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Original Article

Candida albicans—A systematic review to inform the World Health Organization Fungal Priority Pathogens List

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Abstract

Candida albicans is a common fungal pathogen and amongst the leading causes of invasive candidiasis globally. This systematic review examines the characteristics and global impact of invasive infections caused by *C. albicans*. We searched on PubMed and Web of Science for studies reporting on criteria such as mortality, morbidity, drug resistance, preventability, yearly incidence, and distribution/emergence during the period from 2016 to 2021. Our findings indicate that *C. albicans* is the most common *Candida* species causing invasive disease and that standard infection control measures are the primary means of prevention. However, we found high rates of mortality associated with infections caused by *C. albicans*. Furthermore, there is a lack of data on complications and sequelae. Resistance to commonly used antifungals remains rare. Although, whilst generally susceptible to azoles, we found some evidence of increasing resistance, particularly in middle-income settings—notably, data from low-income settings were limited. *Candida albicans* remains susceptible to echinocandins, amphotericin B, and flucytosine. We observed evidence of a decreasing proportion of infections caused by *C. albicans* relative to other *Candida* species, although detailed epidemiological studies are needed to confirm this trend. More robust data on attributable mortality, complications, and sequelae are needed to understand the full extent of the impact of invasive *C. albicans* infections.

Key words: *Candida albicans*, invasive candidiasis, antifungal resistance, mortality, epidemiology.

Introduction

Candida albicans is a diploid polymorphic yeast that is commonly found on skin and mucosal surfaces as part of the normal human microbiome. However, it has considerable pathogenic potential and can be infectious under certain conditions, including weakened immunity, the presence of a critical illness, the presence of implanted medical devices, or whilst on broad-spectrum antibiotics.[1–4] These infections can range from mild skin and mucous membrane infections to severe invasive infections, particularly in individuals with compromised immune systems.[5,6]

Candida albicans is the most isolated fungal species in laboratories, and it is the most common species responsible for invasive candidiasis (IC), a common cause of mortality among immunocompromised patients.[7] Previous studies have shown a wide range of anatomical sites affected by *C. albicans* and defined its complex pathogenesis.[6,8] Its ability to adapt to different host sites and changing host conditions is considered a major factor in its ability to cause a variety of conditions, from mucosal infections to invasive ones.[8]

Preliminary identification is by observation of growth on culture media and microscopic/macroscopic examinations.[9]

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Accurate and rapid identification can be obtained by proteomic (MALDI-TOF) and molecular methods such as RFLPs (using gel electrophoresis), DNA–DNA hybridisation, and polymerase chain reaction.[10]

The incidence of IC is high, at 90 cases per 100 000 patients, and has not shown a decrease in recent years.[11] The high morbidity and mortality associated with IC[5,7] is likely to be in part driven by low clinical suspicion and a lack of sufficiently rapid diagnostic tests, which combine to result in delays administering appropriate treatment.[12] Additionally, there is a growing concern about the impact on clinical outcomes of antifungal resistance in IC. So far, resistance is considered rare in *C. albicans*, although examples such as azole resistance in HIV patients treated with fluconazole for oral candidiasis and echinocandin resistance in cases of *C. albicans* oesophagitis are described.[13]

Prevention of infection is difficult, and there is, as yet, no effective vaccine. Many challenges to developing a vaccine for *Candida* infections have been reported, including the diverse forms of infection caused.[12] However, multiple virulence factors that influence *C. albicans* infections, including adhesion, invasion-promoting enzyme, mycelial growth, and phenotypic change, have been identified as favourable targets for the development of vaccines (as well as antifungal drugs).[12,14]

Candida albicans is a significant public health concern, and the understanding of its epidemiology, risk factors, and the development of resistance to antifungal drugs is of great importance. Despite the worldwide concern, there has been a lack of research to generate robust data from clinical and microbiological studies to support effective diagnosis and treatment. The absence of formal national or regional surveillance systems also leaves clinicians with limited or anecdotal information about local epidemiology and antimicrobial resistance on which to base decisions and treatment strategies.

Considering the increasing global threat of fungal pathogens, the World Health Organization (WHO) established an Expert Group (WHO Advisory Group on the Fungal Priority Pathogen List) in 2020 that advised the WHO during the development of the first ever WHO Fungal Pathogen Priority List (FPPL) published in 2022.[15] This systematic review evaluated the characteristics and global impact of invasive *C. albicans* infections against a set of criteria, including mortality, hospitalisation, and disability, antifungal drug susceptibility testing, preventability, yearly incidence, and global distribution and emergence from 2016 to 2021, and identified knowledge gaps for *C. albicans* to inform the WHO FPPL.

Materials and methods

Search strategies

We conducted a comprehensive search for studies published in English using the PubMed and Web of Science databases. The study was conducted according to PRISMA guidelines.[16]

On PubMed, the search was optimised using medical subject headings (MeSH) and/or keyword terms in the title/abstract for the pathogen and each criterion. The final search used (Candida albicans[MeSH Terms) combined, using AND term, with criteria terms including (mortality[MeSH Terms]) OR (morbidity[MeSH Terms]) OR (hospitalisation[MeSH Terms]) OR (disability[All Fields])) OR (drug resistance, fungal[MeSH Terms]) OR (prevention and control[MeSH Subheading]) OR (disease transmission, infectious[MeSH Terms]) OR (diagnostic[Title/Abstract]) OR (antifungal agents[MeSH Terms]) OR (epidemiology[MeSH Terms]) OR (surveillance [Title/Abstract]).

On Web of Science, MeSH terms are not available and therefore topic search (TS), title (TI), or abstract (AB) search was used. The final search used [TI=('candida albicans') OR TI=('c.albicans')], combined, using AND term, with criteria terms each as topic search, including (mortality) OR (case fatality) OR (morbidity) OR (hospitali∗ation) OR (disability) OR (drug resistance) OR (prevention and control) OR (disease transmission) OR (diagnostic) OR (antifungal agents) OR (epidemiology) OR (surveillance). Symbol ∗ allows a truncation search for variations of the term (e.g., hospitalisation or hospitalization).

All searches were limited to studies from 2016 to 2021. Allowed study types were retrospective/prospective observational studies, randomised controlled trials, guidelines, epidemiology, and surveillance reports, which were published from 2016 to 2021. Studies with fewer than 50 subjects, case reports, conference abstracts, and review articles were excluded, as were studies reporting only on novel drugs or diagnostic tools not registered for clinical use.

Study selection

The final search results from each database were incorporated into the online systematic review software, Covidence® (Veritas Health Innovation, Australia). Duplicates were removed in Covidence®. The remaining articles underwent title and abstract screening based on the inclusion criteria. Full-text screening was performed for the final eligible articles. The title/abstract screening and full-text screenings were performed independently by two reviewers on Covidence®. Any discrepancies were resolved by a third reviewer. No reason was provided for exclusion during title and abstract screening, but they were recorded for exclusions at full-text screening.

If there were any additional articles identified from references of the included articles, these were added. The resulting articles were subject to the final analysis. The extracted data on the outcome criteria were quantitatively or qualitatively synthesised depending on the amount and nature of the data.

Risk of bias assessment

Risk of bias assessment was performed for the included studies on relevant bias criteria, depending on the type of data extracted. Risk of bias tool for randomised trials version 2 (ROB 2) tool was used to assess the randomised controlled trials.[17] Risk of bias in non-randomised studies (RoBANS) tool was used to assess the non-randomised studies.[18] For the overall risk, using the ROB 2 tool, the studies were rated low, high, or some concerns. Using the RoBANS tool, the studies were rated as low, high, or unclear risk.

As the systematic review was intended to inform on specific criteria rather than study outcomes as in traditional systematic reviews, the bias assessment tools were not perfectly suited for the task to assess the bias for the specific criteria. We used each criterion as an outcome of the study and assessed if any bias was expected based on the study design, data collection, or analysis in that study. Following that strategy, studies classified as unclear or high overall risk were still considered for analysis.

