Medical Mycology, 2024, **62**, myae040
https://doi.org/10.1093/mmy/myae040
Review

Candida tropicalis—A systematic review to inform the World Health Organization of a fungal priority pathogens list

Caitlin Keighley[1,2,3,†], Hannah Yejin Kim[1,4,5,†], Sarah Kidd[6,7], Sharon C-A. Chen[1,2], Ana Alastruey[8], Aiken Dao[1,5], Felix Bongomin[9], Tom Chiller[10], Retno Wahyuningsih[11], Agustina Forastiero[12], Adi Al-Nuseirat[13], Peter Beyer[14], Valeria Gigante[14], Justin Beardsley[1,5], Hatim Sati[14,†], C. Orla Morrissey[15,16,†] and Jan-Willem Alffenaar[1,4,5,*,†]

[1]Sydney Infectious Diseases Institute, The University of Sydney, Sydney, NSW, Australia
[2]Centre for Infectious Diseases and Microbiology Laboratory Services, Institute of Clinical Pathology and Medical Research, NSW Health Pathology, Westmead Hospital, Westmead, NSW, Australia
[3]Southern IML Pathology, 3 Bridge St, Coniston, NSW, Australia
[4]Faculty of Medicine and Health, School of Pharmacy, The University of Sydney, Sydney, NSW, Australia
[5]Westmead Hospital, Westmead, NSW, Australia
[6]National Mycology Reference Centre, Microbiology & Infectious Diseases, SA Pathology, Adelaide, SA, Australia
[7]School of Biological Sciences, University of Adelaide, Adelaide, SA, Australia
[8]Mycology Reference Laboratory, National Centre for Microbiology, Instituto de Salud Carlos III, Majadahonda, Madrid, Spain
[9]Department of Medical Microbiology & Immunology, Faculty of Medicine, Gulu University, Gulu, Uganda
[10]Mycotic Diseases Branch, Centers for Disease Control and Prevention, Atlanta, GE, USA
[11]Department of Parasitology, Faculty of Medicine, Universitas Kristen Indonesia, Jakarta, Indonesia
[12]Servicio de Micologia, Laboratorio de Microbiologia, Hospital Britanico, Buenos Aires, Argentina
[13]World Health Organization Regional Office for the Eastern Mediterranean, Cairo 11371, Egypt
[14]AMR Division, World Health Organization, Geneva
[15]The Alfred Hospital, Department of Infectious Diseases, Melbourne, Victoria, Australia
[16]Monash University, Department of Infectious Diseases, Central Clinical School, Faculty of Medicine, Nursing and Health Sciences, Melbourne, Victoria, Australia

*To whom correspondence should be addressed. Jan-Willem Alffenaar, PhD, The University of Sydney, Faculty of Medicine and Health, School of Pharmacy, Pharmacy Building (A15), NSW, 2006, Sydney, Australia. Tel: +61 2 8627 0019; E-mail: johannes.alffenaar@sydney.edu.au
†These authors contributed equally to this work.

Abstract

In response to the growing global burden of fungal infections with uncertain impact, the World Health Organization (WHO) established an Expert Group to identify priority fungal pathogens and establish the WHO Fungal Priority Pathogens List for future research. This systematic review aimed to evaluate the features and global impact of invasive candidiasis caused by *Candida tropicalis*. PubMed and Web of Science were searched for studies reporting on criteria of mortality, morbidity (defined as hospitalization and disability), drug resistance, preventability, yearly incidence, diagnostics, treatability, and distribution/emergence from 2011 to 2021. Thirty studies, encompassing 436 patients from 25 countries were included in the analysis. All-cause mortality due to invasive *C. tropicalis* infections was 55%–60%. Resistance rates to fluconazole, itraconazole, voriconazole and posaconazole up to 40%–80% were observed but *C. tropicalis* isolates showed low resistance rates to the echinocandins (0%–1%), amphotericin B (0%), and flucytosine (0%–4%). Leukaemia (odds ratio (OR) = 4.77) and chronic lung disease (OR = 2.62) were identified as risk factors for invasive infections. Incidence rates highlight the geographic variability and provide valuable context for understanding the global burden of *C. tropicalis* infections. *C. tropicalis* candidiasis is associated with high mortality rates and high rates of resistance to triazoles. To address this emerging threat, concerted efforts are needed to develop novel antifungal agents and therapeutic approaches tailored to *C. tropicalis* infections. Global surveillance studies could better inform the annual incidence rates, distribution and trends and allow informed evaluation of the global impact of *C. tropicalis* infections.

