Medical Mycology, 2024, **62**, myae041
https://doi.org/10.1093/mmy/myae041
Original Article

Candida glabrata (*Nakaseomyces glabrata*): A systematic review of clinical and microbiological data from 2011 to 2021 to inform the World Health Organization Fungal Priority Pathogens List

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Abstract

Recognising the growing global burden of fungal infections, the World Health Organization (WHO) established an advisory group consisting of experts in fungal diseases to develop a Fungal Priority Pathogen List. Pathogens were ranked based on their research and development needs and perceived public health importance using a series of global surveys and pathogen characteristics derived from systematic reviews. This systematic review evaluates the features and global impact of invasive disease caused by *Candida glabrata* (*Nakaseomyces glabrata*). PubMed and Web of Science were searched for studies reporting on mortality, morbidity (hospitalization and disability), drug resistance (including isolates from sterile and non-sterile sites, since these reflect the same organisms causing invasive infections), preventability, yearly incidence, diagnostics, treatability, and distribution/emergence in the last 10 years. *Candida glabrata* (*N. glabrata*) causes difficult-to-treat invasive infections, particularly in patients with underlying conditions such as immunodeficiency, diabetes, or those who have received broad-spectrum antibiotics or chemotherapy. Beyond standard infection prevention and control measures, no specific preventative measures have been described. We found that infection is associated with high mortality rates and that there is a lack of data on complications and sequelae. Resistance to azoles is common and well described in echinocandins—in both cases, the resistance rates are increasing. *Candida glabrata* remains mostly susceptible to amphotericin and flucytosine. However, the incidence of the disease is increasing, both at the population level and as a proportion of all invasive yeast infections, and the increases appear related to the use of antifungal agents.

Key words: *Nakaseomyces glabrata*, *Candida glabrata*, invasive fungal infection, candidaemia, antifungal resistance.

Received: September 11, 2023. **Revised:** December 3, 2023. **Accepted:** April 27, 2024

Introduction

Fungal pathogens cause a high disease burden in humans, animals, and plants and are major threats to global health,[1] although the true burden remains ill-defined. People who are immunocompromised by underlying health conditions such as cancer, critical illness, chronic lung disease, tuberculosis, and HIV or who are taking immunosuppressive drugs are most vulnerable to severe fungal infections.[2,3]

Candida species are important human pathogens. Systematic surveillance by the Centers for Disease Control in the USA shows that they are the fourth-leading cause of all bloodstream infections and third-leading in intensive care settings.[4] Invasive candidiasis is associated with significant morbidity and mortality and considerable economic burden.[5,6]

Over 90% of all cases of candidaemia are caused by five species: *C. albicans*, *C. glabrata* (now called *Nakaseomyces glabrata*), *C. parapsilosis*, *C. tropicalis*, and *C. krusei* (now called *Pichia kudriavzevii*).[7] *Candida glabrata* (*N. glabrata*, hereafter *C. glabrata*) typically causes a minority of candidaemia cases, but the proportion has increased rapidly over recent decades, and it is now occasionally reported causing as many cases as *C. albicans*.[8,9]

Candida glabrata is an important pathogen due to its increasing incidence and emerging resistance to multiple antifungal agents.[10] Infection is associated with a high case fatality rate,[11,12] in addition to adverse impacts on length of hospitalization and disability outcomes.[13] In common with many other fungal infections, diagnosing *C. glabrata* infection can also be challenging as the symptoms are non-specific and can vary depending on the site of infection (e.g., abdominal candidiasis or vaginitis).[14–16] Consequently, preventing and treating *C. glabrata* infections can be difficult due to its unique biological features and increased resistance to multiple antifungal medications, making it a formidable pathogen to manage.[17]

In recognition of the increasing global health threat of invasive fungal infections, the World Health Organization (WHO) established an advisory group consisting of experts in fungal diseases to develop a Fungal Priority Pathogen List (WHO FPPL). The WHO FPPL was based on a discrete choice experiment conducted among international fungal disease experts, with individual pathogens ranked using pre-defined criteria. Because surveillance of fungal infection is often *ad hoc*, data about the true incidence and health burden of *C. glabrata* are incomplete. Therefore, these pre-defined criteria were established through a series of systematic reviews, such as this one, which examines *C. glabrata* against the following set of criteria: mortality, hospitalization and disability, antifungal drug resistance, preventability, yearly incidence, and global distribution and emergence over 10 years. The review also identifies knowledge gaps and consequent research needed to improve outcomes from severe infections caused by *C. glabrata*.

Methods

Search strategies

We conducted a comprehensive search for publications in English using the PubMed and Web of Science databases. The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.[18] We included papers containing data on both adult and paediatric *C. glabrata* infections provided they: included data on at least one pre-specified criterion; were retrospective/prospective observational studies, randomised controlled trials, guidelines, epidemiology studies, or surveillance reports; and contained data for the 10 years from January 2011 to February 2021. We excluded studies reporting on non-human data; case reports/conference abstracts/reviews; studies on the novel antifungal drugs (preclinical, early phase, not licensed) or novel diagnostic tools (not registered for clinical use); and *in vitro* studies of resistance mechanisms.

On PubMed, we optimised the search using medical subject headings (MeSH) and/or keyword terms in the title/abstract for each pathogen and criterion. The final search used (candida glabrata[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, because MeSH terms are not available, we used topic search (TS), title (TI), or abstract (AB) search. The final search used [TI=('candida glabrata') OR TI=('c.glabrata')], combined, using AND term, with criteria terms each as TS, 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).

Study selection

We imported search results from each database into the online systematic review software, Covidence® (Veritas Health Innovation, Australia) and removed duplicates. The inclusion criteria were retrospective/prospective observational studies, randomised controlled trials, guidelines, epidemiology, surveillance reports, published within the last 10 years (2011–2021), reporting adults and paediatric data, including data on the fungal pathogen, and data on at least one criterion. Exclusion criteria were studies reporting on non-human data (e.g., animals, plants) or non-fungal data (e.g., bacteria), no data on relevant pathogen or criteria, case reports or conference or abstracts or reviews, drugs without marketing authorization, *in vitro* papers on resistance mechanisms, and articles published in non-English languages. Articles underwent title and abstract screening by two independent reviewers (H.Y.K. and J.B.) based on the inclusion criteria, with no reasons provided for exclusion at this stage. Two independent reviewers (H.Y.K. and J.B.) performed full-text screening for the final eligible articles on Covidence®. A third reviewer resolved any discrepancies (J.W.A.). Excluded articles were recorded with reasons when excluded during full-text screening. If any additional articles were identified from references of the included articles, these were added. The resulting articles were subject to the final analysis.

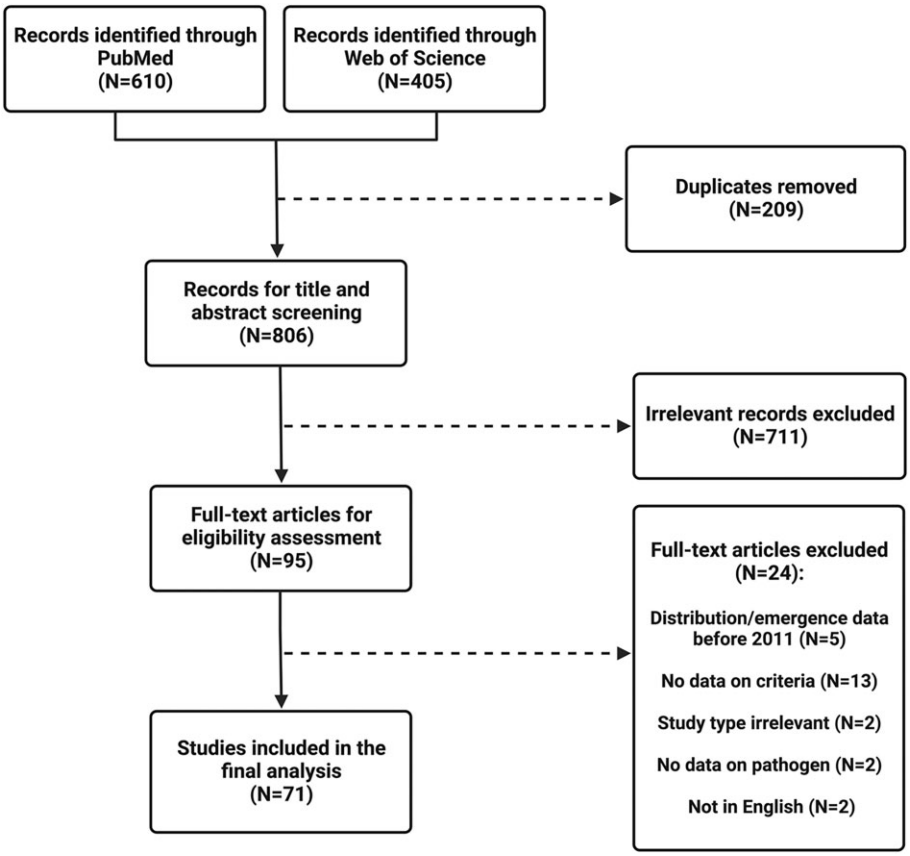

Figure 1. Flow diagram for selection of studies included in the systematic review. Based on: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097.

Data collection and synthesis

Data from the final included studies were extracted for relevant criteria (by H.Y.K. and J.B.). The extracted data were checked by the second reviewer (J.W.A.) (initially a 10% check, then expanded to 20% and more if needed, depending on the type of extent of observed errors). The extracted data on the outcome criteria were qualitatively and/or quantitatively synthesised depending on the amount and nature of the data.

Risk of bias assessment

The risk of bias for included articles was assessed by two independent reviewers (H.Y.K. and J.B.). We used the risk of bias tool for randomised trials version 2 (ROB 2) tool for randomised controlled trials.[19] The risk of bias in non-randomised studies (RoBANS) tool was used to assess the non-randomised studies.[20] 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.

For the purposes of this review, we considered each criterion as an outcome of the study and assessed if any bias was expected based on the study design, data collection, and analysis methods for that outcome. Studies that were classified as having an unclear or high overall risk were still eligible for inclusion with cautious interpretation.

Results

Study selection

PubMed and Web of Science Core Collection database searches yielded 610 and 405 articles, respectively. After removing duplicates, 806 articles underwent title/abstract screening (by H.Y.K. and J.B.). After excluding non-relevant articles, 95 underwent full-text screening (by H.Y.K. and J.B.). After excluding articles based on the full-text review, 71 studies were included in the final analysis. A third reviewer (J.W.A.) resolved discrepancies between the two reviewers. A flow diagram outlining the study selection is shown in Figure 1.