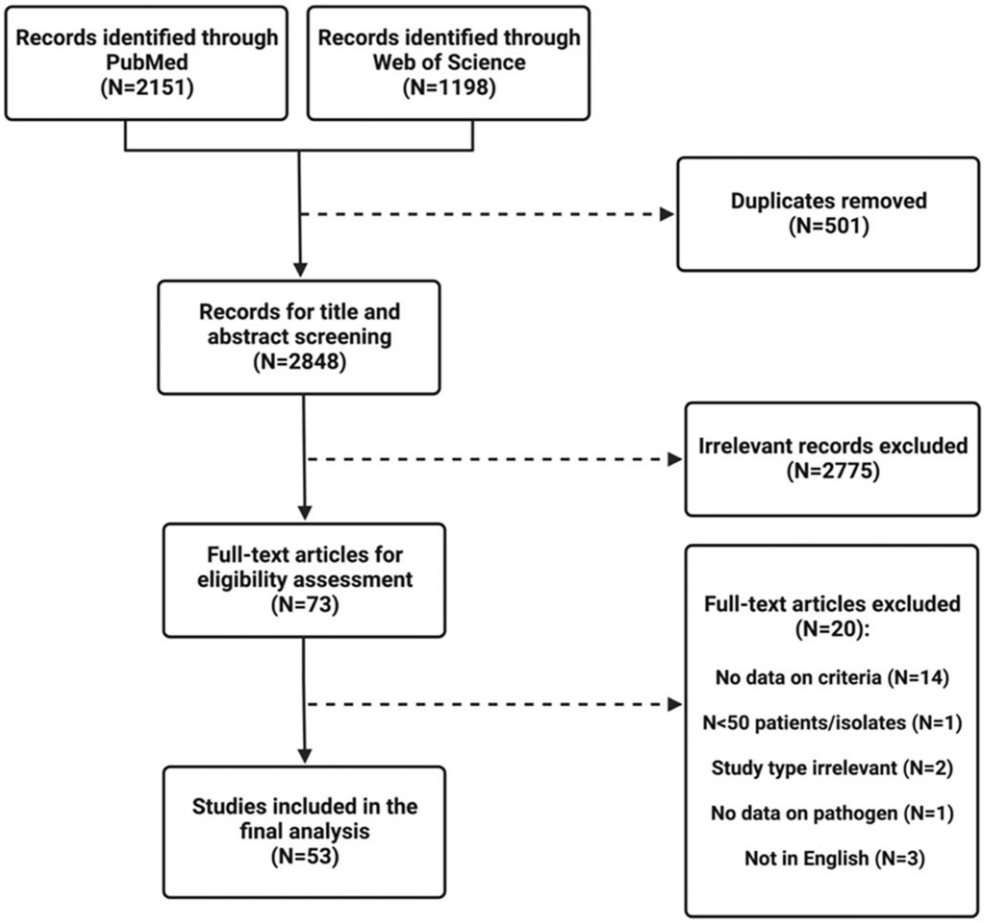

Figure 1. Flow diagram for selection of studies included in the systematic review based on the PRISMA statement.

Conference abstracts were not assessed due to limited resources meaning that reporting bias cannot be properly assessed.

Results

Study selection

PubMed and Web of Science Core Collection databases searched between 1 June 2016 and 1 June 2021 yielded 2151 and 1198 articles, respectively. A total of 53 studies were included in the final analysis (Fig. 1).

Risk of bias

Overall risk of bias for each study is presented in Table 1. Of the included studies, 39 were classified as low risk of bias in all domains assessed. For 14 studies, the risk of bias was classified as unclear. For 12 studies, the risk of bias was unclear because management of confounding variables was poorly described; for 7 studies, the issue was potential selection biases; and for 5 studies, measuring susceptibility, the risk of bias was unclear as methods were poorly described or used inconsistently.

Mortality rate

The most frequently described mortality types were in-hospital and 30-day mortality (Table 2). In-hospital mortality ranged from 3.3%[30] to 52.2%,[51] whilst 30-day mortality ranged from 23.4%[48] to 60.1%.[28] For most studies (20/26), in-hospital and 30-day mortality were in the range of 20%–50%. The lowest rates of mortality were described for children and neonates (e.g., 3.3% in China reported by Fu et al.[30] and 8% in Italy described by Mesini et al.,[46] both of which studies carried a low risk of bias and contained $n = 69$ and $n = 180$ patients, respectively). Most studies involved either critically ill or neutropenic patients, but the two groups had broadly similar mortality outcomes. Shahin et al. was the largest study specifically describing mortality for *C. albicans* infection, with $n = 235$ and a low risk of bias. This UK study focused on critically ill patients in the ICU and documented mortality in the critical care unit or 34.9%, and in-hospital mortality of 49.5%.[57]

Antifungal susceptibilities

In total, 36 studies reported susceptibility of *C. albicans* isolates to antifungal drugs. The details of those studies (including study type, sample size, and country of origin) are summarised in appendix Table A1. Most studies reported on susceptibility of isolates collected during cohort studies and were both retrospective ($n = 17$) and prospective ($n = 4$) in nature.

The next major study type was laboratory surveillance ($n = 11$), amongst which were the three largest studies, with >1000 isolates from multiple sites in multiple countries.[21,22,40] All three of these studies had a low risk of bias.

Table 1. Risk of bias.

First author	Overall risk of bias	Reference
Ahangarkani	Low	19
Benedict	Low	20
Castanheira	Low	21
Castanheira	Low	22
Chandrasekar	Low	23
Chen	Low	24
Cuervo	Low	25
Dagi	Unclear	26
Dogan	Low	27
Eliakim-Raz	Low	28
Fay	Unclear	29
Fu	Low	30
Ghanem-Zoubi	Low	31
Gong	Low	32
Gonzalez-Lara	Unclear	33
Guo	Low	34
Hsu	Low	35
Issler-Fisher	Low	36
Jamil	Unclear	37
Jeon	Unclear	38
Kakeya	Unclear	39
Kritikos	Low	40
Kumar	Low	41
Lal	Low	42
Lee	Low	43
Li	Low	44
Lindberg	Low	45
Mesini	Low	46
Muderris	Low	47
Murri	Low	48
Patel	Unclear	49
Peron	Unclear	50
Raja	Unclear	51
Ramla	Low	52
Ramos	Low	53
Ryan	Low	54
Schwab	Unclear	55
Seyoum	Unclear	56
Shahin	Low	57
Sharifynia	Unclear	58
Shin	Low	59
Tasneem	Unclear	60
Tedeschi	Low	61
Ueda	Low	62
UluKilic	Low	63
van der Geest	Low	64
Wu	Low	65
Xiao	Low	66
Ying	Unclear	67
Zhang	Low	68
Zhang	Low	69
Zhong	Low	70
Zhou 2019	Low	71

Of the smaller sample sizes, there were 13 studies with 100–1000 isolates and 21 with less than 100 isolates.

Data on drug susceptibility to azoles and other antifungal drugs are presented in Tables 3 and 4, respectively. A variety of methods were used to measure susceptibility, and there was great heterogeneity in how results were reported. We focus on reporting resistance percentages, according to CLSI or EUCAST methodologies as used in the study. Overall, these data from the last 5 years show that *C. albicans* was mostly susceptible to the major antifungal drug classes. The two large global studies showed overall low rates of resistance against azoles, echinocandins, polyenes, and 5-flucytosine.[21,22] However, there was a signal of regional variation, with 5.4% of Asia Pacific and 10.1% of South American isolates showing non-wild-type susceptibility to posaconazole. Of the 28 studies reporting azole susceptibility, 9 reported rates of resistance over 5%, ranging from 5% to 62%, with the majority lying between 5% and 25%. All of these studies were from middle-income countries: Kumar et al. India 2020,[41] Fay et al. Brazil 2019,[29] Sharifynia et al. Iran 2019,[58] Zhang et al. China 2019,[68] Zhang et al. China 2020,[70] Zhou et al. China 2019,[71] Ying et al. China 2016,[67] Lal et al. Pakistan 2019,[42] and Tasneem et al. Pakistan.[60] Of these, only Zhang et al. China 2019[68] and Zhang et al. China 2020[70] reported strictly invasive isolates, with fluconazole/voriconazole resistance rates of 3%/6% and 3%/10%, respectively. Although it was focused on non-sterile site isolates, the report from Kumar was notable in that they detected ~50% of high vaginal isolates of *C. albicans* were resistant to both fluconazole and voriconazole, whilst resistance was <5% from other body sites. The authors offered no explanation for this, but it is likely to indicate regular treatment for recurrent vulvovaginal infection.

Some 27 studies reported susceptibility to other antifungals (including anidulafungin, caspofungin, micafungin, amphotericin B, and flucytosine). The large global surveys by Castanheira et al. in 2017 and 2020[21,22] reported resistance rates <1%, and none of the other studies reported rates >5%.

Annual incidence and global distribution

Most established national estimates of the incidence of IC suggest rates between 2 and 10/100 000 population/year, with approximately 70% of all cases caused by *C. albicans*. However, none of the studies identified here from the past 5 years reported a population-based incidence estimate for invasive infection with *C. albicans*. Eight studies reported in-hospital incidence for various populations, using a wide range of different measures, as presented in Table 5.