Key words: *Candida tropicalis*, candidaemia, invasive fungal infection, global epidemiology, mortality.

Introduction

Candida tropicalis is important as a cause of invasive candidiasis with high mortality.[1–5] Whilst the 30-day mortality of candidaemia lingers unchanged at 30%–40%,[6–9] that of *C. tropicalis* bloodstream infections has been reported to be as high as 52%.[10] This heightened mortality emphasizes the critical need for a deeper understanding of the factors contributing to the virulence of *C. tropicalis* and the development of effective treatment strategies. The proportion of *Candida* bloodstream infections caused by *C. tropicalis* waspreviously surpassed by *C. albicans*, *Nakaseomyces glabratus* (previously *C. glabrata* complex) and/or *C. parapsilosis* complex,[6,11,12] however, in

Received: September 9, 2023. **Revised:** January 14, 2024. **Accepted:** April 29, 2024

Southeast Asia and South America it has overtaken and has been reported as the first or second most important cause of *Candida* bloodstream infections.[13,14]

The shift in the epidemiology of infections from *C. albicans* to non-*albicans Candida* and other yeast spp., including *C. tropicalis*, has been associated with increasing resistance to antifungal agents.[1,15,16] This phenomenon underscores the urgency of monitoring and addressing antifungal resistance, particularly in the context of *C. tropicalis* infections. Notably, an Australian report described an increase in resistance from rare, <2%, to 16.7% a decade later.[16,17] Thus, data focusing on *C. tropicalis* and its differentiation from other *Candida* spp. are important.

As part of the WHO development of the first FPPL, this systematic review aimed to evaluate the features and global impact of invasive candidiasis caused by *C. tropicalis*. The criteria for evaluation included mortality, hospitalisation and disability, antifungal drug resistance, preventability, yearly incidence, global distribution, and emergence in the last 10 years. Identified knowledge gaps for *C. tropicalis* were highlighted for further research. By addressing these gaps, this review contributes to a more comprehensive understanding of the clinical and epidemiological aspects of *C. tropicalis* infections, thus informing strategies for its management and control.

Materials and Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[18] Adherence to PRISMA guidelines enhances the transparency and reproducibility of this review's methodology. PubMed and Web of Science databases were used. Eligibility criteria for studies were any population including adults and children, reports with specific data on *Candida tropicalis* infection or of isolates, observational studies, randomised controlled trials, guidelines, epidemiology, or surveillance reports and, publication between 1 January 2011 and 19 February 2021.

Reports were eligible if they included data on at least one of the prespecified criteria being mortality, hospitalisation and disability, antifungal drug resistance, preventability, yearly incidence, global distribution, and emergence over the last 10 years. Studies reporting on non-human data including animals and plants, studies not reporting on *C. tropicalis*, studies with no data on the prespecified criteria above, case reports, conference abstracts and reviews, reports on novel antifungal agents in pre-clinical, early phase trials or not licenced, *in vitro* papers on resistance mechanisms and papers not written in English were excluded.

Search strategy

On PubMed, the search was optimized using the medical subject headings (MeSH) with keyword terms in the title or abstract for each criterion (not case sensitive). The final search used (*Candida tropicalis*[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 tropicalis*') OR TI=('*C. tropicalis*')], 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 articles from each database were imported into a reference manager, Endnote®.

Study selection

The final search results from each database were incorporated into the online systematic review software, Covidence® (Veritas Health Innovation, Sydney, Australia). Duplicates were removed in Covidence®. The remaining articles underwent title and abstract screening based on the inclusion criteria. No reason was provided for article exclusion during title and abstract screening. Full-text screening was performed for the final set of eligible articles; excluded articles were recorded with reasons. All of the title, abstract and full-text screenings were performed independently by two reviewers (HK, CK) using Covidence®. Discrepancies were resolved by a third reviewer (JWA). Additional articles identified from the references of the included articles were added and screened. The resulting articles were subject to the final analysis (Figure 1).

Data collection

Data from the final list of included studies were extracted for the relevant criteria. The extracted data was checked by the second reviewer (20% check).