Risk of bias

The risk of bias for each study is presented in Table 1. Thirty studies were classified as low risk of bias in all domains. Sixteen studies were classified as unclear risk of bias, mostly due to uncertainties around selection of participants or isolates, but also because of unclear reporting of results and/or correction for confounding variables. Twenty-five studies were classified as high risk. In these studies, the risk was principally related to selection bias, with included patients or isolates being unrepresentative. The other common cause for a high risk of bias was incomplete reporting (for example, where tests were listed in the 'Methods' section but not reported in the 'Results' section).

Table 1. Risk of bias.

First author	Year	Risk of bias level	References
Al-Baqsami	2020	Low	34
Amanloo	2018	High	78
Andersen	2016	High	35
Arastehfar	2020	High	79
Arastehfar	2019	High	48
Astvad	2018	Low	58
Awad	2018	High	60
Ben-Ami	2012	Low	80
Beyda	2014	Low	55
Biswas	2018	Unclear	43
Bordallo-Cardona	2019	High	21
Bourgeois	2014	Unclear	81
Byun	2018	Unclear	23
Castanheira	2017	Low	82
Chapman	2017	Low	66
Chen	2017	Low	83
Cuenca-Estrella	2011	High	49
Delliere	2016	Low	84
Deorukhkar	2016	Low	85
Eschenauer	2013	Low	22
Farmakiotis	2015	Low	30
Figueiredo-Carvalho	2017	Unclear	86
Fraser	2020	High	87
Goemaere	2018	Unclear	41
Gonzalez-Lara	2017	High	24
Guinea	2014	Low	50
Guo	2017	Low	51
Guzel	2013	High	33
Hesstvedt	2017	High	36
Hou	2017	Unclear	44
Hou	2018	High	52
Hu	2019	High	88
Kakeya	2018	Low	89
Kamikawa	2014	High	54
Kaplan	2019	High	90
Katsuragi	2014	Low	39
Khalifa	2020	Unclear	56
Khan	2020	High	37
Khatib	2016	Unclear	26
Kiasat	2019	High	91
Kilic	2016	High	25
Klotz	2016	Unclear	46
Ko	2018	Low	27
Le	2017	Low	31
Lei	2018	Low	92
Lindberg	2019	Unclear	93
Lott	2012	High	53
Madeiros	2019	Low	94
Malani	2011	Unclear	64
Maraki	2019	Low	67
McCarty	2018	High	95
Meletiadis	2017	High	96
Miranda-Cadena	2018	Low	40
Morales-Lopez	2017	High	97
Moretti	2013	Low	61
Nakamura-Vasconcelos	2017	Unclear	47
Pfaller	2012	High	59
Pham	2014	Unclear	28
Puig-Asensio	2016	Low	29
Rajendran	2016	Low	65
Singh	2018	Low	98
Smyth	2018	Low	63
Szweda	2015	Unclear	45
Tang	2014	Low	32
Tapia	2012	Unclear	62
Tóth	2019	Low	57
Vatanshenassan	2019	High	99
Vergidis	2016	High	100
Xiao	2015	Low	38
Yao	2019	Unclear	42

Analysis of results against pre-selected criteria

Mortality

Fifteen studies reported mortality from invasive disease caused by *C. glabrata*, using different time points covering both early and late mortality (see Table 2). Most studies reported crude mortality rather than attributable mortality. Mortality was high and variable across studies. The studies ranged in size from 29 patients to 1380. Fifteen were retrospective cohorts, and one was a prospective cohort. Three retrospective studies reported a 7-day mortality of 9%–20%.[21–23] Eight retrospective studies reported 30-day mortality ranging from 19% to 49%.[21–28] The highest reported mortality of 49% ($n = 77$) was in a mixed general hospital population in the USA—the risk of bias in that study was related to unclear handling of confounding variables, but these would not have impacted mortality. The only prospective study reported a 14-day mortality rate of 13%[29] consistent with the other studies and had a low risk of bias. Mortality, specifically in patients with cancer, ranged from 38% to 45%.[30–32]

Inpatient care

Only one study (Table 3) reported on length of stay following *C. glabrata* candidaemia ($n = 82$), with an average length of stay of 26 days (range 0–165 days).[21] However, the overall risk of bias in this study was high due to selective outcome reporting and unclear control of confounders.

Complications and sequelae

None of the studies we included reported on complications or sequelae related to *C. glabrata* infection.

Antifungal resistance

Sixty studies reported on antifungal susceptibility. An overview of study type, size, and country of origin for these data is presented in Table 4. Susceptibility of non-sterile site isolates is reported alongside sterile site isolates, since these reflect the same organisms causing invasive infections. Twenty-four studies were limited to laboratory surveillance, 22 were retrospective cohort studies, 11 were prospective cohort studies, with two cross-sectional studies and one case control study. Risk of bias was generally lowest in the laboratory surveillance studies, and is discussed further in relation to specific findings. Sample sizes varied from 27 isolates up to 7225. There were 23 studies with fewer than 100 isolates, 33 included 100–1000 isolates, and 4 included more than 1000 isolates (of all *Candida* species). Studies were predominantly conducted in high-income countries. The following

Table 2. Mortality.

Author	Year	Study design	Study site	Study period	Country	Level of care	Population description	Number of patients	Mortality type	*N/N*, %
Arastehfar et al.[79]	2020	RCS	MC	2005–2019	Turkey	Tertiary	All patient	107	Crude mortality (not otherwise defined)	59/107 55.1%
Arastehfar et al.[48]	2019	RCS	MC	2015–2018	Iran	ND	Any patients	65	Case fatality (not otherwise defined)	23/65 35.4%
Bordallo-Cardona[21]	2019	RCS	SC	2007–2016	Spain	Tertiary	Patients with candidaemia or endocarditis	82	7-day mortality, 30-day mortality, late (>30-day mortality), and overall—crude	7 day: 13/81 16% 30 day: 24/81 29.6% Late: 11/81 13.6% Overall: 35/81 43.2%
Byun et al. [23]	2018	RCS	MC	2009–2010 and 2014	Korea	Tertiary	All patients with *C. glabrata* candidaemia	185	Cumulative case fatality at 7-, 30-, and 60-days	7 day: 19.5% 30 day: 39.5% 60 day: 47.0%
Eschenauer [22]	2013	RCS	MC	2002–2011	USA and Taiwan	Tertiary	All patients with *C. glabrata* candidaemia who received either fluconazole or echinocandin therapy	224	7-day all-cause mortality 28-day all-cause mortality	7 day—8.5% 28 day—21.4%
Farmakiotis [30]	2015	RCS	SC	2005–2013	USA	Tertiary	Patients attending a cancer centre	146	28-day all-cause mortality	28 day 58/146 40%
Gonzalez-Lara[24]	2017	RCS	MC	2008–2014	Mexico	Tertiary	All hospital patients	149	30-day all-cause mortality	19/28 19%
Khatib et al. [26]	2016	RCS	SC	2007–2015	USA	Tertiary	Adult patients with candidaemia	77 isolates	30-day all-cause mortality	49.40%
Kilic et al.[25]	2016	RCS	SC	2010–2016	Turkey	Tertiary	Adults and children with candidaemia	41	30-day all-cause mortality	39.6% (among all non-*albicans* species)
Ko et al.[27]	2018	RCS	MC	2010–2016	Korea	Tertiary	Adults with *C. glabrata* candidemia, treated with standard antifungal	197	30-day all-cause mortality	73/197 37.1%
Le et al.[31]	2017	RCS	SC	2005–2013	USA	Tertiary	Adult cancer patients with fluconazole SDD *C. glabrata* candidaemia	68	28-day all-cause mortality	26/68 38.24%
Pham et al. [28]	2014	RCS	MC	2008–2013	USA	Various	Adults and children with candidaemia	1 380	30-day all-cause mortality	42%
Puig-Asensio et al.[29]	2016	PCS	MC	2010–2011	Spain	Various	Adult patients >16 with *C. glabrata* candidaemia	94	14-day all-cause mortality	6/69 13.04%
Smyth[63]	2018	RCS	MC	2011–2017	UK	Tertiary	Adults with candidaemia	124	30-day all-cause mortality	7/33 21.2%
Tang et al.[32]	2014	RCS	SC	2009–2012	Taiwan	Tertiary	Adult cancer patients with candidaemia	29	In-hospital mortality (all cause)	13/29 44.83%

Notes: MC = multi-centre, ND = not determined, PCS = prospective cohort study, RCS = retrospective cohort study, SC = single centre.

Table 3. Length of stay.

Author	Publication year	Study design	Study sites	Study period	Country	Level of care	Population description	Number of patients	Length of stay
Bordallo-Cardona	2019	Retrospective cohort study	Single centre	2007–2016	Spain	Tertiary	Adults and children with candidaemia	82	26 (range 0–165)

low- or middle-income countries each contributed more than one study: China ($n = 6$), Turkey ($n = 4$), Iran ($n = 3$), Brazil ($n = 2$), and India ($n = 2$). We identified no studies from countries in Africa.

Data on drug susceptibility to azoles and other antifungal drugs are presented in Tables 5 and 6, respectively. A variety of methods were used to measure susceptibility, and there was great heterogeneity in how results were reported, some of it potentially invalid (i.e., isolates categorised as susceptible to fluconazole). We have reported resistance (or non-wild-type) as a percentage, according to CLSI or EUCAST methodologies as used in the study, and as defined by the respective bodies at the time of the particular study.

Rates of resistance to against fluconazole ranged from 0% to 48%. Of 52 studies, only two reported resistance rates of 0%[24,33] and they both carried a high risk of bias related to selection of isolates. Al-Baqsami's study reporting a resistance rate of 48% in a single centre in Kuwait had a low risk of bias, and included 76 isolates from various body sites.[34] A total of 16 studies reported fluconazole resistance rates of more than 10%,[25,28,29,35–47] including many large studies with a low risk of bias. Studies reporting susceptibility to voriconazole ($n = 30$) and posaconazole ($n = 13$) described rates of resistance ranging from 0% to 68.8% and 0% to 29.4%, respectively. Resistance rates of greater than 10% were reported for voriconazole in 15 studies.[35,38,39,41–46,48–53] Non-wild-type minimum inhibitory concentration (MIC) rates for posaconazole of greater than 10% were reported in two studies.[43,45] Only one study tested isavuconazole MICs and reported an MIC range of <0.016–0.25, and an MIC90 0.15 mg/l. Four studies provided clear evidence of azole resistance rates increasing over time.[23,37,44,54]

Data on susceptibility to echinocandins were presented in 45 studies, in which a mixture of testing methods and reporting was used. See Table 6. Rates of resistance were generally less than 5% for anidulafungin, caspofungin, and micafungin but highly variable, with ranges of 0%–9.3%, 0%–63%, and 0%–15.4%. Four publications reported resistance to caspofungin in >10% of isolates,[30,55–57] with Toth et al. and Khalifa et al. reporting rates of 63% (Hungary) and 32.6% (Japan), respectively. Neither of these latter two studies had a high risk of bias. However, it is worth noting that caspofungin is not considered a good resistance marker and does not have a breakpoint for EUCAST. Additionally, three studies described decreasing susceptibility to echinocandins over time.[28,58,59] Resistant or non-wild-type phenotypes were reported uncommonly for either amphotericin B or flucytosine—generally <2%, and not more than 10% in any of the included studies.