Eighteen studies reported on the proportion of *Candida* infections that were caused by *C. albicans* (Table 6). The majority reported that the proportion was between 30% and 70%. Those reporting changes over time all noted a decreasing proportion of infections caused by *C. albicans*.

Candida albicans is globally distributed. Its incidence at the population level and the proportion of candidaemia it causes vary, but these differences may be related to features other than geography, such as consumption of antifungal agents, population demographics, and the prevalence of underlying conditions associated with infection.

Inpatient care and the length of stay in hospital

Length of hospital stay was reported in seven studies from a range of low-, middle-, and high-income settings (Table 7). Lengths of stay were generally in the range of 2–4 weeks and up to 2 months. It is not possible to determine how much of this length of stay is attributable to the infection or to the underlying condition.

Complications, sequelae, and disabilities

Two studies reported complications from *C. albicans* infection, specifically, metastatic infection resulting from bloodstream infection (Table 8). In a study of 225 candidaemia pa-

Table 2. Mortality.

Author/year	Study design		Study period	Country	Level of care	Population	Population description (*N*)	No. of patients with pathogen (*N*)	Mortality type, *N*/*N* (%)
Ahangarkani et al., 2020	PBS	MC	January 2017–August 2019	Iran	Tertiary	Children	Nosocomial candidaemia in patients undergoing intensive immunosuppressive therapy	54	All-cause mortality for nosocomial candidaemia: 44/109 (40%). Of this, 36% was attributable to *C. albicans*
Chandrasekar et al., 2018	Pooled *ad hoc* analysis of phase 3 trials	MC	NA	NA	NA	Adults and children	Neutropenic patients with candidaemia and invasive candidiasis ($N = 77$)	Neutropenic patients = 19, Non-neutropenic patients = 295	Overall mortality in neutropenic patients: 36/77 (46.8%) Overall mortality in non-neutropenic patients: 218/608 (35.9%)
Fu et al., 2017	RCS	SC	2012–2015	China	Tertiary	Children	Neonatal candidaemia ($n = 69$)	69	*Candida albicans* was associated with a mortality rate of 3.3%.
Ghanem Zoubi et al., 2019	RCS	SC	2009–2017	Israel	Tertiary	Adults	Patients with candidaemia and treated with fluconazole ($n = 158$)	66	In-hospital mortality 27/66 40.9%
Gong et al., 2016	PCS	MC	2009–2011	China	ICUs	NA	ICU patients with invasive candidiasis ($n = 306$)	98	In-hospital mortality 29.6%
Gonzalez-Lara et al., 2017	LBS	MC	2008–2014	Mexico City	Tertiary	NA	Patients with candidaemia ($n = 149$)	60	30-days mortality 38% (56/149). Not specified for *C. albicans*
Hsu et al., 2018	RCS	MC	2004–2015	Taiwan	Tertiary	Children	Hospitalised paediatric and neonatal patients with candidaemia ($n = 281$)	155	Mortality attributable to candidaemia Neonatal—32 (28.3%) Non-neonatal—40 (17.5%) In-hospital all-cause mortality Neonatal—41/96 (42.7%) Non-neonatal—47/185 (25.4%) Not specified for *C. albicans*
Lee et al., 2018	CCS	SC	2003–2015	Taiwan	Tertiary	Children	Paediatric patients with candidaemia 319 episodes of candidaemia occurring in 262 patients	148	30-day mortality 35/148 (23.6%) (day ≤7: 17/148 11.55%; day 8–30: 18/148 12.2%)
Li et al., 2017	CCS	SC	2006–2013	China	Tertiary	NA	Cancer patients with candidaemia ($n = 80$)	44	In-hospital mortality 12/44 27.3%
Dogan et al., 2020	PCS	MC	2015–2018	Turkey	NA	Adults	Candidaemia patients ($n = 342$)	162	10-day mortality 63/162 38.9%

Table 2. Continued

Author/year	Study design		Study period	Country	Level of care	Population	Population description (*N*)	No. of patients with pathogen (*N*)	Mortality type, *N*/*N* (%)
Mesini et al., 2017	PCS	SC	2005–2015	Italy	Tertiary	Children	Paediatric patients with invasive *Candida* infection $n = 262$	180	In-hospital mortality 14/180 8%
Raja et al., 2021	Retrospective and prospective study	MC	January 2006–June 2017	UK	Tertiary	NA	Patients with candidaemia ($n = 100$)	46	In-hospital mortality 24/46 52.2%
Ramos et al., 2016	PBS	MC	April 2010 and May 2011	Spain		NA	Patients with candidaemia (study was focused on outcome for mixed candidaemia)	336 cases of monomicrobial *C. albicans* candidaemia	30-day mortality 223/737 30.3% (for all monomicrobial candidaemias) 111/737 15.1% deaths attributable to candidaemia (for all monomicrobial candidaemias) [Mortality higher for mixed candidaemia, 73.3%]
Eliakim Raz et al., 2016	RCS	SC	2007–2014	Israel	Secondary and tertiary	NA	Patients with candidaemia ($n = 106$)	52 patients	30-day mortality rate, 60.1% (not specified for *C. albicans*) 90-day mortality rate 74.5% (not specified for *C. albicans*)
Muderris et al., 2020	RCS	SC	January 2015 and December 2017	Turkey	Tertiary	Adults	Patients with candidaemia ($n = 163$)	44	30-day mortality 15/44 30.6%
Murri et al., 2016	PCS	SC	November 2012–April 2014	Italy	Secondary	Adults	Patients with candidaemia ($n = 130$)	76	30-day mortality 23.4%
Ryan et al., 2019	PBS	SC	January 2004 and August 2018	Ireland	Tertiary	Adults	ICU patients with candidaemia ($n = 74$)	41	30-day mortality 12/41 (29%)
Ueda et al., 2019	RCS	MC	2010 and 2016	Japan	NA	Adults	Non-neutropenic patients with candidaemia who underwent ophthalmic examination ($n = 781$)	608	28-day mortality rate was 21.1% (not specified for *C. albicans*)
Ulu Kilic et al., 2017	RCS	MC	January 2010 and 2016	Ethiopia	Tertiary	NA	Patients with candidaemia ($n = 351$)	169	30-day mortality 61/169 (36.1%)

Table 2. Continued

Author/year	Study design		Study period	Country	Level of care	Population	Population description (*N*)	No. of patients with pathogen (*N*)	Mortality type, *N*/*N* (%)
Van der Geest et al., 2016	RCS	SC	January 2010 and December 2014	The Nether-lands	Tertiary	NA	Critically ill patients with invasive *Candida* infection ($n = 124$)	75	28-day mortality—41% (not specified for *C. albicans*)
Schwab et al., 2018	PCS	MC	2006–2015	Germany	Tertiary	NA	Patients with ICU acquired primary bloodstream infections (PBSI)	Not specified	30-days mortality—24.6%
Shahin et al., 2016	Prospective cohort study with modeling	MC	July 2009 and April 2011	UK	Tertiary	Adults	Non-neutropenic, critically ill adult patients	235 *Candida albicans* invasive fungal disease	Critical care unit mortality 82/235 (34.9%) In-hospital mortality 93/235 (49.5%)
Zhang et al., 2020	RCS	SC	January 2012–December 2018	China	Tertiary	Adults	Adult surgical patients with candidaemia ($n = 172$)	58	In-hospital mortality 19.2%
Zhang et al., 2019	RCS	SC	January 2012–October 2017	China	Tertiary	Adults	Adult hospitalised cases of candidaemia ($n = 179$)	64	Crude 30-day mortality 23/64 35.9%
Zhong et al., 2020	RCS	SC	1 January 2013 to 31 December 2018	China	Tertiary	Adults	Adult patients with *Candida albicans* bloodstream infection (CA-BSI) ($n = 117$)	93	28-day mortality (*n*,%) 31 (33.3%) 60-day mortality (*n*,%) 34 (36.6%) In-hospital mortality (*n*,%) 37 (39.8%)
Wu et al., 2018	RCS	SC	1 January 2010 and 31 December 2010	Taiwan	Tertiary	Adults	Patients with candidaemia ($n = 253$)	115	14-day mortality: 46/115 (40%) 30-day mortality: 62/115 (53.9%)

CCS = case control study; LSS = lab surveillance study; MC = multi-centre; NA = not available; PBS = population-based surveillance; PCS = prospective cohort study; RCS = retrospective cohort study; SC = single centre.