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 randomized trials version 2 (ROB 2) tool was used to assess the randomised controlled trials.[19] The risk of bias in non-randomized 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 as low, high risk or some concerns. Using the RoBANS tool, the studies were rated as having 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 particular study. Following that strategy, studies classified as unclear or high overall risk were still considered for analysis.

Data extraction

The extracted data on the outcome criteria were quantitatively or qualitatively synthesised depending on the amount and nature of the data.

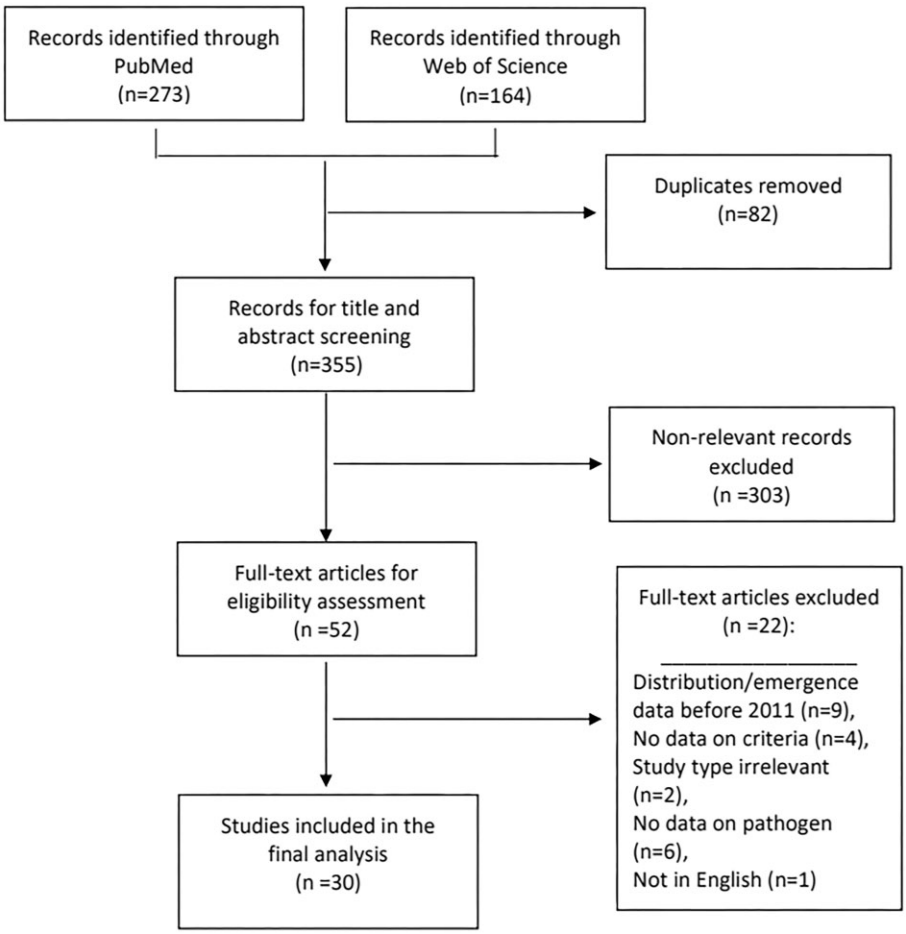

Figure 1. Flow diagram for selection of studies included in the systematic review. *Based on:* Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement.[57]

Results

Study selection

PubMed and Web of Science Core Collection databases searched between 1 January 2011 and 19 February 2021 yielded 273 and 164 articles, respectively. Duplicates were removed and the remaining, 355 articles underwent title/abstract screening. After excluding non-relevant articles, 52 articles underwent full-text screening. After excluding articles based on the full-text review, 30 studies were included in the final analysis, including 436 patients from 25 countries. A flow diagram outlining the process of study selection is shown in Figure 1.

Risk of bias

Overall risk of bias for each study is presented in Table 1. Of the included studies, 14 were classified as having a low risk of bias in all the domains assessed. Nine studies were classified as unclear risk of bias, mostly due to the potential selection biases caused by unclear eligibility criteria or population groups, or unclear confirmation/consideration of confounding variables. Seven studies were classified as high risk, because of the selection bias due to inadequate considerations in the selection of patients or eligibility criteria.