Preventability

Only one paper examined preventative measures against *C. glabrata* infection. This study found that attention to infection prevention and control could reduce the risk, but it did not quantify the magnitude of the effect.[26] Risk factors for infection with *C. glabrata* are presented in Table 7. Several studies highlighted the association between antifungal use and the risk of *C. glabrata* infection, including at the national,[36] institutional,[60,61] and individual patient levels.[41,55,62] The evidence regarding whether diabetes was specifically a risk factor for *C. glabrata* infection was mixed; one study found an odds ratio of 2.55 ($P = .001$) associated

Table 4. Studies reporting drug susceptibility.

Author year	Study design	Study sites	Study period	Country	Level of care	Population description	Number of patients	Number of isolates	Samples collected from
Al-Baqsami 2020[34]	LS	SC	2007–2017	Kuwait	Tertiary	All patients	ND	75	Urogenital tract ($n = 29$), respiratory tract ($n = 20$), bloodstream ($n = 12$), ascitic/cavitary fluid ($n = 3$), wound ($n = 3$), skin ($n = 2$), and other miscellaneous (peritoneal dialysis fluid, percutaneous endoscopic gastrostomy site, rectum, bed sore, pus, and from an unknown site) sites ($n = 6$)
Amanloo 2018[78]	RCS	MC	ND	Iran	ND	ND	50	50	Blood, body swabs, urine, and various
Andersen 2016[35]	LS	MC	2003–2011	Norway	Various	ND	ND	183	Oral, GI tract, respiratory, and blood
Arastehfar 2019[48]	RCS	MC	2015–2018	Iran	ND	Any patients	65	70	The majority of the isolates (86.1%; $n = 56$) were recovered from blood, followed by central venous catheters and abdominal fluids, each at 3.08% ($n = 2$ each), and abdominal wounds, dialysis fluid, cerebro-spinal fluid (CSF), double lumen (DL), and triple lumen (TL), each at 1.54% ($n = 1$ each)
Arastehfar 2020[79]	RCS	MC	2005–2019	Turkey	Tertiary	All patient	107	107	Blood
Astvad 2018[58]	LS	MC	2012–2015	Denmark	All levels	All patients	Unclear	617	Blood
Ben-Ami 2012[101]	PCS	MC	2005–2007	Israel	Tertiary	All patients with candidaemia	Unclear	69	Blood
Ben-Ami 2013[80]	PCS	MC	2005–2007	Israel	Tertiary	All candidaemia	Unclear	69	Blood
Beyda 2014[55]	RCS	SC	2009–2012	USA	Tertiary	All patients with *C. glabrata* candidaemia	72	72	Blood
Biswas 2018[43]	LS	MC	2002–2017	Australia	Tertiary	Any patient with candidaemia	51	51	Blood
Bordallo-Cardona 2019[21]	RCS	SC	2007–2016	Spain	Tertiary	Patients with candidaemia or endocarditis	82	92	Blood and heart valve
Bourgeois 2014[81]	Lab quality assurance	MC	2009–2010	France	Tertiary	Any patients	ND	193	29 were from blood cultures, 17 from abdominal sterile sites, 25 from deep pulmonary samples, 113 from urine samples, and 9 were from different sites in multi-colonised patients
Byun 2018[23]	RCS	MC	2009–2010 and 2014	Korea	Tertiary	All patients with *C. glabrata* candidaemia	185	209	Blood

Table 4. Continued

Author year	Study design	Study sites	Study period	Country	Level of care	Population description	Number of patients	Number of isolates	Samples collected from
Castanheira 2017[82]	CSS	MC	2014–2015	29 countries (not include afro region, China or India)	Unclear	Unclear	Unclear	514 non-duplicates	Bloodstream infections (n = 1930 strains), hospitalised patients with pneumonia (n = 806), patients with skin and skin structure infections (n = 95), patients with intra-abdominal infections (n = 35), patients with urinary tract infections (n = 33), and other/unknown specimens (n = 658)
Chapman 2017[66]	CSS	MC	2014–2015	Australia	Tertiary	All patients with candidaemia	Unclear	133	Blood
Chen 2017[83]	LS	SC	2007–2012	Taiwan	Tertiary	All patients	ND	92 unique isolates	Blood
Cuenca-Estrella 2011[49]	LS	MC	2003–2009	Spain	Various	All patients	682	682	Blood cultures and other deep sites, such as tissue samples and internal body fluids, 10% were isolated from oropharyngeal exudates, and the remaining 20% were isolated from vaginal exudates, skin samples, and other specimens
Delliere 2016[84]	PCS	SC	2015–2016	France	Tertiary	All patients	147	268	Any source blood, body swabs, sputum, and vaginal
Deorukhkar 2016[85]	RCS	SC	2007–2014	India	ND	All patients	53	53	Blood
Eschenauer 2013[22]	RCS	MC	2002–2011	USA and Taiwan	Tertiary	All patients with *C. glabrata* candidaemia who received either fluconazole or echinocandin therapy	224	224	Blood
Farmakiotis 2015[30]	RCS	SC	2005–2013	USA	Tertiary	Patients attending a cancer centre	146	146	Blood
Figueiredo-Carvalho 2017[86]	LS	MC	1998–2015	Brazil	Tertiary	All patients	Unclear	91	Gastric aspirate (n = 1); renal abscess secretion (n = 1); pleural fluid (n = 1); secretion of surgical drain (n = 1); secretion of postoperative wound (n = 1); ascitic fluid (n = 2); abdominal secretion (n = 3); peritoneal fluid(n = 4); sputum (n = 4); venous catheter (n = 4); bronchoalveolar lavage (n = 5); vaginal secretion (n = 7); faeces (n = 9); tracheal secretion (n = 10); urine (n = 13); and blood (n = 25)

Table 4. Continued

Author year	Study design	Study sites	Study period	Country	Level of care	Population description	Number of patients	Number of isolates	Samples collected from
Fraser 2020[87]	LS	MC	2003–2018	UK	Various	All patients	ND	7225	All sites
Goemaere 2018[41]	RCS	SC	2004–2015	Belgium	Tertiary	All hospital patients	187	187	Blood
Gonzalez-Lara 2017[24]	RCS	MC	2008–2014	Mexico	Tertiary	All hospital patients	149	149	Blood
Guinea 2014[50]	PCS	MC	2010–2011	Spain	Various	All patients with fungaemia	ND	103	Blood
Guo 2017[51]	PCS	MC	2012–2013	China	Tertiary	Adults and children with invasive yeast infection	181	181 (out of 1201 total yeasts)	Blood or other sterile site
Guzel 2013[33]	PCS	SC	2011	Turkey	Tertiary	Premenopausal women at outpatient clinic	495	52 (of total 129 *Candida* isolates)	Vagina swab
Hesstvedt 2017[36]	RCS	MC	2010–2011	Denmark, Norway, Finland, Sweden	National surveillance	Adults and children with candidaemia	ND	292 *C. glabrata* (out of total 1263 *Candida*)	Blood
Hou 2017[44]	PCS	MC	2009–2014	China	ND	All patients with *C. glabrata* candidaemia	411	411	Any sterile site: blood cultures, 23.1% were from ascitic fluid, 5.1% (21/411) from pus and 4.6% (19/411) from venous catheter. $N = 76$ were obtained from bile, pleural fluid, and other sterile body fluids
Hou 2018[52]	LS	MC	2015	China	Various	All patient's adult and child with *C. glabrata* in blood	158	158	Blood
Kamikawa 2014[54]	PCS	SC	2012–2013 (+historical comparison 2006–2007)	Japan	Tertiary	Adults investigated for oral candidiasis	ND	36	Oral swab/saliva
Kaplan 2019[102]	LS	SC	ND	Turkey	Tertiary	ND	ND	103	Urine, lower respiratory tract, blood, tissue, cerebral spinal fluid, and vaginal swabs
Katsuragi 2014[39]	RCS	SC	2007–2011	Japan	Tertiary	Adults in general hospital	Unclear	776 total (21 from blood)	Sputum, urogenital, stool, sterile site, blood, skin, and other
Khalifa 2020[56]	LS	MC	1998–2019	Japan	ND	Adults and children	43	58	Various sterile and non-sterile sites
Khan 2020[37]	LS	MC	2011–2018	Kuwait	Various	Adult and children from various hospitals in Kuwait	1410	1410	Various sterile and non-sterile sources
Kiasat 2019[103]	RCS	MC	2017–2018	Iran	Various	Adult women with vulvovaginal candidiasis	ND	61	Vaginal swabs
Klotz 2016[46]	RCS	MC	2008–2012	Germany and Austria	Tertiary	Adults and children with *C. glabrata* candidaemia	64	64	Blood

Table 4. Continued

Author year	Study design	Study sites	Study period	Country	Level of care	Population description	Number of patients	Number of isolates	Samples collected from
Ko 2018[27]	RCS	MC	2010–2016	Korea	Tertiary	Adults with *C. glabrata* blood stream infection, treated with standard antifungal	197	197	Blood
Lei 2018[92]	LS	SC	2012–2016	China	Tertiary	Patients with invasive candidiasis	Unclear	207	Blood, sputum, bronchoscopy, urine, ascitic fluid, bile, and tissue biopsy specimens
Lindberg 2019[93]	RCS	MC	2013–2016	Sweden	Various	Adults and children with presumed sepsis	ND	27	Blood
Lott 2012[53]	LS	MC	2007–2010	USA	Various	Any patient with *C. glabrata* isolates (candidaemia group and commensal group)	90 in candidaemia group + 111 commensal group	201	Blood (90), any body site not causing infection (111)
Maraki 2019[67]	PCS	SC	2012–2017	Greece	Tertiary	Consecutive adult women with symptoms of vulvovaginitis	168	168	Vaginal swab
McCarty 2018[95]	LS	SC	2005–2015	USA	Tertiary	All patients with candidaemia	ND	832 *C. glabrata* (of total 3876 *Candida* spp.)	'Clinical isolates' various sources
Meletiadis 2017[96]	LS	MC	2002–2004	ND	ND	Trial participants with invasive and oesophageal candidiasis	ND	86	ND
Miranda-Cadena 2018[40]	RCS	SC	2003–2013	Spain	Tertiary	Adult patients with clinical oral candidiasis	Unclear	114	Oral swab
Morales-Lopez 2017[97]	LS	MC	1984–2014	Argentina	Various	Isolates referred to reference lab	ND	122	Various sterile and non-sterile sites
Nakamura-Vasconcelos 2017[47]	RCS	SC	ND	Brazil	Tertiary	Female outpatients	60	60	Vaginal swabs
Pfaller 2012[59]	LS	MC	2001–2010	Global	Various	Any patient with *C. glabrata* candidaemia, from surveillance networks	1669	1669	Blood
Pham 2014[28]	RCS	MC	2008–2013	USA	Various	Adults and children with candidaemia	1380	1380	Blood
Puig-Asensio 2016[29]	PCS	MC	2010–2011	Spain	Various	Adult patients > 16 with *C. glabrata* candidaemia	94	94	Blood
Singh 2018[98]	LS	MC	2012–2016	India	Various	Adults and children with candidiasis	210	210	Blood and sputum
Szweda 2015[45]	LS	MC	2008–2012	Poland	Various	Adults and children with *Candida* isolates	ND	81	Various non-sterile sites