Table 3. Drug susceptibility to azoles.

Author/year	MIC method	Fluconazole	Isavuconazole	Itraconazole	Posaconazole	Voriconazole
Ahangarkani et al., 2020	CLSI-M60	GM: 0.192 Range: 0.063–4 MIC50: 0.125 MIC90: 2	GM: 0.017 Range: 0.016–0.063 MIC50: 0.016 MIC90: 0.031	ND	GM: 0.024 Range: 0.016–0.125 MIC50: 0.016 MIC90: 0.125	GM: 0.020 Range: 0.008–0.125 MIC50: 0.016 MIC90: 0.063
Castanheira et al., 2017	CLSI M59	MIC50: 0.12 MIC90: 0.25 S: 99.6% R: 0.4%	ND	ND	MIC50: 0.03 MIC90: 0.06	MIC50: 0.008 MIC90: 0.015 S: 99.9% R: <0.1%
Castanheira et al., 2020	CLSI-M60	R: 0.4% R (Asia Pacific): 0.0% R (Europe): 0.1% R (Latin America): 1.0% R (North America): 1.1%	ND	ND	R (Asia Pacific): 5.4% R (Europe): 1.2% R (Latin America): 10.1% R (North America): 4.2% NWT: 3.1%	R: 0.1% R (Asia Pacific): 0.0% R (Europe): 0.1% R (Latin America): 0.0% R (North America): 0.0%
Benedict et al., 2018	CLSI M27-A3	R (Neonates): 1.6% Age: 31 days to <1 year: 5.0% Ages 1–19 years: 0%	ND	ND	ND	ND
Lal et al., 2019	CLSI M44	S: 100% SDD: 0% R: 0%	ND	S: 29% SDD: 37.68% R: 62.3%	ND	S: 88.40% SDD: 11.6% R: 0%
Chen et al., 2017	CLSI M 27-S3 and S4	Range: 0.12–64 MIC50: 0.5 MIC90: 1 S: 96.5% SDD: 2.6% R: 0.9%	ND	ND	ND	Range: 0.003–0.5 MIC50: 0.008 MIC90: 0.03 S: 99.7% SDD: 0.3% R: 0%
Kumar et al., 2020	CLSI M27 and M60	High vaginal swab ($N = 59$) S: 50.85% R: 49.15% Urine ($N = 59$) S: 53% R: 6% Blood ($N = 7$) S: 85.7% I: 14.3% R: 0% E. Tube ($N = 12$) S: 100% R: 0% BAL ($N = 8$) S: 100% R: 0% I: 0% Bile ($N = 1$) S: 100% R: 0% Pus ($N = 1$) S: 100% R: 0%	ND	ND	ND	High vaginal swab ($N = 59$) S: 49.2% R: 50.9% Urine ($N = 59$) S: 98.3% R: 1.7% Blood ($N = 7$) S: 100% R: 0% I: 0% E. Tube ($N = 12$) S: 75% R: 25% BAL ($N = 8$) S: 75% R: 12.5% I: 12.5% Bile ($N = 1$) S: 100% R: 0% Pus ($N = 1$) S: 100% R: 0%

Table 3. Continued

Author/year	MIC method	Fluconazole	Isavuconazole	Itraconazole	Posaconazole	Voriconazole
		Sputum ($N = 5$) S: 100% R: 0% Swab ($N = 1$) S: 100% R: 0%				Sputum ($N = 5$) S: 100% R: 0% Swab ($N = 1$) S: 100% R: 0%
Gonzalez-Lara et al., 2017	CLSI-M27 A3 and its updated version in M27-S4.	Range: ≤1–8 MIC50: 1 MIC90: 1 S: 93.3% SDD: 3.3% R: 3.3%	ND	ND	ND	Range: ≤0.12 MIC50: 0.12 MIC90: 0.12 S: 100% SDD: 0% R: 0%
Guo et al., 2017	CLSI M27-S4	Range: 0.064–8 MIC50: 0.25 MIC90: 1 S: 99.4% SDD: 0.3% R: 0.3%	ND	Range: 0.016–2 MIC50: 0.25 MIC90: 0.5 S: 30.9% SDD: 67.9% R: 1.2%	ND	Range: 0.008–0.5 MIC50: 0.016 MIC90: 0.064 S: 99% SDD: 1% R: 0%
Jeon et al., 2019	VITEK 2 AST-YS07	S: 96.1% I: 1.9% R: 1.9%	ND	ND	ND	S: 92.2% I: 0% R: 7.8%
Li et al., 2017	ATB FUNGUS 3	Range: ≤1–16 MIC50: ≤1 MIC90: 2 S: 97.7%	ND	Range: <0.125–0.25 MIC50: ≤0.125 MIC90: ≤0.125 S: 97.7%	ND	Range: ≤0.06–1 MIC50: ≤0.06 MIC90: 0.25 S: 100%
Lindberg et al., 2019	Sensititre YeastOne EUCAST CBPs	Range: 0.12–4 MIC50: 0.25 MIC90: 0.5 S: 99%	ND	Range: 0.015–0.12 MIC50: 0.03 MIC90: 0.06 S: 97%	Range: 0.008–0.12 MIC50: 0.015 MIC90: 0.03 S: 99%	Range: 0.008–0.25 MIC50: 0.008 MIC90: 0.015 S: 99%
Dagi et al., 2016	CLSI-M27, A3	Range: 0.12–2.0 MIC50: 0.25 MIC90: 0.5 S: 100% SDD: 0% R: 0%	ND	ND	Range: <0.015–0.12 MIC50: <0.015 MIC90: 0.03 WT: 100%	Range: <0.015–0.06 MIC50: <0.015 MIC90: 0.03 S: 100% SDD: 0% R: 0%
Dogan et al., 2020	CLSI	Range: 0.125–0.5 MIC50: 0.125 MIC90: 0.125 S: 100% R: 0%	ND	ND	Range: 0.03–0.06 MIC50: 0.03 MIC90: 0.03 S: 100% R: 0%	Range: 0.015–0.03 MIC50: 0.015 MIC90: 0.03 S: 100% R: 0%
Ramla et al., 2016	Sensititre YeastOne	Range: <0.12–1 MIC50: <0.12–0.12 S: 100%	ND	Range: <0.015–0.06 MIC50: 0.03 S: 100%	Range: <0.008–0.06 MIC50: 0.015 S: 97.1%	Range: <0.008–0.03 MIC50: <0.008 S: 100%
Eliakim Raz et al., 2016	Etest	S: 96.2% R: 3.8%	ND	S: 100% R: 0%	ND	S: 100% R: 0%
Fay et al., 2019	CLSI M44-A2 Disk diffusion test	S: 69.2% SDD: 11.5% R: 19.2%	ND	ND	ND	ND

Table 3. Continued

Author/year	MIC method	Fluconazole	Isavuconazole	Itraconazole	Posaconazole	Voriconazole
Peron et al., 2016	CLSI (M27-A3 and M27-S4)	Range: <0.125–0.5 S: 100%	ND	Range: ≤0.015–0.125 S: 100%	ND	Range: ≤0.015–0.06 S: 100%
Ryan et al., 2019	Sensititre YeastOne	S: 98% R: 2%	ND	S: 95% R: 5%	ND	ND
Seyoum et al., 2020	VITEK 2 compact system using YST-21343 and AST-YS07 cards	S: 98% I: 22% R: 0%	ND	Not done	ND	S: 100%
Sharifynia et al., 2019	(CLSI) M27-A3	Range: 0.0125–>64 MIC50: 1 MIC90: 64 R: 16.1%	ND	Range: 0.016–>16 MIC50: 0.062 MIC90: 16 R: 21.9%	ND	ND
Zhang et al., 2020	CLSI broth dilution	Range: ≤0.5–16 MIC50: ≤1 MIC90: 4 S: 86.2% SDD: 10.3% R: 3.4%	ND	Range: 0.062–1 MIC50: ≤0.125 MIC90: 0.25	ND	Range: ≤0.03–≤ 4 MIC50: 0.06 MIC90: ≤1 S: 84.5% SDD: 5.2% R: 10.3%
Zhang et al., 2019	ATB FUNGUS 3 with clinical breakpoints (CBPs) defined by the CLSI or EUCAST	Range: ≤0.5–16 MIC50: ≤1 MIC90: 1 S: 89.1% SDD: 7.8% R: 3.1%	ND	Ranges: 0.062–1 MIC50: ≤0.125 MIC90: 0.125	ND	Ranges: ≤0.03–4 MIC50: ≤0.06 MIC 90: 0.125 S: 89.1% SDD: 4.7% R: 6.3%
Zhong et al., 2020	ATB FUNGUS 3 with clinical breakpoints (CBPs) defined by the CLSI or EUCAST	S: 95.3% I: 4.7% R: 0%	ND	S: 96.6% I: 1.1% R: 2.2%	ND	S: 100.0% I: 0% R: 0%
Zhou et al., 2019	CLSI M44 A2	S: 82% R: 18%	ND	S: 83% R: 17%	ND	S: 100% R: 0%
Tasneem et al., 2017	CLSI M44-A	S: 81.3% I: 0% R: 18.8%	ND	Not done	ND	S: 79.7% I: 0% R: 20.3%
Xiao et al., 2020	ATB FUNGUS 3	S: 95.2%	ND	S: 100%	ND	S: 97.6%
Ying et al., 2016	ATB FUNGUS 3	S: 95/115 (83%) SDD: 12/115 (10%) R: 8/115 (7%)	ND	ND	ND	S: 93/115 (81%) SDD: 6/115 (5%) R: 16/115 (14%)