Deaths

Mortality data are summarized in Table 2. Overall mortality due to *C. tropicalis* candidaemia was as high as 55%–60% (105/186).[1,21] Five studies reported on the 30-day mortality rates in *C. tropicalis* candidaemia patients ranging from 32% to 52%.[2,10,11,22,23] Overall mortality rates in paediatric patients with invasive *C. tropicalis* infections were 26%–40%.[24,25]

Inpatient care

Hospital length of stay due to *C. tropicalis* could not be assessed due to a lack of data from the included studies.

Complications and sequelae

Disability due to *C. tropicalis* could not be assessed due to a lack of data from the included studies.

Antifungal resistance

In total, 25 studies reported on the drug susceptibility or resistance rates of *C. tropicalis*. Details of these studies are presented in Table 3. Drug susceptibility to azoles and other antifungal drugs are presented in Tables 4 and 5, respectively.

Table 1. Risk of bias

Author	Publication year	Risk (low, high, unclear)	Reference
Al-obaid et al.	2017	High	58
Arastehfar, Daneshnia, et al.	2020	Low	1
Arastehfar et al.	2020	Low	21
You et al.	2020	Unclear	23
Zhou et al.	2019	High	59
Castanheira et al.	2020	Low	26
Chapman et al.	2017	Low	16
Chen et al.	2019	Low	31
Eliakim-Raz et al.	2016	Unclear	60
Fan et al.	2017	High	32
Fernández-Ruiz et al.	2015	Low	11
Guinea et al.	2014	Unclear	[-]
Guo et al.	2017	High	39
Jordan et al.	2014	High	24
Kang et al.	2017	Low	22
Karadag-Oncel et al.	2015	Low	25
Katsuragi et al.	2014	Low	35
Khadka et al.	2017	Low	33
Ko et al.	2019	Unclear	2
Liu et al.	2019	Unclear	10
Medeiros et al.	2019	Low	27
Megri et al.	2020	Unclear	4
Siopi et al.	2020	Low	28
Tang et al.	2014	Low	40
Tasneem et al.	2017	Unclear	29
Toda et al.	2019	Low	34
Wang et al.	2020	Unclear	36
Wang et al.	2020	Unclear	37
Wang et al.	2016	High	61
Xiao et al.	2015	Low	30
Yfsudhason et al.	2015	High	38

Resistance rates to fluconazole were variable between studies. A majority of the studies reported resistance rates of 0%–18%,[10,16,21,26–34] with up to 3–4-fold increases in fluconazole resistance rates in the last 10 years[16,31,32] though differences in methodology should be noted, as well as unclear interpretation of trailing endpoints. Four studies reported resistance rates as high as 36%–42% to fluconazole,[35–38] from non-sterile sites. Similarly, non-wild type (non-WT) rates for itraconazole ranged from 0% to 26%,[30–32,34,38,39] in most of the studies, except in three reporting rates of 41%–73%.[16,35,37] For voriconazole, resistance rates were also generally comparable ranging from 0% to 22%,[10,16,21,26,28,30–32,35,39] except in two studies by Wang et al. reporting 41%–44% resistance rates[36,37] largely from urogenital tract isolates. Fan *et al*. and Siopi *et al*. reported 0% non-WT rates for posaconazole.[28,32] In contrast, two studies reported high posaconazole non-wild type rates of 71%–83%.[16,31] Chen *et al*. reported cross-resistance or non-wild type rate to itraconazole, voriconazole, and posaconazole in patients with fluconazole-resistant *C. tropicalis* infection.[31] It should be noted however that these authors applied EUCAST breakpoints to a methodology designed for CLSI breakpoints, and it was not clear whether duplicate isolates from the same patient were included.

Resistance rates to echinocandins, including anidulafungin, caspofungin and micafungin were low (0%–1%).[16,21,26,28,30–32,39] Similarly, *C. tropicalis* isolates showed a low non-WT rate to amphotericin B (0% in most studies)[16,26,27,29–32,39] and to 5-flucytosine (0%–4%).[16,30–32,35,39]

Preventability

Risk factors for invasive *C. tropicalis* infections included leukaemia (OR 4.77) and chronic lung disease (OR 2.62)[11] compared with infections caused by other *Candida* species (Table 6). Renal impairment and high Acute Physiology and Chronic Health Evaluation II (APACHE II) score were also associated with *C. tropicalis* candidaemia compared with non-*albicans Candida* candidaemia ($P < .001$).[2] A higher proportion of paediatric intensive care unit (PICU) patients with invasive *C. tropicalis* infections were more likely to have prolonged neutropenia compared with other *Candida* species infections (42% vs. 7.5%) ($P < .05$).[24]