Table 4. Continued

Author year	Study design	Study sites	Study period	Country	Level of care	Population description	Number of patients	Number of isolates	Samples collected from
Tapia 2012[62]	Case control study	MC	1998–2006	USA	Tertiary	Cases: Adult patients with *C. glabrate* candidaemia; controls adult patients with non-glabrata candidaemia	68	51	Blood
Toth 2019[57]	LS	SC	2005–2018	Hungary	Tertiary	Patients with *Candida* isolates	81	81	Various sterile and non-sterile sites
UluKilic 2017[25]	RCS	SC	2010–2016	Turkey	Tertiary	Adults and children with candidaemia	41	41	Blood
Vatanshenassan 2019[99]	LS	MC	ND	Austria, Israel, Germany, the Nether-lands, and the United States	ND	ND	ND	100	Blood, urine, and superficial wound
Xiao 2015[38]	PCS	MC	2009–2012	China	Various	All patients with invasive *Candida*	Unclear	261	Not stated
Yao 2019[42]	LS	MC	ND	China	Tertiary	All patients with positive fungal culture	59	59	Various sterile and non-sterile

Notes: CSS = cross sectional study, LS = lab surveillance MC = multi-centre, ND = not determined, PCS = prospective cohort study, RCS = retrospective cohort study, SC = single centre.

Table 5. Drug susceptibility to azoles.

Author year	MIC method	Fluconazole	Itraconazole	Posaconazole	Voriconazole
Al-Baqsami 2020[34]	Etest EUCAST BP	MIC range: 0.125–>32 Modal MIC: 0.25 %R 36/75–48%	ND	ND	ND
Amanloo 2018[78]	CLSI broth microdilution	MIC Range: 0.5–64 %S: 41/50 82%* %SDD: 5/50 10% %R: 4/50 8%	NA	NA	0.016–4 46/50 92% 3/50 6% 1/50 2%
Andersen 2016[35]	Etest EUCAST BP	S%: 0% I%: 82% R%: 18%	NA	NA	31.2% 0% 68.8%
Arastehfar 2019[48]	CLSI M27-A3	MIC range: 2–64 *n*/*N* %R: 1/65 1.5% GM MIC: 10.11	0.064–2 0/65 0% 0.51	0.032–1 0/65 0% 0.41	0.064–16 12/65 18.5% nWT 0.32
Arastehfar 2020[79]	CLSI broth microdilution	Range: 0.5–64 *n*/*N* R: 4/107 3.7% MIC50: 8 MIC90: 64 GM: 2.86	0.032–0.25 0/107 0% 0.125 0.25 0.125	NA	0.032–0.25 0/107 0% 0.032 0.125 0.032
Astvad 2018[58]	EUCAST E.Def 7.3	MIC range: 0.25–128 *n*/*N* %R: 55/603 9.1%	ND	ND	0.032–8 49/603 8.1% nWT
Ben-Ami 2012[101]	CLSI M27-A3	*n*/*N* %R: 6/68 8.8%	NA	NA	NA
Biswas 2018[43]	Sensititre YeastOne CLSI BP	*n*/*N* %R: 13/51 25.5%	ND	15/51 29.4% nWT	30/51 58.8% nWT
Bordallo-Cardona 2019[21]	EUCAST E.Def 7.3	*n*/*N* R%: 4/90 4.9%	ND	ND	ND
Byun 2018[23]	CLSI M27-A	*n*/*N* R%: 16/209 7.7%	ND	ND	17/209 8.1%
Castanheira 2017[82]	CLSI broth microdilution	%R: 8.0 MIC50: 4 MIC90: 16	ND	NA 0.5 1.0	NA 0.12 0.5
Chapman 2017[66]	Sensititre YeastOne CLSI BP	MIC range: 1–256 MIC90: 32 GM MIC: 8.39 S or WT%: NA SDD or I%: 93.2 R or NWT%: 6.8	0.06–>16 1 0.48 97 NA 0.8	0.006–>8 2 0.69 97.7 NA 3.0	0.03–8 0.5 0.24 90.2 NA 9.8
Chen 2017[83]	Sensititre YeastOne CLSI M27-S4 BP	MIC range: 1–256 MIC50: 0.25 MIC90: 0.12 *n*/*N* %R: 5/92 5.4% *n*/*N* %SDD: 87/92 5.9% *n*/*N* %S: 0/92 0%*	ND	ND	0.008–2 0.12 0.5 NA NA NA
Cuenca-Estrella 2011[49]	EUCAST broth microdilution	ND	ND	ND	MIC range: 0.05–>8.0 *n*/*N* % R: 283/682 41%
Delliere 2016[84]	Etest EUCAST v8.0 BP	MIC50: 16 MIC90: 256 *n*/*N* R%: 42/268 15.7%	ND	ND	ND

Table 5. Continued

Author year	MIC method	Fluconazole	Itraconazole	Posaconazole	Voriconazole
Deorukhkar 2016[85]	Screened by disc diffusion, resistance confirmed with CLSI M27-A3	*n*/*N* %R: 15/53 28.3%	ND	ND	ND
Eschenauer 2013[22]	CLSI broth microdilution	*n*/*N* %S: 56/122 46%∗ *n*/*N* %SDD: 49/122 40% *n*/*N* %R: 17/122 14%	ND	ND	ND
Farmakiotis 2015[30]	CLSI broth microdilution	*n*/*N* R%: 30/146 21%	ND	ND	ND
Figueiredo-Carvalho 2017[86]	CLSI M27-A3	MIC range: 0.58→64 MIC50: 16 MIC90: 64 GM MIC: 0.61 *n*/*N* %R: 9/91 9.9%	0.016–4 0.25 0.5 0.22 5/91 5.5%	ND	ND
Goemaere 2018	EUCAST E.Def 7.2	MIC range: 1–512 *n*/*N* R%: 20/187 10.7 *n*/*N* SDD%: 167/187 89.3	MIC range: 0.0078–8 *n*/*N* nWT%: 15/187 8.0%	ND	MIC range: 0.0313–8 *n*/*N* R%: 123/187 65.8%
Gonzalez-Lara 2017[24]	Vitek 2 AST-YS07 CLSI BP	MIC range: <1–64 MIC50: 4 MIC90: 8 *n*/*N* R%: 2/30 6.6% *n*/*N* SDD %: 28/30 93.3% *n*/*N* S%: 0*	ND	ND	ND
Guinea 2014[50]	EUCAST E.Def 6.1; and CLSI M27-A3	EUCAST: MIC range: 0.5–>64 GM: 3.074 MIC90: 16 *n*/*N* %R: 5.8% CLSI: MIC range: <1→64 GM: 10 MIC90: 64 *n*/*N* %R: 9.6%	EUCAST: MIC range: <0.015–>8 GM: 0.127 MIC90: 1 *n*/*N* %R: NA CLSI ND	EUCAST: MIC range: <0.015–>8 GM: 0.124 MIC90: 0.5 *n*/*N* %R: NA CLSI: MIC range: 0.015–>2 GM: 0.25 MIC90: 1.0 *n*/*N* %R: 2.9%	EUCAST: MIC range: <0.0015–8 GM: 0.12 MIC90: 0.5 *n*/*N* %R: NA CLSI: MIC range: 0.003–>2 GM: 0.11 MIC90: 0.5 *n*/*N* %R: 10.2%
Guo 2017[51]	CLSI broth microdilution, M27-S4 BP	Range: 0.064–128 MC50: 8 MIC90: 32 R%: 7.2 SDD%: 92.8 S/WT: 0*	0.016–32 0.5 2 5% 0% 95%	ND	0.008–8 0.125 1 10.5% 0% 89.5%
Guzel 2013[33]	CLSI M27-A3	Range: 0.25–32 *n*/*N* R%: 0/52 0%	0.125–16 3/52 5.8%	ND	ND
Hesstvedt 2017[36]	EUCAST broth microdilution	*n*/*N* R: 87/292 29.79%	ND	ND	ND

Table 5. Continued

Author year	MIC method	Fluconazole	Itraconazole	Posaconazole	Voriconazole
Hou 2017[44]	Sensititre YeastOne CLSI M27-S4 BP	Range: 1–256 MIC90: 64 MIC50: 16 R/nWT %: 16.5%	0.12–16 1 0.5 6.8%	0.25–8 2 1 7.3%	0.03–8 2 0.25 28.7%
Hou 2018[52]	CLSI broth microdilution M27-S4	R%: 8.9% MIC50: 16 MIC90: 32	%nWT: 5.1%	%nWT: 6.3%	%nWT: 19.0%
Kamikawa 2014[54]	ASTY broth microdilution (Kyokuto Pharmaceutical Inc.) CLSI BP	MIC range: 2–>64 MIC50: 16 MIC90: 64 *n*/*N* R%: 2/36 5.56%	MIC range: 0.06–>8 MIC50: 1 MIC90: >8 *n*/*N* R%: 24/36 66.7%	ND	ND
Kaplan 2019[90]	CLSI M27-A3	MIC range: 1–>64 MIC50: 4 MIC90: 8 *n*/*N* %R: 4/103 3.8%	ND	MIC range: 0.06–>16 MIC50: 0.5 MIC90: 1.0 *n*/*N* %nWT: 5/103 4.9%	MIC range: 0.06–>16 MIC50: 0.25 MIC90: 0.5 *n*/*N* %nWT: 7/103 6.8%
Katsuragi 2014[39]	ASTY broth microdilution CLSI BP	MIC range: 8–>64 MIC50: 16 MIC90: 64 %R: 19.1%	1–>8 2 8 100%	ND	0.25–>8 0.5 1 14.3%
Khalifa 2020[56]	Yeast Like Fungi FP (Eiken Chemical, Tokyo, Japan) CLSI BP	MIC range: 1–64 MIC GM: 5.46 %R/%nWT: 2/43 4.7%	0.12–4 0.29 1/43 2.3%	ND	0.03–8 0.12 4/43 9.3%
Khan 2020[37]	Etest CLSI BP	2011–2014 Range: 0.016–256 GM: 6.95 *n*/*N* R%: 15/594 2.53% 2015–2018 Range: 0.125–256 GM: 15.16 *n*/*N* R%: 73/631 11.57%	ND	ND	ND
Kiasat 2019[103]	EUCAST E.Def 7.3.1	MIC range: 1–64 MIC50: 2 MIC90: 4 *n*/*N* % R/nWT: 1/61 1.6%	0.5–8 2 4 8/61 13%	0.031–4 0.25 0.5 2/61 3.3%	0.031–1 0.125 0.25 0/61 0%
Klotz 2016[46]	EUCAST E.Def 7.2	MIC range: 4–128 MIC50: 16 MIC90: 128 *n*/*N* R %: 16/64 25%	ND	ND	0.03–16 0.5 4 19/64 30%
Ko 2018[27]	VITEK 2 AST CLSI BP	%R: 4.9%	ND	ND	ND
Lei 2018[92]	ATB FUNGUS 3	MIC range: 1–128 MIC50: 2 MIC90: 16	MIC range: 0.24–4 MIC50: 0.25 MIC90: 4	ND	MIC range: 0.0625–8 MIC50: 0.125 MIC90: 1