Note: Susceptibility values are expressed as minimum inhibitory concentrations (MICs) in mg/l (EUCAST) or mg/ml (CLSI). GM = geometric mean, MIC50 = minimum inhibitory concentration of 50% of isolates, MIC90 = minimum inhibitory concentration of 90% of isolates; S, susceptible; SDD = susceptible dose dependent; I = intermediate; R = resistant; WT = wild-type; NWT = non-wild-type. ND = not determined. Data are given as provided in source documents.

Table 4. Drug susceptibility to other antifungal drugs.

Author/year	MIC method	Anidulafungin	Caspofungin	Micafungin	Amphotericin B	Flucytosine
Ahangarkani et al., 2020	CLSI-M60	GM: 0.022 Range: 0.008–4 MIC50: 0.008 MIC90: 0.25	ND	GM: 0.018 Range: 0.008–1 MIC50: 0.008 MIC90: 0.25	GM: 0.291 Range: 0.016–1 MIC50: 0.25 MIC90: 0.5	GM: 0.080 Range: 0.063–1 MIC50: 0.063 MIC90: 0.125
Castanheira et al., 2017	CLSI M59	MIC50: 0.015 MIC90: 0.03 S: 99.9% R: 0%	MIC50: 0.015 MIC90: 0.03 S: 99.8% R: 0.2%	MIC 50: 0.015 MIC90: 0.03 S: 99.8% R: 0.2%	MIC50: 1 MIC90: 1 WT: 100% NWT: 0%	ND
Castanheira et al., 2020	CLSI-M60	R: 0.1% R (Asia Pacific): 0% ($N = 203$) R (Europe): 0.1% ($N = 763$) R (Latin America): 0% ($N = 99$) R (North America): 0% ($N = 261$)	ND	R: 0.2% R (Asia Pacific): 0% ($N = 203$) R (Europe): 0.3% ($N = 763$) R (Latin America): 0% ($N = 99$) R (North America): 0% ($N = 261$)	R (Asia Pacific): 0% ($N = 203$) R (Europe): 0% ($N = 763$) R (Latin America): 0% ($N = 99$) R (North America): 0% ($N = 261$) NWT: 0%	ND
Benedict et al., 2018	CLSI M27-A3	Neonates R: 0% Non-neonate infants (ages 31 days to <1 year) R: 0% Non-infant children (ages 1–19 years) R: 1.6%	Neonates R: 0% Non-neonate infants (ages 31 days to <1 year) R: 0% Non-infant children (ages 1–19 years) R: 1.6%	Neonates R: 0% Non-neonate infants (ages 31 days to <1 year) R: 0% Non-infant children (ages 1–19 years) R: 1.6%	ND	ND
Lal et al., 2019	CLSI M44	ND	ND	ND	S: 95.7% SDD: 4.4% R: 0%	ND
Chen et al., 2017	CLSI M 27-S3 and S4	Range: 0.06–1 MIC50: 0.015 MIC90: 0.12 S: 99.4% I: 0.3% R: 0.3%	Range: 0.008–1 MIC50: 0.12 MIC90: 0.5 S: 99.7% I: 0% R: 0.3%	Range: 0.008–1 MIC50: 0.008 MIC90: 0.015 S: 99.7% I: 0% R: 0.3%	ND	ND
Kritikos et al., 2018	Sensititre YeastOne	NWT: 2.85%	NWT: 1.4%	NWT: 1.27%	ND	ND

Table 4. Continued

Author/year	MIC method	Anidulafungin	Caspofungin	Micafungin	Amphotericin B	Flucytosine
Kumar et al., 2020	CLSI M27 and M6	ND	High vaginal swab S: 100% I: 0% R: 0% Urine S: 100% I: 0% R: 0% Blood S: 100% E. Tube S: 100% BAL S: 100% Bile S: 100% Pus S: 100% Sputum S: 100% Swab S: 100%	ND	High vaginal swab (HVS) S: 96.6% I: 1.7% R: 1.7% Urine S: 98.4% I: 0% R: 1.7% Blood S: 100% E. Tube S: 100% BAL S: 87.5% R: 12.5% Bile S: 100% Pus S: 100% Sputum S: 100% Swab S: 100%	ND
Gonzalez-Lara et al., 2017	CLSI-M27 S4	ND	Range: ≤0.25–1 MIC50: 0.25 MIC90: 0.25 S: 93.3% SDD: 1.6% R: 5%	Range: ≤0.06–1 MIC50: 0.06 MIC90: 0.06 S: 96.6% SDD: 1.6% R: 1.6%	ND	ND
Guo et al., 2017	CLSI M27-S4	ND	Range: 0.008–0.5 MIC50: 0.125 MIC90: 0.25 S: 97.9% I: 2.1% R: 0%	Range: 0.008–0.5 MIC50: 0.008 MIC90: 0.064 S: 99.7% I: 0.3% R: 0%	Range: 0.016–1 MIC50: 0.5 MIC90: 1 S: 100% I: 0% R: 0%	Range: 0.064–128 MIC50: 0.064 MIC90: 0.125 S: 97.5% I: 0% R: 2.5%
Jeon et al., 2019	VITEK 2 AST-YS07	ND	S: 100% I: 0% R: 0%	S: 100% I: 0% R: 0%	S: 94.1% I: 2% R: 3.9%	S: 100% I: 0% R: 0%
Li et al., 2017	ATB FUNGUS 3	ND	ND	ND	Range: ≤0.5–1 MIC50: ≤0.5 MIC90: 1	Range: ≤4–16 MIC50: ≤4 MIC90: ≤4 S: 95.5%
Lindberg et al., 2019	Sensititre YeastOne EUCAST CBPs	Range: 0.015–0.12 MIC50: 0.03 MIC90: 0.06 S: 83% (EUCAST) S: 100% (CLSI)	Range: 0.015–0.12 MIC50: 0.03 MIC90: 0.06 S: 100% (CLSI)	Range: 0.008–0.06 MIC50: 0.008 MIC90: 0.015 S: 97%(EUCAST) S: 100% (CLSI)	Range: 0.25–1 MIC50: 0.5 MIC90: 1 S: 100% (EUCAST)	Range: 0.06–0.5 MIC50: 0.06 MIC90: 0.12

Table 4. Continued

Author/year	MIC method	Anidulafungin	Caspofungin	Micafungin	Amphotericin B	Flucytosine
Dagi et al., 2016	CLSI-M27, A3	Range: 0.015–0.12 MIC50: 0.015 MIC90: 0.03 S: 100% I: 0% R: 0%	Range: ≤0.008–0.12 MIC50: 0.015 MIC90: 0.06 S: 100% I: 0% R: 0%	ND	Range: 0.12–1.0 MIC50: 0.12 MIC90: 0.25 S: 100% I: 0% R: 0%	ND
Dogan et al., 2020	CLSI	ND	Range: 0.03–0.25 MIC50: 0.06 MIC90: 0.25 R: 0%	ND	Range: 0.5–1 MIC50: 1 MIC 90: 1 R: 0%	ND
Ramla et al., 2016	Sensititre YeastOne	Range: <0.015–0.06 MIC50: 0.03 S: 100%	Range: 0.015–0.06 MIC50: 0.03 S: 100%	Range: <0.008–0.015 MIC50: <0.08 S: 100%	Range: <0.12–0.25 MIC50: 0.25 S: 100%	Range: <0.06–>64 MIC50: 0.06 S: 94.2%
Eliakim Raz et al., 2016	Etest	R: 0%	R: 0%	ND	R: 1.9%	ND
Peron et al., 2016	CLSI (M27-A3 and M27-S4)	ND	Range: 0.015–0.125 S: 100%	ND	Range: 0.125–1.00 S: 100%	Range: 0.125–1.00 S: 100%
Ryan et al., 2019	Sensititre YeastOne	ND	S: 100% I: 0% R: 0%	ND	S: 100% I: 0% R: 0%	S: 97% I: 0% R: 3%
Seyoum et al., 2020	VITEK 2 compact system using YST-21343 and AST-YS07	ND	S: 96.2% I: 0% R: 3.8%	S: 96.2% I: 0% R: 3.8%	ND	S: 96% I: 3% R: 1%
Sharifynia et al., 2019	(CLSI) M27-A3	ND	Range: 0.008–8 MIC50: 0.125 MIC90: 0.5 R: 0.6%	ND	ND	ND

