the breakpoints are not known for majority of emerging fungal agents. Awareness campaign and development of diagnostic mycology laboratories at every corner of globe are the need of the hour.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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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