Table 5. Continued

Author year	MIC method	Fluconazole	Itraconazole	Posaconazole	Voriconazole
Lindberg 2019[93]	Sensititre YeastOne CLSI BP	MIC range: 2–128 MIC50: 16 MIC90: 16 %R: 3%	0.25–1 0.5 1 97%	0.12–2 1 2 ND	0.06–2 0.25 1 ND
Lott 2012[53]	CLSI M27-A3	*n*/*N* %R: 22/201 10.95%	ND	ND	MIC > 2 (R, and SDD) *n*/*N* %R + SDD: 25/201 12.44%
Maraki 2019[67]	Vitek 2 AST CLSI	*n*/*N* %S: 0* *n*/*N* %SDD: 166/168 98.8% *n*/*N* %R: 2/168 1.2%	ND	ND	*n*/*N* %S: 163/168 97% *n*/*N* %SDD: 0 0% *n*/*N* %R: 5/168 3%
Meletiadis 2017[96]	EUCAST broth microdilution	Range: 1–>32 MIC50: 4 MIC90: 8 %R: 2.3%	Range: 0.031–16 MIC50: 0.25 MIC90: 0.5 %R: 1.2%	Range: 0.063–16 MIC50: 0.125 MIC90: 0.25 %R: 2.3%	Range: 0.031–8 MIC50: 0.125 MIC90: 0.25 %R: 1.7%
Miranda-Cadena 2018[40]	Modified CLSI M44-A2 disc diffusion (plus CLSI M27-A3 broth microdilution for fluconazole only)	Disc %S: 93/114 81.6%* %SDD: 7/114 6.14% %R: 14/114 12.3% Broth microdilution %R: 2.86% MIC range: 0.25–64 MIC50: 4 MIC90: 2	%S: 103/114 90.4% %SDD: 8/114 7.02% %R: 3/114% 2.63%	ND	ND
Nakamura-Vasconcelos 2017[47]	CLSI M27-A3 broth microdilution	MIC range: 0.25–64 MIC50: 32 MIC90: 64 %R: 15%	0.03–8.0 0.25 2.0 21.67%	ND	ND
Pfaller 2012[59]	CLSI broth microdilution	*n*/*N* %R: 162/1669 9.7%	ND	ND	ND
Pham 2014[28]	CLSI Broth microdilution	*n*/*N* %R: 142/1380 10.3%	ND	ND	ND
Puig-Asensio 2016[29]	CLSI M27-A3 and EUCAST E.Def 7.1 and E.Def 7.2	EUCAST MIC range: 0.5– >64 MIC90: 16 %R: 6/94 6.4% CLSI MIC range: 1–>64 MIC90: 64 %R: 10/94 10.6%	ND	ND	EUCAST MIC range: 0.015–8 MIC 90: 0.5 %R: NA CLSI MIC range: 0.003–>2 MIC 90: 0.5 %R: NA
Singh 2018[98]	CLSI broth microdilution M27-A3, M27-S4 BP	MIC range: 0.25–32 GM: 1.84 MIC50: 2 MIC90: 4	MIC range: 0.032–0.5 GM: 0.05 MIC50: 0.06 MIC90: 0.12	MIC range: <0.016–0.25 GM: 0.02 MIC50: 0.03 MIC90: 0.06	MIC range: 0.032 GM: 0.03 MIC50: 0.03 MIC90: 0.06

Table 5. Continued

Author year	MIC method	Fluconazole	Itraconazole	Posaconazole	Voriconazole
Szweda 2015[45]	Sensititre YeastOne CLSI BP	*n*/*N* %R: 18/81 22.22%	*n*/*N* %nWT: 15/81 18.52%	*n*/*N* %nWT: 15/81 18.52%	*n*/*N* %nWT: 22/81 27.16%
Tapia 2012[62]	CLSI broth microdilution	*n*/*N* %R: 8/51 16%	ND	ND	ND
Toth 2019[57]	CLSI broth microdilution	MIC range: 0.25–>32 MIC50: 2 MIC90: 16 %R: 4.9%	ND	ND	ND
UluKilic 2017[25]	CLSI M27-A3	*n*/*N* %R: 9/41 21.95%	ND	ND	ND
Xiao 2015[38]	Sensititre YeastOne CLSI BP	MIC range: 0.5–>256 GM MIC: 13.86 %R/nWT: 14.2%	MIC range: 0.06–>16 GM MIC: 0.73 %R/nWT: 9.2%	MIC range: 0.03–>8 GM MIC: 1.03 %R/nWT: 10%	MIC range: 0.008–4 GM MIC: 0.22 %R/nWT: 11.9%
Yao 2019[42]	ATB Fungus 3 CLSI BP	*n*/*N* %R: 12/59 20.3% MIC50: 4 MIC90: 64	*n*/*N* nWT%: 13/59 22%	ND	*n*/*N* nWT%: 27/59 45.7%

Notes: Susceptibility is expressed as mg/l unless indicated otherwise. ND = not done, MIC50/MIC90 = minimum inhibitory concentration 50%/90%. BP = breakpoints. S/SDD/I/R% = susceptible/susceptible dose dependent/intermediate/resistant%, nWT = non-wild-type.
*Data presented as reported in paper. Note that CLSI have no susceptible category for fluconazole vs. *C. glabrata* (*N. glabrata*) and therefore validity of reported data unclear.

Table 6. Drug susceptibility to other anti-fungal agents.

Author year	MIC method	Anidulafungin	Caspofungin	Micafungin	Amphotericin B	Flucytosine*
Al-Baqsami 2020[34]	Etest	MIC range: ND	<0.008–0.75	<0.008–0.25	<0.008–4	NA
	EUCAST BP	Modal MIC: ND	0.25	0.016	0.19	
		n/*N* %R: ND	4/75—5.3%	5/75—6.6%	5/75—6.6%	
Amanloo 2018[78]	CLSI broth microdilution	MIC range: ND	0.008–0.25	ND	0.0313–1	ND
		%S: ND	50/50 100%		50/50 100%	
		%I: ND	0/50 0%		0/50 0%	
		%R: ND	0/50 0%		0/50 0%	
Andersen 2016[35]	Etest, EUCAST BP	S%: 98.9%	ND	98.6%	99.5%	ND
		I%: 0%		0%	0%	
		R%: 1.1%		1.4%	0.5%	
Arastehfar 2019[48]	CLSI M27-A3	MIC range: ND	0.125–1	NA	0.25–2	NA
		n/*N* %R: ND	41/65 63.1% nWT		1/65 1.5%	
		GM MIC: ND	0.41		0.57	
Arastehfar 2020[79]	CLSI broth microdilution	Range: 0.016–0.25	ND	0.016–0.12	0.12–2	ND
		n/*N* %R: 0/107 0%		0/107 0%	1/107 0.9%	
		MIC50: 0.03		0.016	0.5	
		MIC90: 0.06		0.016	1	
		GM: 0.063		0.063	1	
Astvad 2018[58]	EUCAST E. Def 7.3	MIC range: 0.015–2	ND	0.008–2	0.015–2	ND
		n/*N* %R: 16/603 2.7%		12/603 2.0%	9/603 1.5%	
Beyda 2014[55]	Sensititre YeastOne CLSI BP	ND	MIC range: 0.03–0.5	ND	ND	ND
			n/*N* %R: 8/72 11%			
			n/*N* %I: 18/72 25%			
			n/*N* %S: 46/72 64%			
			MIC50: 0.12			
			MIC90: 0.5			
Biswas 2018[43]	Sensititre YeastOne CLSI BP	ND	4/51 7.8%	ND	0/51 0% nWT	0/51 0% nWT
Bordallo-Cardona 2019[21]	EUCAST E.Def 7.3	*n*/*N* R%: 1/91 1.1%	*n*/*N* R%: 1/91 1.1%	ND	ND	ND
		GM MIC: 0.015	GM MIC: 0.023			
Bourgeois 2014[81]	CLSI (BP from Arendrup et al.)	ND	MIC range: 0.03–16	ND	ND	ND
			MIC50: 0.25			
			MIC90: 0.25			
			n/*N* %R: 2/193 1.04%			
Byun 2018[23]	CLSI broth microdilution	ND	ND	0/209 0%	0/209 0%	ND
Castanheira 2017[82]	CLSI broth microdilution	%R: 2.5%	2.5%	2.3%	0%	ND
		MIC50: 0.06	0.03	0.015	1	
		MIC90: 0.12	0.06	0.03	1	
Chapman 2017[66]	Sensititre YeastOne CLSI BP	MIC range:	1.03–0.5	0.008–0.15	<0.12–4	<0.06–>64
		<0.015–0.12	0.12	0.015	1	0.03
		MIC90: 0.06	0.06	0.01	0.6	0.04
		GM MIC: 0.03	94.7	99.2	99.2	98.5
		S or WT%: 100	4.5	0	NA	NA
		I%: 0	0.8	0.8	0.8	1.5
		R of nWT%: 0				
Chen 2017[83]	Sensititre YeastOne CLSI M27-S4 BP	MIC range: 0.015–4	0.03–1	0.08–0.25	ND	ND
		MIC50: 0.06	0.06	0.008		
		MIC90: .12	0.25	0.015		
		n/*N* %R: 0/92 0%	1/92 1.1%	2/92 2.2%		
		n/*N* %I: 6/92 6.5%	11/92 12%	0		
		n/*M* %S: 86/92 93.5%	80/92 87%	90/92 97.8%		