Table 4. Continued

Author/year	MIC method	Anidulafungin	Caspofungin	Micafungin	Amphotericin B	Flucytosine
Zhang et al., 2020	EUCAST	ND	ND	ND	Ranges: ≤0.25–1 MIC50: ≤0.5 MIC90: 0.5 S: 100%	ND
Zhang et al., 2019	ATB FUNGUS 3 with clinical breakpoints (CBPs) defined by the CLSI or EUCAST	ND	ND	ND	Range: ≤0.25–1 MIC50: ≤0.5 MIC90: 0.5 S: 100%	ND
Zhong et al., 2020	ATB FUNGUS 3 with clinical breakpoints (CBPs) defined by the CLSI or EUCAST	ND	ND	ND	S: 100.0%	S: 96.8% R: 3.2%
Zhou et al., 2019	CLSI M44 A2	ND	S: 100% R: 0%	S: 100% R: 0%	S: 100% R: 0%	ND
Tasneem et al., 2017	CLSI M44-A2	ND	ND	ND	S: 97.7% R: 2.3%	ND
Xiao et al., 2020	ATB FUNGUS 3	ND	S: 100% R: 0%	ND	S: 97.6% R: 2.4%	ND

Note: Susceptibility values are expressed as minimum inhibitory concentrations (MICs) in mg/l (EUCAST) or mg/ml (CLSI). GM = geometric mean, MIC50 = minimum inhibitory concentration of 50% of isolates, MIC90 = minimum inhibitory concentration of 90% of isolates; S, susceptible; SDD = susceptible dose dependent; I = intermediate; R = resistant; WT = wild-type; NWT = non-wild-type. ND = not determined. Data are given as provided in source documents.

Table 5. Annual incidence.

Author/year	Study design	Study design	Study period	Country	Level of care	Population	Population description (*N*)	No. of patients with pathogen (*N*)	Incidence (annual, other)
Ahangarkani et al., 2020	PBS	MC	January 2017–August 2019	Iran	Tertiary	Children	Nosocomial candidaemia in patients undergoing intensive immunosuppressive therapy	54	4.1/1000 is the incidence for candidaemia overall
Benedict et al., 2018	LBS	MC	2009–2016	USA	Not specified	Children	Paediatric candidaemia	209	Neonates 31.5/100 000 births in 2009 10.7–11.8/100 000 births between 2012 and 2015 Infants 52.1/100 000 in 2009 15.7–17.5 between 2012 and 2015 Non-infant children 1.8/100 000 in 2009 0.8/100 000 in 2014.
Fu et al., 2017	RCS	SC	2012–2015	China	Tertiary	Children	Neonatal candidaemia	69	The incidence of candidaemia was 1.4% of births. 43.5% *C. albicans*
Gong et al., 2016	PCS	MC	2009–2011	China	ICUs	Not specified	ICU patients with invasive candidiasis ($n = 306$)	98	The incidence rate of invasive *Candida* infection was 0.32%; (total) 40.1% *C. albicans*
Hsu et al., 2018	RCS	MC	2004–2015	Taiwan	Tertiary	Children	Hospitalised paediatric and neonatal patients with candidaemia ($n = 281$)	155	Incidence rate per 100 000 inpatient days Neonatal—26.9 Infant PICU—147.2 Infant general wards—16.7 Incidence rate per 10 000 admissions Neonatal—55.0 Infant PICU—88.5 Infant general wards—7.5
Ramos et al., 2016	PBS	MC	April 2010 and May 2011	Spain	Not specified	Not specified	Patients with candidaemia (study was focused on outcome for mixed candidaemia)	336 cases of monomicrobial *C. albicans* candidaemia	0.89/1000 admissions
VanderGeest et al., 2016	RCS	SC	January 2010 and December 2014	The Nether-lands	Tertiary	Not specified	Critically ill patients with invasive *Candida* infection ($n = 124$)	75	Incidence of invasive candidiasis was 10 per 1000 ICU admissions (not specifically *C. albicans*)
Shahin et al., 2016	Prospective cohort study with modeling	MC	July 2009 and April 2011	UK	Tertiary	Adults	Non-neutropenic, critically ill adult patients	235 *Candida albicans* invasive fungal disease	The incidence of *Candida* IFD developed during the critical care unit stay was 3.1 cases per 1000 admissions

LBS = laboratory-based surveillance; MC = multi-centre; NA = not available; PBS = population-based surveillance; PCS = prospective cohort study; RCS = retrospective cohort study; SC = single centre.

Table 6. Proportion of invasive candidiasis caused by *C. albicans*.

Author/year	Study design		Study period	Country	Population description (*N*)	Proportion of invasive candidiasis caused by *C. albicans*
Ahangarkani et al., 2020	PBS	MC	January 2017–August 2019	Iran	Nosocomial candidaemia in patients undergoing intensive immunosuppressive therapy	*Candida albicans* 54/109 candidaemia (49%)
Lal et al., 2019	RCS	SC	December 2018–December 2019	Pakistan	Patients with *Candida* associated urinary tract infection	*Candida albicans* 69/168 invasive candiduria (41.1%)
Kumar et al., 2020	RCS	MC	December 2015 and June 2018	India	All patients (sterile and non-sterile isolates	*Candida albicans* 153/228 isolates (67.0%) High vaginal swabs = 59/76 (78%) Urine samples = 59/77 (78%) Blood samples = 7/23 (31%) Endotracheal tube = 12/21 (53%)
Jamil et al., 2017	PCS	SC	January–October 2014	Pakistan	Chronic kidney disease inc transplant	*Candida albicans* 114/164 isolates (69.5%) from sterile and non-sterile sites
Lee et al., 2018	Case control study	SC	2003–2015	Taiwan	Paediatric patients with candidaemia	*Candida albicans* 148/319 candidaemia episodes (46.4%)
Li et al., 2017	Case control study	SC	2006–2013	China	Cancer patients with candidaemia ($n = 80$)	*Candida albicans* 44/80 candidaemia episode (55.0%)
Lindberg et al., 2019	LBS	SC	2013–2016	Sweden	Patients with candidaemia ($n = 143$)	*Candida albicans* 93/143 candidaemia episode (65%)
Ramla et al., 2016	PBS	SC	Not stated	South Africa	Adult cancer patients scheduled for either radiation or chemotherapy, with oral *Candida* infection ($n = 109$)	Normal healthy individuals C. *albicans* 21/49 (42.8%) Cancer patients *Candida albicans* 29/59 (49.15%)
Fay et al., 2019	RCS	MC	2003–2015	Brazil	Adults and children with superficial and systemic fungal infections	*Candida albicans* 450/840 fungal pathogen isolates (53.6%) *Candida albicans* 450/486 *Candida* isolates (92.6%)
Ueda et al., 2019	RCS	MC	2010 and 2016	Japan	Adult non-neutropenic patients with candidaemia	*Candida albicans* 120/154 candidaemia (77.9%)