Table 6. Continued

Author year	MIC method	Anidulafungin	Caspofungin	Micafungin	Amphotericin B	Flucytosine*
Delliere 2016[84]	Etest EUCAST BP v8.0	MIC50: ND MIC90: ND *n*/*N* %R: ND	ND	0.016 0.023 2/268 0.7%	ND	ND
Farmakiotis 2015[30]	CLSI broth microdilution	ND	*n*/*N* I%: 24/146 16% *n*/*N* R%: 15/146 10.3%	ND	ND	ND
Figueiredo-Carvalho 2017[86]	CLSI M27-A3	MIC range: ND MIC50: ND MIC90: ND GM MIC: ND *n*/*N* % R: ND	ND	0.016–1 0.06 0.25 0.08 14/91 15.4%	0.06–8 0.5 2 0.61 9/91 9.9%	0.12–0.12 0.12 0.12 0.12 0/91 0%
Fraser 2020[87]	Anidulafungin, micafungin: CLSI broth microdilution. Caspofungin: Etest with CLSI BP	*n*/*N* % R: 10/1117 0.9%	8/548 1.5%	6/218 2.8%	ND	ND
Goemaere 2018[41]	EUCAST E.Def 7.2	MIC range: 0.0039–0.25 *n*/*N* R%: 5/187 2.7%	MIC range: 0.0039–0.25 *n*/*N* R%: 0/187 0%	MIC range 0.0039–0.25 *n*/*N* R%: 1/187 0.5%	MIC range: 0.0078–1 *n*/*N* R%: 0/187 0%	ND
Gonzalez-Lara 2017[24]	Vitek 2 AST-YS07 CLSI BP	ND	MIC range: <0.25–1 MIC50: 0.25 MIC90: 0.25 *n*/*N* R%: 1/30 3.3% *n*/*N* I %: 0 *n*/*N* S%: 29/30 96.6%	MIC range: <0.006–0.5 MIC50: 0.06 MIC90: 0.06 *n*/*N* R%: 1/30 3.3% *n*/*N* I %: *n*/*N* S%: 29/30 96.6%	ND	ND
Guinea 2014[50]	EUCAST E.Def 6.1; and CLSI M27-A3	EUCAST: MIC range: <0.03–0.5 GM: 0.031 MIC90: 0.03 *n*/*N* %R: 0.97% CLSI: MIC range: <0.007–1 GM: 0.032 MIC90: 0.06 *n*/*N* %R: 1.0%	EUCAST: MIC range: 0.25–1 GM: 0.44 MIC90: 1 *n*/*N* %R: NA CLSI: MIC range: 0.007–2 GM: 0.15 MIC90: 0.25 *n*/*N* %R: 1.0%	EUCAST MIC range: GM: 0.133 MIC90: 0.12 *n*/*N* %R: NA CLSI MIC range: 0.007–2 GM: 0.016 MIC90: 0.03 *n*/*N* %R: 1.0%	EUCAST MIC range: <0.03–0.5 GM: 0.106 MIC90: 0.25 *n*/*N* %R: 0/103 0% CLSI MIC range: 0.03–1.0 GM: 0.19 MIC90: 0.5 *n*/*N* %R: 0/103 0%	EUCAST MIC range: <0.12–>64 GM: 0.133 MIC90: 0.12 *n*/*N* %R: ND CLSI ND
Guo 2017[51]	CLSI microbroth dilution	Range: ND MC50: ND MIC90: ND R%: ND I%: ND S/WT: ND	0.008–0.5 0.125 0.125 1.1% 7.2% 91.7%	0.008–0.125 0.016 0.064 0% 1.7% 98.3%	0.125–2 0.5 1 0% 0% 100%	0.064–128 0.064 0.064 1.1% 0% 98.9%
Hesstvedt 2017[36]	EUCAST broth microdilution	*n*/*N* R%: 5/292 1.71%	ND	ND	ND	ND
Hou 2017[44]	Sensititre YeastOne CLSI M27-S4 BP	Range: <0.015–>8 MIC90: 0.06 MIC50: 0.03 R/nWT%: 0.5%	<0.008–>8 0.12 0.06 0.5%	<0.008–>8 0.015 0.015 0.5%	<0.12–2 1 0.5 0%	<0.06–>64 0.06 0.06 0.2

Table 6. Continued

Author year	MIC method	Anidulafungin	Caspofungin	Micafungin	Amphotericin B	Flucytosine*
Hou 2018[52]	CLSI broth microdilution	R%: 1.9%	R%: 1.9%	R%: 1.9%	R%: 0%	R%: 0%
Kamikawa 2014[54]	ASTY broth microdilution CLSI BP	ND	ND	MIC range: 0.03–4 MIC50: 0.125 MIC90: 1.0 *n*/*N* %R: 1/36 2.78%	MIC range: 0.125–>16 MIC50: 0.5 MIC90: 1.0 %R: 0%	MIC range: <0.125–64 MIC50: <0.125 MIC90: 8 *n*/*N* nWT%: 1/36 2.78%
Kaplan 2019[90]	CLSI M27-A3	MIC range: <0.015–0.06 MIC50: <0.015 MIC90: 0.03 *n*/*N* %R: 0/103 0%	MIC range: <0.015–0.06 MIC50: 0.015 MIC90: 0.015 *n*/*N* %R: 0/103 0%	ND	MIC range: 0.5–2 MIC50: 1.0 MIC90: 2.0 *n*/*N* %nWT: 0/103 0%	ND
Katsuragi 2014[39]	CLSI M27-S3	ND MIC50: ND MIC90: ND %R: ND	ND	<0.03–0.06 <0.03 0.06 NA	0.13–1 0.5 1 NA	<0.16–0.25 <0.13 0.13 0
Khalifa 2020[56]	CLSI broth microdilution M27-Ed4	MIC range: ND GM MIC: ND *n*/*N* %R: ND	0.12–8 0.40 14/43 32.6%	0.015–2 0.02 2/43 4.7%	0.5–1.0 0.86 0/43 0%	0.12–64 0.15 2/43 4.7%
Khan 2020[37]	Etest CLSI	ND	2011–2014 Range: 0.002–1 GM: 0.12 *n*/*N* R%: 5/594 0.84% 2015–2018 Range: 0.002–1.5 GM: 0.11 *n*/*N* R%: 9/631 1.43%	ND	2011–2014 Range: 0.002–32 GM: 0.1 *n*/*N* R%: 0/594 0% 2015–2018 Range: 0.002–8 GM: 0.12 *n*/*N* R%: 0/631 0%	ND
Klotz 2016[46]	EUCAST E.Def 7.2	MIC range: 0.03–2 MIC50: 0.06 MIC90: 0.06 *n*/*N* R%: 1/64 1.6%	0.016–16 0.03 0.06 0/64 1.6%	0.016–1 0.016 0.016 1/1.6 1.6%	0.125–0.25 0.25 0.5 0/64 0%	ND
Ko 2018[27]	VITEK 2 AST CLSI BP	%R: ND	0%	5.30%	6.50%	ND
Lindberg 2019[93]	Sensititre YeastOne CLSI BP	MIC range: 0.015–0.06 MIC50: 0.03 MIC90: 0.03 CLSI %R: 0%	0.03–0.25 0.06 0.12 0%	0.008–0.03 0.015 0.015 0%	0.25–2 1 1 ND	0.06–2 0.06 0.06 ND
Lott 2012[53]	CLSI M27-A3	ND	ND	ND	*n*/*N* %R: 0/201 0%	ND
Maraki 2019[67]	Vitek 2 AST CLSI BP	ND	ND	ND	*n*/*N* %S: 168/168 100% *n*/*N* %R: 0/168 0%	*n*/*N* %S: 166/168 98.8% *n*/*N* %SDD: 0/168 0% *n*/*N* %R: 2/168 1.2%

Table 6. Continued

Author year	MIC method	Anidulafungin	Caspofungin	Micafungin	Amphotericin B	Flucytosine*
Meletiadis 2017[96]	EUCAST broth microdilution	Range: 0.008–0.063 MIC50: 0.031 MIC90: 0.063 %R: 0.0%	ND	Range: 0.004–0.031 MIC50: 0.016 MIC90: 0.0315 %R: 0.0%	Range: 0.25–1 MIC50: 0.5 MIC90: 1.0 %R: 0.0%	ND
Morales-Lopez 2017[97]	CLSI broth microdilution M27-A3, M27-S4 BP	Range: 0.015–0.06 %R: 0%	0.015–0.25 0%	ND	ND	ND
Nakamura-Vasconcelos 2017[47]	CLSI M27-A3 broth microdilution	MIC range: ND MIC50: ND MIC90: ND %R: ND	ND	ND	0.25–4.0 1.0 1.0 3%	ND
Pfaller 2012[59]	CLSI broth microdilution	2001–2004 *n*/*N* %R: 0/110 0% 2006–2010 *n*/*N* R%: 15/162 9.3%	2001–2004 *n*/*N* %R: 0/110 0% 2006–2010 *n*/*N* R%: 15/162 9.3%	2001–2004 *n*/*N* %R: 0/110 0% 2006–2010 *n*/*N* R%: 13/162 8.0%	ND	ND
Pham 2014[28]	CLSI broth microdilution	MIC range: 0.008–4 *n*/*N* %R: 43/1380 3.1%	MIC range: 0.015–16 *n*/*N* %R: 45/1380 3.3%	MIC range: 0.008–4 *n*/*N* %R: 50/1380 3.6%	ND	ND
Puig-Asensio 2016[29]	CLSI M27-A3 and EUCAST E.Def 7.1 and E.Def 7.2	EUCAST MIC 90: 0.03 MIC range: 0.03–0.5 %R: 1/94 1.1% CLSI MIC 90: 0.06 MIC range: 0.007–1 %R: 1/94 1.1%	EUCAST MIC 90: 1 MIC range: 0.25–1 %R: NA CLSI MIC 90: 0.25 MIC range: 0.007–>2 %R: 1/94 1.1%	EUCAST MIC 90: 0.03 MIC range: 0.03–1 %R: 1/94 1.1% CLSI MIC 90: 0.03 MIC range: 0.007–2 %R: 1/94 1.1%	ND	ND
Singh 2018[98]	CLSI broth microdilution M27-A3 M27-S4	MIC range: 0.032–0.25 GM: 0.12 MIC50: 0.125 MIC90: 0.125	MIC range: 025–4 GM: 1.31 MIC50: 1 MIC90: 1	MIC range: <0.016–0.032 GM: 0.01 MIC50: 0.015 MIC90: 0.015	MIC range: <0.016–1 GM: 0.21 MIC50: 0.25 MIC90: 0.5	MIC range: 0.125 GM: 0.12 MIC50: 0.12 MIC90: 0.12
Szweda 2015[45]	Sensititre YeastOne CLSI BP	*n*/*N* %R: 0/81 0%	*n*/*N* %R: 0/81 0%	*n*/*N* %R: 0/81 0%	*n*/*N* %R: 0/81 0%	*n*/*N* %R: 3/81 3.70%
Toth 2019[57]	CLSI broth microdilution	MIC range: 0.008–0.12 MIC50: 0.03 MIC90: 0.06 %R: 0%	MIC range: 0.12–1 MIC50: 0.5 MIC90: 0.5 %R: 63%	MIC range: 0.008–0.06 MIC50: 0.03 MIC90: 0.06 %R: 0%	MIC range: 0.25–2 MIC50: 0.5 MIC90: 1.0 %R:	ND
UluKilic 2017[25]	CLSI M27-A3	ND	*n*/*N* %R: 0/31 0%	ND	ND	ND
Vatanshenassan 2019[99]	CLSI broth microdilution	*n*/*N* S%: 65/100 65% *n*/*N* I %: 26/100 26% *n*/*N* R%: 9/100 9%	ND	ND	ND	ND
Xiao 2015[38]	Sensititre YeastOne CLSI BP	MIC range: <0.015–0.25 GM MIC: 0.03 %R/nWT: 0.4%	MIC range: <0.008–0.25 GM MIC: 0.07 %R/nWT: 0%	MIC range: 0.008–0.06 GM MIC: 0.01 %R/nWT: 0%	MIC range: <0.12–1 GM MIC: 0.58 %R/nWT: 0%	MIC range: 0.06–0.5 GM MIC: 0.03 %R/nWT: 0%
Yao 2019[42]	ATB Fungus 3 CLSI BP	ND	ND	ND	*n*/*N* %R: 0/59 0%	*n*/*N* %R: 0/59 0%