Table 6. Continued

Author/year	Study design		Study period	Country	Population description (*N*)	Proportion of invasive candidiasis caused by *C. albicans*
Ulu Kilic et al., 2017	RCS	MC	January 2010 and 2016	Ethiopia	Patients with candidaemia ($n = 351$)	*Candida albicans* 169/351 candidaemia (48.1%) Non-*albicans* candidaemia varied by service Haematology: 19/36 (52.7%) Paediatric ICU: 22 (45.8%) Medical ICU: 16 (47.0%) General surgery ICU: 26 (60.4%) Recovery ICUs: 8 (34.8%)
Seyoum et al., 2020	LBS	SC	January 2018 to September 2018	Ethiopia	NA	*Candida albicans* 104/208 non-sterile *Candida* isolates (49.8%)
Zhang et al., 2020	RCS	SC	January 2012 to December 2018	China	Adult surgical patients with candidaemia ($n = 172$)	*Candida albicans* 58/172 candidaemia episodes (33.7%) % by year 2012 ($n = 24$); 32% 2013 ($n = 23$); 30% 2014 ($n = 11$); 19% 2015 ($n = 18$); 20% 2016 ($n = 43$); 41% 2017 ($n = 17$); 33% 2018 ($n = 36$); 32%
Zhang et al., 2019	RCS	SC	January 2012 to October 2017	China	Adult hospitalised cases of candidaemia ($n = 179$)	*Candida albicans* 64/180 candidaemia episodes (35.6%) % by year 2012 ($n = 27$); 30% 2013 ($n = 28$); 35% 2014 ($n = 19$); 36% 2015 ($n = 27$); 30% 2016 ($n = 51$); 40% 2017 ($n = 28$); 35%
Tedeschi et al., 2016	RCS	MC	January 2012 to December 2013	Italy	Adult patients with candidaemia cared for in Internal Medical Wards ($n = 232$)	*Candida albicans* 136/232 candidaemia episodes (59%) % by service Tertiary care teaching hospitals 63% General hospitals with 400–700 beds: 49% General and community hospitals with 200–400 beds: 50% Community hospitals with less than 200 beds: 68%
Xiao et al., 2020	RCS	MC	January 2008 to December 2017	China	ICU patients with fungal bloodstream infections ($n = 81$)	*Candida albicans* 42/98 candidaemia episodes (43%) Over the 10-year study period, the prevalence of *C. albicans* decreased, whilst other *Candida* spp. increased each year
Ying et al., 2016	RCS	MC	November 2013 and January 2014	China	Adults with vulvovaginal candidiasis ($n = 135$)	*Candida albicans* 115/135 clinical isolates (85%)
Ahangarkani et al., 2020	PBS	MC	January 2017 to August 2019	Iran	Nosocomial candidaemia in children undergoing intensive immunosuppressive therapy	54 *C. albicans*/109 candidaemia episodes (49%)

LBS = laboratory-based surveillance; MC = multi-centre; NA = not available; PBS = population-based surveillance; PCS = prospective cohort study; RCS = retrospective cohort study; SC = single centre.

Table 7. Length of stay.

Author/year	Study design		Study period	Country	Level of care	Population	Population description (*N*)	No. of patients with pathogen (*N*)	Length of stay
Ryan et al., 2019	PBS	SC	January 2004 and August 2018	Ireland	Tertiary	NA	ICU patients with candidaemia ($n = 74$)	41	The mean ICU LOS was 21 days
Ulu Kilic et al., 2017	RCS	MC	January 2010 and 2016	Ethiopia	Tertiary	NA	Patients with candidaemia ($n = 351$)	169	LoS prior to candidaemia 16 (0–120)
VanderGeest et al., 2016	RCS	SC	January 2010 and December 2014	The Nether-lands	Tertiary	NA	Critically ill patients with invasive *Candida* infection($n = 124$) Group A: patients who stepped-down to fluconazole. Group B: patients only treated with an echinocandin	75	Length of ICU stay (days) Group A (26) Group B (16)
Shahin et al., 2016	Prospective cohort study with modeling	MC	July 2009 and April 2011	UK	Tertiary	Adults	Non-neutropenic, critically ill adult patients	235	Median length of stay (days [IQR]) Critical care unit 12 (6–24) Acute hospital 33 (15-58)
Zhang et al., 2019	RCS	SC	January 2012–October 2017	China	Tertiary	Adults	Adult hospitalised cases of candidaemia ($n = 179$)	64	Median length of stay (days [IQR]) 28 (21–38)
Zhong et al., 2020	RCS	SC	1 January 2013–31 December 2018	China	Tertiary	Adults	Adult patients with *Candida albicans* bloodstream infection (CA-BSI) ($n = 117$)	93	Total ICU stay days (IQR) 8.0 (0.0–31.5) Total hospitalisation days (IQR) 33.0 (15.0–51.0) Hospital stay prior to candidaemia (days) (IQR) 12.0 (2.0–26.5)
Wu et al., 2018	RCS	SC	1 January 2010 and 31 December 2010	Taiwan	Tertiary	Adults	Patients with candidaemia ($n = 253$) 270 candidaemia episodes in 253 adult patients during the study period	115	Length of stay in days 58.8

MC = multi-centre; NA = not available; PBS = population-based surveillance; RCS = retrospective cohort study; SC = single centre.

Table 8. Complications/sequelae.

Author/year	Study design		Study period	Country	Level of care	Population	Population description	No. of patients with pathogen	Complications/sequelae
Shin et al., 2020	RCS	MC	2007–2016	Korea	Tertiary	Adults	Patients with candidaemia ($n = 225$)	82	4.4% of *C. albicans* patients had serious sequelae (distant infection of eye, heart, or bone)—OR vs. non-*albicans Candida* was 5.12 in multivariable regression
Ueda et al., 2019	RCS	MC	2010 and 2016	Japan	Not specified	Adults	Non-neutropenic patients with candidaemia who underwent ophthalmic examination ($n = 781$)	608	Following candidaemia: Incidence of possible ophthalmologic candidiasis 20% Incidence of confirmed ophthalmologic candidiasis 12.8%

MC = multi-centre; RCS = retrospective cohort study.

tients, Shin et al.[59] found that 4.4% of the 82 patients with *C. albicans* had metastatic infection—an odds ratio of 5.12 ($P < .001$) compared to patients with non-*albicans* candidaemia. Ueda et al.[62] found that 12.8% of patients in Japan with *C. albicans* candidaemia had subsequent ophthalmologic infection. In both cases, patients were specifically screened for infection.

Preventability

The search identified eight papers highlighting risk factors for invasive disease caused by *C. albicans* (see Table 9) but none addressing the effectiveness of risk factor mitigations. The risk factors generally reflect those well established for candidaemia—i.e., the presence of central venous catheters, use of broad-spectrum antibiotics, administration of total parenteral nutrition, recent surgery, and immunosuppression (including chronic kidney or liver disease, diabetes, and critical illness). In paediatric population, premature birth and admission to the ICU were significant risk factors. The presence of multiple risk factors was frequently reported. Dogan et al. reported that *C. albicans* candidaemia was associated with a higher rate of mortality compared to non-*albicans* candidaemia.

Trends in the last decade

Six studies were identified that reported specifically on the 5-year trends for *C. albicans* (Table 10). They generally found that the proportion of *Candida* infections caused by this organism was decreasing over time. Benedict et al.[20] and Ryan et al.[54] also found that the overall incidence of candidaemia was decreasing over time in paediatric and adult populations.

Discussion

Candida albicans is an important fungal pathogen, widely distributed across the globe, which results in a high but ill-defined burden of disease and associated healthcare costs.[72]

In-hospital estimates of incidence and species distribution indicate that both the proportion and number of infections caused by *C. albicans* have decreased relative to other *Candida* species in both paediatric and adult populations over the past few decades. Most established national estimates of the incidence of IC suggest rates between 2 and 10/100 000 population annually,[73] but we found no population-based incidence estimates for invasive infection with *C. albicans* published in the study period, representing a significant gap in the literature. Although several studies were found reporting on hospital-level incidence for various populations, the lack of robust multi-country population-weighted incidence estimates is a concern.

A broad range of mortality rates for in-hospital and 30-day mortality were described, with most studies finding rates of 20%–50%. Hospital lengths of stay of 2–4 weeks (and up to 40–60 days in patients with endocarditis)[74,75] were found and are a reasonable starting estimate. The literature suggests that complications such as endophthalmitis and endocarditis are rare (<10%) in adults and older children, but higher in neonates (10%–50%).[76–78] However, these rates for mortality, complications, and hospital lengths of stay are highly dependent on clinical presentations, underlying conditions, site of infection and clinical services available—furthermore, they fail to define what is attributable to the infection itself. Well-designed prospective epidemiological studies are needed to fill these knowledge gaps.

Our search indicates that antifungal resistance is relatively uncommon globally, and particularly in sterile site isolates. Some studies did report high rates of azole resistance (ranging from 20% to 60%), especially amongst non-sterile site isolates from middle-income settings.[29,41,58,71,42,60] This is alarming given that invasive disease is caused by commensal organisms. The highest rate of azole resistance in a study with exclusively blood-derived isolates was 10% resistance to voriconazole.[69] Robust and systematic surveillance systems are needed to monitor the threat of azole resistance.

Modes of transmission for *C. albicans* are well understood. Several studies reported on the risk factors for infection with

Table 9. Risk factors.

Author/year	Study design		Study period	Country	Level of care	Population	Population description (*N*)	No. of patients with pathogen (*N*)	Risk factors/impact
Ahangarkani et al., 2020	PBS	MC	January 2017–August 2019	Iran	Tertiary	Children	Nosocomial candidaemia in patients undergoing intensive immunosuppressive therapy	54	Multiple underlying conditions were common for all candidaemias. CVC use (97.24%), chemotherapy (59.63%), previous broad-spectrum antibiotic therapy or prophylaxis (66.05%), previous corticosteroid therapy or prophylaxis (57.79%), prolonged ICU stay (48.62%), previous fluconazole therapy or prophylaxis (46.78%), mechanical ventilation (40.36%), TPN (32.11%), catheters other than CVC (nephrostomy tube, ventriculoperitoneal and peritoneal shunt, and urine catheter) (25.6%), haemodialysis (8.25%), recent abdominal surgery (17.43%) and transplantation (7.3%). *Candida albicans* vs. non-*albicans* infection was relatively less likely in patients with neutropaenia
Benedict et al., 2018	LBS	MC	2009–2016	USA	Not specified	Children	Paediatric candidaemia	209	Risk factors included premature birth and ICU admission. Haematologic malignancy was the most common underlying condition among non-infant children with candidaemia
Lal et al., 2019	RCS	SC	December 2018–December 2019	Pakistan	Tertiary	Not specified	Patients with *Candida albicans* urinary tract infection	69	Age >45 years, female sex, previous use of antibiotics, urinary catheterisation and stay in ICU >1 week
Fu et al., 2017	RCS	SC	2012–2015	China	Tertiary	Children	Neonatal candidaemia ($n = 69$)	69	Standard risk factors for candidaemia were observed, including CVC, ventilation, prolonged antibiotics, but the authors did not specifically quantify for *C. albicans*
Hsu et al., 2018	RCS	MC	2004–2015	Taiwan	Tertiary	Children	Hospitalised paediatric and neonatal patients with candidaemia ($n = 281$)	155	Most cases occurred in infants with very low birth weight. Other risk factors: Central intravenous catheter (CVC) (94.2%), use of broad-spectrum antibiotics (91.8%), stay in an ICU (69.3%), receipt of parenteral nutrition (64.6%), and underlying neurological sequelae (36.0%). The majority had ≥4 risk factors and/or underlying illness were identified. Candidaemia in general, not specific to *C. albicans*

Table 9. Continued

Author/year	Study design		Study period	Country	Level of care	Population	Population description (*N*)	No. of patients with pathogen (*N*)	Risk factors/impact
Cuervo et al., 2017	RCS	MC	2006–2015	Spain and Argentina	Tertiary	Adults	Candidaemia of urinary tract source $n = 128$	68	Not specified for *C. albicans*, but in general—chronic kidney disease (53.9%), neoplasms (52.3%), and diabetes mellitus (47.7%) were the most frequent comorbidities. Antibiotic therapy (89.8%), undergoing surgical intervention (39.8%), corticosteroid therapy (22.7%), and the use of other immunosuppressive drugs (10.2%) were the most common other risk factors for candidaemia. Effect size not estimated
Dogan et al., 2020	PCS	MC	2015–2018	Turkey	Not stated	Adults	Candidaemia patients ($n = 342$)	162	*Candida albicans* infection compared to non-*albicans* (OR = 1.7 [1.06–2.82]; $P = .027$) was significantly associated with mortality. Risks for acquisition not assessed
Raja et al., 2021	Retrospective and prospective study	MC	January 2006–June 2017	UK	Tertiary	Not specified	Patients with candidaemia ($n = 100$) A total of 102 episodes of candidaemia on 100 patients	*Candida albicans* was the leading cause of candidaemia which accounted for 45% (46) of all episodes	The risk factors in *C. albicans* and non-*C. albicans* groups were comparable which included intensive care unit (ICU) stay (15% vs. 10%), the presence of intravascular line (35% vs. 42%), previous antibiotic exposure (39% vs. 49%), surgical intervention (19% vs. 19%), mechanical ventilation (5% vs. 8%), total parenteral nutrition (30% vs. 27%) and urinary catheters (33 vs. 38) The comorbidities in both groups (*C. albicans* and non-*C. albicans*) were solid organ cancer (15&14), haematology malignancy (1&3), steroid use (14&13), diabetes (9&7), and chemotherapy (2&4). Main sources of candidaemia in *C. albicans* were line (12), respiratory (10) and urinary tracts (6)

LBS = laboratory-based surveillance; MC = multi-centre; NA = not available; PBS = population-based surveillance; PCS = prospective cohort study; RCS = retrospective cohort study; SC = single centre.

Table 10: Trends in the last 10 years.

Author/year	Study design		Study period	Country	Trends last 10 years
Benedict et al., 2018	LBS	MC	2009–2016	USA	The incidence in neonates decreased from 31.5 cases/100 000 births in 2009 to 10.7 to 11.8 cases/100 000 births between 2012 and 2015, the incidence in infants decreased from 52.1 cases/100 000 in 2009 to 15.7 to 17.5 between 2012 and 2015, and the incidence in non-infant children decreased steadily from 1.8 cases/100 000 in 2009 to 0.8 in 2014
Chen et al., 2017	Retrospective descriptive analysis	SC	2007–2012	Taiwan	Increasing trend for the proportion of non-*albicans Candida* species of all *Candida* isolates ($P = .04$)
Kakeya et al., 2018	PBS	MC	2003–2014	Japan	The frequency of *C. albicans* was 58.2% in 2003, approx. 40% for 2005–2011, approx. 30% in 2012 and 2014, (with a temporary increase to 49.5% in 2013) Proportion of *C. albicans* infections was significantly more in the first half of the study period, compared to second half (42.5% vs. 37.4%) $P = .03$
Raja et al., 2021	Retrospective and prospective study	MC	January 2006–June 2017	UK	The number of *C. albicans* candidaemias fluctuated every year with no clear linear trend
Eliakim Raz et al., 2016	RCS	SC	2007–2014	Israel	Allowing for variations in candidaemia rate, *C. albicans* remains the overall leading cause of *Candida* BSI, but the proportion of candidaemis caused by *C. albicans* fell from 52.8% to 35.5% during the study period
Ryan et al., 2019	PBS	SC	January 2004 and August 2018	Ireland	A reduction in the incidence of *C. albicans* was observed from 2004 to 2018

LBS = laboratory-based surveillance; MC = multi-centre; PBS = population-based surveillance; RCS = retrospective cohort study; SC = Single centre.

C. albicans, which are broadly similar to those identified for all IC. Some studies also provided evidence on mitigation strategies, such as prophylaxis in neonates[79] and prophylaxis in haematology patients,[80] but the evidence base for effective strategies needs to be developed and tested in a variety of settings to inform future guidelines.

Our review is subject to several limitations that must be acknowledged. First, there may be publication bias because we did not retrieve studies on epidemiology and antifungal resistance from low- and middle-income countries. This could be due to a lack of research in these areas or because studies were published locally with limited funding and not indexed in international databases. Second, our search strategy may have been subject to selection bias, as we only included data produced by traditional commercial or academic publishers. Third, we were unable to evaluate the impact of the COVID-19 pandemic on *C. albicans* infections as our review only included papers published until February 2021. Therefore, it is crucial to interpret our findings with caution and to consider these limitations when drawing conclusions.

Nevertheless, we conducted a comprehensive systematic review on *C. albicans*, which gathered a wealth of data and identified major areas where existing data need to be strengthened. One of the notable strengths of our study is its emphasis on the need for stronger surveillance systems and epidemiology studies. This is crucial as it can provide a better understanding of the disease burden and global distribution of *C. albicans*, as well as identify at-risk populations and dispersion patterns. With this information, preventative measures can be developed and implemented more effectively. Our study also emphasises the need for a better understanding of the clinical manifestations and susceptibility profiles for different molecular types of *C. albicans*. This knowledge could potentially inform individualised treatment options, leading to better outcomes for patients.

This review has helped to inform the ranking of pathogens in the WHO FPPL. It has gathered a wealth of data on *C. albicans* in one place, but also identified major areas where existing data need to be strengthened. These include accurate estimates of disease burden, better evidence for infection

prevention strategies, and improved systemic surveillance of emerging antifungal resistance.

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