Note: Susceptibility is expressed as mg/l unless indicated otherwise. ND = not done. MIC/50/90 = minimum inhibitory concentration/50%/90%. BP = breakpoints. S/SDD/I/R%= susceptible/susceptible dose dependent/intermediate/resistant%. nWT = non-wild-type.
*Data are reported as they appear in sources documents. CLSI has no clinical breakpoints for flucytosine; the validity of data categorised as S, I, or R are unclear.

Table 7. Risk factors.

Author year	Study design	Study design	Study period	Country	Level of care	Population description	Number of patients	Risk factors
Arastehfar 2019[48]	Retrospective cohort study	MC	2015–2018	Iran	No defined	Any patients	65	Other infections and tumors (47.7%) Trauma and surgery (20.00%) Metabolic disorders (9.23%) Haematology disease (7.69%) Autoimmune disease and liver and kidney dysfunctions (each 4.62%) Gastrointestinal bleeding (GIB; 3.08%) Poisoning (1.54%) Elderly (median age 58)
Awad 2018[60]	Retrospective cohort study	SC	2010–2015	Lebanon	Tertiary	All patients	ND	Increasing consumption of antifungal correlated with increasing proportion *Candida* isolates being *C. glabrata* (Spearman's coefficient 0.13, i.e., weak correlation) OBSGYN dept had highest proportion of *C. glabrata* amongst non-*albicans* isolates
Ben-Ami 2012[101]	Prospective cohort study	MC	2005–2007	Israel	Tertiary	All patients with candidaemia	Not clear	OR for candidaemia being caused by *C. glabrata* Prior exposure to metronidazole OR 3.2 (1.7–6.0, $P < .001$) Poor performance status OR 1.8 ($P = .04$) Neutropenia OR 0.1 ($P = .03$) Presence of CVC OR 0.4 ($P = .02$)
Ben-Ami 2013[80]	Prospective cohort study	MC	2005–2007	Israel	Tertiary	All candidaemia	ND	Hospital >600 bed vs. < 600 bed: 0.23/100 000 pt days vs. 0/100 000 pt days ($P = .002$) Rate of candidaemia was the same in different institutions, but the proportion caused by *C. glabrata* or other fluconazole resistant isolates was much higher in bigger hospital with more services, esp haem-onc (no stats specifically for *C. glabrata*)

Table 7. Continued

Author year	Study design	Study design	Study period	Country	Level of care	Population description	Number of patients	Risk factors
Beyda 2014[55]	Retrospective cohort study	SC	2009–2012	USA	Tertiary	All patients with *C. glabrata* candidaemia	72	OR for infection with caspo resistant *C. glabrata* Prior echinocandin exposure OR 9.88 (95% CI 4.67–84.65; $P \leq .01$)
Bordallo-Cardona 2019[21]	Retrospective cohort study	SC	2007–2016	Spain	Tertiary	Patients with candidaemia or endocarditis	82	CVC, TPN, antimicrobial use, surgery (especially abdominal), immunosuppression, impact not measured
Goemaere 2018[41]	Retrospective cohort study	SC	2004–2015	Belgium	Tertiary	All hospital patients	187	Duration of fluconazole (days) prior (OR 1.13 [1.01–1.26, $P = .041$])
Guo 2017[51]	Prospective cohort study	MC	2012–2013	China	Tertiary	Adults and children with invasive yeast infection	181	Risk increased with age (impact not defined)
Hesstvedt 2017[36]	Retrospective cohort study	MC	2010–2011	Denmark, Norway, Finland, and Sweden	National surveillance	Adults and children with candidaemia	Unlcear	Consumption of azoles nationally (OR not calculated)
Hu 2019[88]	Retrospective cohort study	SC	2010–2013	China	Tertiary	Adults attending mucosal disease clinic	165 *C. glabrata* patients (9769 oral candidiasis)	Immune deficiency especially HIV were common underlying conditions for invasive disease
Khatib 2016[26]	Retrospective cohort study	SC	2007–2015	USA	Tertiary	Adult patients with candidaemia	Unclear	OR for *C. glabrata* vs. *C. albicans*: diabetes 2.55 (1.46–4.48, $P = .001$) and abdominal surgery 3.36 (1.72–6.58, $P < .001$)
Lindberg 2019[93]	Retrospective cohort study	MC	2013–2016	Sweden	Various	Adults and children with presumed sepsis	ND	Older age (impact not defined)
Malani 2011[64]	Prospective cohort study	ND	2006–2008	USA	Various inc community	Adults in community, hospital, and care homes	62	OR for colonization: Increasing age by 1 year: 1.01 (1.001.1.03, $P = .03$) Dentures: 3.1 (1.8–5.3, $P < .001$) Community dwelling: 0.45 (0.26–0.77, $P = .004$) Diabetes and psychotropic drugs were not relevant
Moretti 2013[61]	Retrospective cohort study	SC	2006–2010	Brazil	Tertiary	All adult and child patients with candidaemia, except neonates	35	Heavy use of fluconazole in hospital service (not quantified)

Table 7. Continued

Author year	Study design	Study design	Study period	Country	Level of care	Population description	Number of patients	Risk factors
Smyth 2018[63]	Retrospective cohort study	MC	2011–2017	UK	Tertiary	Adults with candidaemia	124	Found diabetes and age were NOT risk factors
Tapia 2012[62]	Case control study	MC	1998–2006	USA	Tertiary	Cases: Adult patients with C glabrata candidaemia; controls adult patients with non-glabrata candidaemia	68	Risk for *C. glabrata* vs. other candidaemia (all $P < .05$): <7 day admission: 3.71 (1.81–7.61) Abdo surgery <30 day: 2.76 (1.49–5.10) Fluconazole use <30 day: 2.21 (1.03–4.75) No renal failure: 2.18 (1.18–4.02)
Ulu Kilic 2017[25]	Retrospective cohort study	SC	2010–2016	Turkey	Tertiary	Adults and children with candidaemia	41	Central line present 89% non-*albicans* vs. 76.9% *albicans* candidaemias
Vergidis 2016[100]	Retrospective cohort study	SC	2012–2013	USA	Tertiary	Adult with abdominal candidiasis	45	Two or more prior abdo surgeries: 47% *C. glabrata* vs. 22% other *Candida* sp., $P = .007$.

Notes: MC = multi-centre, ND = not determined, SC = single centre.

with diabetes,[26] while two others found no association.[63,64] No studies investigated the impact of modifying these risk factors.

Annual incidence

The annual incidence of *C. glabrata* candidaemia, as reported in six studies is summarised in Table 8. The incidence ranged from 0.67 to 2.66 per 100 000 population per year, but all population-based estimates were derived from high-income settings. More studies reported *C. glabrata* candidaemia as a proportion of all candidaemia episodes, as shown in Table 9. In the majority of these studies, *C. glabrata* was responsible for 10%–30% of candidaemia episodes, with a range of 1.69%–45.2%.

Current global distribution

Candida glabrata is a globally distributed yeast species, with no studies reporting geographic limits. Its incidence at the population level and the proportion of candidaemias it causes can vary, but these differences may be influenced by factors beyond geography, such as the use of antifungal agents, population demographics, and the prevalence of underlying conditions associated with infection.

Trends in last 10 years

Of the 17 studies that reported on changes in incidence or prevalence of *C. glabrata* infections (see Table 10), 12 described increases. Rajendran et al.[65] reported a doubling in prevalence from 21% to 45% as a proportion of all candidaemias, which was similarly observed in other large studies.[32,41,54,61,66] Three of these studies had a low risk of bias. Four studies found the proportion of infections caused by *C. glabrata* to be stable, though with some variation.[26,28,39,67]

Discussion

Candida glabrata (now *N. glabrata*) is a common pathogenic yeast.[68] *Candida glabrata* infections are a concern due to their increasing incidence and reduced susceptibility to commonly used antifungal agents.[69] The incidence of *C. glabrata* bloodstream infections has been increasing in recent years, and it is now one of the leading causes of candidemia in some regions of the world.[70]

Risk factors associated with *C. glabrata* infections include the use of broad-spectrum antimicrobials, immunosuppressive therapies, invasive medical procedures, and hospitalisation. One of the major clinical challenges with *C. glabrata* infections is its resistance to antifungal agents, particularly azoles. Although echinocandins are the recommended first-line therapy for invasive candidiasis, they are unavailable in many low- and middle-income settings, with the result that azoles are still frequently relied upon.[71] *Candida glabrata* has an intrinsically reduced susceptibility to azoles. There is also increasing incidence of the acquisition of frank resistance to these and other antifungal agents, such as echinocandins,[72] with several reports suggesting high rates of resistance to caspofungin and micafungin.[7,73,74]

Our systematic review examined the burden of *C. glabrata* and its implications for global health. A notable finding is that of the 71 studies included in the final analysis, only 30 were assessed as having a low risk of bias. Not only are available data sparse, but they are often collected and reported in ways that

Table 8. Annual incidence.

Author year	Study design	Study sites	Study period	Country	Number of patients	Annual incidence (per 100 000 population/year)
Astvad 2018[58]	Laboratory surveillance	Multi-centre (13 labs)	2012–2015	Denmark	617	2.66
Ben-Ami 2013[80]	Prospective cohort study	Multi-centre (18 hospitals)	2005–2007	Israel	69	0.85
Chapman 2017[66]	Cross sectional study	Multi-centre (29 labs)	2014–2015	Australia	133	2.41
Hesstvedt 2017[36]	Retrospective cohort study	Multi-centre (national ref labs)	2010–2011	Denmark, Norway, Finland, and Sweden	292 *C. glabrata* (out of total 1263 *Candida*)	Denmark 2.92 Finland 0.72 Norway 0.46 Sweden 0.67
Puig-Asensio 2016[29]	Prospective cohort study	Multi-centre (29 hospitals)	2010–2011	Spain	94	1.08
Rajendran 2016[65]	Retrospective cohort study	Multi-centre (11 health boards)	2012–2013	UK	98	1.85

Table 9. Proportion of invasive candidiasis caused by *C. glabrata*.

Author year	Study design	Study sites	Study period	Country	Proportion of invasive candidiasis caused by *C. glabrata* (*N. glabrata*)
Awad 2018[60]	Retrospective cohort study	SC	2010–2015	Lebanon	197 *C. glabrata*/1377 all *Candida* spp. isolated (14%)
Cuenca-Estrella 2011[49]	Laboratory surveillance	MC	2003–2009	Spain	16.1% of all candidaemia 682/4226
Deorukhkar 2016[85]	Retrospective cohort study	SC	2007–2014	India	*Candida glabrata* was 31.5% of all candidaemia
Gonzalez-Lara 2017[24]	Retrospective cohort study	MC	2008–2014	Mexico	30 *C. glabrata*/149 candidaemia 20.1%
Guinea 2014[50]	Prospective cohort study	MC	2010–2011	Spain	103/781 episodes of fungaemia 13.2%
Guo 2017[51]	Prospective cohort study	MC	2012–2013	China	181 *C. glabrata*/1153 invasive *Candida* isolates 15.7% 85 *C. glabrata*/457 blood stream isolates 18.6%
Hesstvedt 2017[36]	Retrospective cohort study	MC	2010–2011	Denmark, Norway, Finland, and Sweden	% of all candidaemias Denmark - 29% Finalnd 18% Norway 11.7% Sweden 15.4%
Hu 2019[88]	Retrospective cohort study	SC	2010–2013	China	165/9769 - 1.69% oral *Candida* isolates
Kamikawa 2014[54]	Prospective cohort study	SC	2012–2013 (+ historical comparison 2006–2007)	Japan	36/154 oral candidiasis caused by *C. glabrata* 23.4%
Lei 2018[92]	Lab surveillance	SC	2012–2016	China	207 *C. glabrata*/2099 *Candida* spp. 9.86% invasive isolates
Lindberg 2019[93]	Retrospective cohort study	MC	2013–2016	Sweden	27 *C. glabrata*/143 patients with fungaemia 19%
Malani 2011[64]	Prospective cohort study	ND	2006–2008	USA	62 *C. glabrata*/408 total *Candida* isolates, 15.2%
McCarty 2018[95]	Other: Lab surveillance	SC	2005–2015	USA	832 *C. glabrata*/3876 *Candida* spp. (21.47%) various sites
Medeiros 2019[94]	Retrospective cohort study	SC	2011–2016	Brazil	6 *C. glabrata*/51 candidaemia 11.76%
Meletiadis 2017[96]	Lab surveillance	MC	2002–2004	No stated	86 *C. glabrata*/1099 *Candida* isolates 7.83% various sites
Miranda-Cadena 2018[40]	Retrospective cohort study	SC	2003–2013	Spain	114 *C. glabrata*/1328 *Candida* isolates 8.6%
Moretti 2013[61]	Retrospective cohort study	SC	2006–2010	Brazil	35 *C. glabrata*/313 candidaemia 11.18%
Puig-Asensio 2016[29]	Prospective cohort study	MC	2010–2011	Spain	103 *C. glabrata*/773 candidaemia 13.4%
Rajendran 2016[65]	Retrospective cohort study	MC	2012–2013	UK	98 *C. glabrata* of/217 candidaemia 45.2%
Smyth 2018[63]	Retrospective cohort study	MC	2011–2017	UK	34 *C. glabrata* of 126 candidaemia 26.98%
Tang 2014[32]	Retrospective cohort study	SC	2009–2012	Taiwan	29 *C. glabrata*/242 candidaemia 11.98%
Tapia 2012[62]	Case control study	MC	1998–2006	USA	68/246 27.6%
UluKilic 2017[25]	Retrospective cohort study	SC	2010–2016	Turkey	41 *C. glabrata* BSI out of 351 candidaemia - 11.7%
Vergidis 2016[100]	Retrospective cohort study	SC	2012–2013	USA	45 *C. glabrata* out of 180 *Candida* abdo infections 25%

Notes: MC = multi-centre, ND = not determined, SC = single centre.

are either not systematic or not transparent. There is a need for standardised, comprehensive surveillance systems and studies.

Although the burden of disease is clearly substantial, it is difficult to quantify since robust global estimates of incidence are unavailable and there is a paucity of clinical metadata on deaths, disability, other complications, and length of hospital stay. The high mortality rates observed may reflect the severity of underlying diseases, but without well-designed epidemiological studies, this can be difficult to fully assess. Future studies should focus on collecting secure clinical data from patients, including complications and sequelae of *C. glabrata* infections in patients.

The antifungal resistance data in this study were particularly robust, revealing high rates of resistance in azoles and, to a lesser extent, echinocandins. It is noteworthy that resistance to echinocandins in this species is especially important

Table 10. Trends in the last 10 years.

Author year	Study design	Study sites	Study period	Country	Trends in the last 10 years
Arastehfar 2020[79]	Retrospective cohort study	MC	2005–2019	Turkey	$n = 19$ 2005–2014 vs. $n = 35$ 2015–2019–>total number of candidaemia caused by *C. glabrata* increasing
Astvad 2018[58]	Other: Laboratory surveillance	MC	2012–2015	Denmark	Increasing proportion candidaemias. 31.8% in 2012–2015. Annual change in OR for *C. glabrata* 1.11 $P < .001$.
Chapman 2017[66]	Cross sectional study	MC	2014–2015	Australia	Proportion of candidaemia caused by *C. glabrata* increased by 1.7 fold from 2004 (to 26.7%)
Goemaere 2018[41]	Retrospective cohort study	SC	2004–2015	Belgium	Increasing 0.08/10 000 pt days in 2005 to 0.53/10 000 pt days in 2013
Hu 2019[88]	Retrospective cohort study	SC	2010–2013	China	Proportion of patients with *C. glabrata* mono-infection doubled from 8 (0.3%) to 16 (0.68%) from 2010 to 2013
Kakeya 2018[89]	Retrospective cohort study	MC	2003–2014	Japan	*Candida glabrata* was significantly more common in 2008–2014 of the study period, compared to 2003–2007 (11.6% vs. 17.8%, $P = .003$)
Kamikawa 2014[54]	Prospective cohort study	SC	2012–2013 (+ historical comparison 2006–2007)	Japan	14.1% of all oral candidiasis caused by *C. glabrata* in 2006–2007, increase to 32.1% in 2012–2013
Katsuragi 2014[39]	Retrospective cohort study	SC	2007–2011	Japan	Stable at 20% as proportion of all *Candida* isolates
Khatib 2016[26]	Retrospective cohort study	SC	2007–2015	USA	Proportion candidaemia caused by *C. glabrata* varies up and down over time (range 16.7%–46.4%)
Maraki 2019[67]	Prospective cohort study	SC	2012–2017	Greece	No change over time
McCarty 2018[95]	Other: Lab surveillance	SC	2005–2015	USA	Not possible to extract accurately, but proportion *C. glabrata* to *Candida* spp. has increased
Moretti 2013[61]	Retrospective cohort study	SC	2006–2010	Brazil	Increasing from 2008 (4.8%) to 2010 (23.5%)
Pham 2014[28]	Retrospective cohort study	MC	2008–2013	USA	Numbers not reported but states proportion is stable
Rajendran 2016[65]	Retrospective cohort study	MC	2012–2013	UK	Increased to 45.2% of candidaemia species from 21% in 2007
Tang 2014[32]	Retrospective cohort study	SC	2009–2012	Taiwan	Increasing (<5% in 2009 to 15% in 2012)
UluKilic 2017[25]	Retrospective cohort study	SC	2010–2016	Turkey	Increasing as proportion of candidaemia from 2010 to 2015

Notes: MC = multi-centre, SC = single centre.

due to its intrinsic high MICs to azoles. Several high-quality studies from diverse geographic locations have reported rates of resistance greater than 10% in both classes, which aligns with previous clinical data. Moreover, several reports have documented the rise in echinocandin resistance, and there are several papers demonstrating resistance development under echinocandin treatment.[75–77] Despite these findings, the impact of antifungal resistance on clinical outcomes remains poorly quantified.

While the acquisition of invasive candidiasis is generally understood, there is currently insufficient high-quality data to inform on its preventability. Although several risk factors have been identified, it is unclear whether modifying them would reduce the incidence of the disease. One study suggested that standard infection prevention and control measures were helpful, but it failed to quantify the impact. Host immunity plays a significant role in the development of invasive candidiasis. Further studies into prophylaxis are needed

to understand the best approaches, particularly given increasing rates of resistance.

One major limitation of this study is that there were few studies retrieved from low- and middle-income countries, which may indicate publication bias. Possible explanations include limited funding and technical capability resulting in fewer studies in those regions and potentially compounded by our inability to include non-English language literature.

Another major limitation is that due to our cutoff date for publication inclusion (February 2021), we could not evaluate the impact of the COVID-19 pandemic on *C. glabrata* infections in this systematic review. Future studies may investigate the impact of the COVID-19 pandemic on *C. glabrata* infected patients.

Candida glabrata (*N. glabrata*) is a significant fungal pathogen that poses a high but ill-defined burden on patients and healthcare systems worldwide. It is a global pathogen with increasing incidence and high mortality rates. Antifungal resistance rates are high and increasing, especially for the first-line agents—azoles and echinocandins. Careful and ongoing systematic surveillance is needed to better define the burden of infection, including complications, disabilities, and sequelae. Amongst research priorities for this pathogen should be the development of new antifungal agents to combat resistance and the evaluation and implementation of strategies to prevent infection from occurring in the first place.

Acknowledgement

This work, and the original report entitled 'WHO Fungal Priority Pathogens List to Guide Research, Development, and Public Health Action', was supported by funding kindly provided by the Governments of Austria and Germany (Ministry of Education and Science). We acknowledge all members of the WHO Advisory Group on the Fungal Priority Pathogens List (WHO AG FPPL), the commissioned technical group, and all external global partners, as well as Haileyesus Getahun (Director Global Coordination and Partnerships Department, WHO), for supporting this work. The authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policies, or views of the World Health Organization.

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Conflict of interests

The authors declare no conflict of interest.

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Received: September 11, 2023. **Revised:** December 3, 2023. **Accepted:** April 27, 2024