Annual incidence

Two studies reported on the annual incidence rates of *C. tropicalis* (Table 7). Fernández-Ruiz et al. reported an annual incidence of 0.62 cases per 100 000 population, based on the observation of 59/752 (7.8%) of candidaemia episodes involving *C. tropicalis* in Spain.[11] In Australia, based on the observation of *C. tropicalis* accounting for 4%–5% of candidaemia cases, an annual incidence of *C. tropicalis* was estimated at 0.11 cases per 100 000 population.[16]

Current global distribution

Data on the prevalence of *C. tropicalis* in different regions were observed to be limited. In addition to the studies reporting *C. tropicalis* incidence in Australia and Spain (Ta-

Table 2. Mortality

Author	Year	Study design		Study period	Country	Level of care	Population description	Number of patients	Mortality type	N/N, %
Arastehfar, Daneshnia, et al. [1]	2020	Retrospective cohort study	Multi-centre	09/2014–02/2019	Iran	Not stated	Patients with candidaemia	62	Overall mortality	37/62, 59.6%
Arastehfar et al. [21]	2020	Retrospective cohort study	Multi-centre	2010–2019 (variable per site)	Turkey	Tertiary	Patients with candidaemia	127	Overall mortality	68/124, 54.8%
You et al. [23]	2020	Retrospective cohort study	Multi-centre	01/2011–12/2018	China	Tertiary	Haematology patients with candidaemia	90	30-day mortality	30-day mortality: 30/90, 33.3% 8-day mortality: 20/90, 22.2%
Fernández-Ruiz et al. [11]	2015	Retrospective cohort study	Multi-centre	05/2010–04/2011	Spain	Tertiary	Patients with candidaemia	59	30-day mortality	18/56, 32%
Jordan et al. [24]	2014	Retrospective cohort study	Multi-centre	01/2008–12/2009	Spain	Tertiary	Paediatric intensive care patients with invasive candidiasis	19	Overall mortality	5/19, 26.30%
Kang et al. [22]	2017	Retrospective cohort study	Multi-centre	2007–2014	Korea	Tertiary	Patients with candidaemia	46	30-day mortality	18/44, 34%
Karadag-Oncel et al. [25]	2015	Retrospective cohort study	Single centre	01/2004–12/2012	Turkey	Tertiary	Candidaemic children; febrile neutropaenic patients and premature infants excluded	20	30-day mortality	8/20, 40%
Ko et al. [2]	2019	Retrospective cohort study	Multi-centre	01/2010–02/2016	Korea	Tertiary	>16 years old with non-albicans candidaemia	263	30-day mortality	116/163, 44.1%
Liu et al. [10]	2019	Retrospective cohort study	Multi-centre	07/2011–06/2014	Taiwan	Tertiary	Adults aged > 20 years with candidaemia	248	30-day mortality	129/248, 52%
Medeiros et al. [27]	2019	Retrospective cohort study	Single centre	01/2011–12/2016	Brazil	Tertiary	All patients	14	30-day mortality	6/14, 42%
Megri et al. [4]	2020	Retrospective cohort study	Multi-centre	2016–2019	Algeria	Tertiary	All patients	16	In-hospital	13/16, 82%
Tang et al. [40]	2014	Retrospective cohort study	Single centre	2009–2012	Taiwan	Tertiary	Adult patients with cancer	52	In-hospital	25/52, 48%

Table 3. Studies reporting drug susceptibility/resistance

Author	Year	Study design		Study period	Country	Level of care	Population description	Number of patients	Number of isolates	Samples collected from
Al-obaid et al. [58]	2017	Retrospective cohort study	Single centre	03/2015–10/2015	Kuwait	Tertiary	All patients	54	63	Blood, genito-urinary, respiratory and digestive tracts and wounds
Arastehfar, Daneshnia, et al. [1]	2020	Retrospective cohort study	Multi-centre	09/2014–02/2019	Iran	Not stated	Patients with candidaemia	62	64	Blood
Arastehfar et al. [21]	2020	Retrospective cohort study	Multi-centre	2010–2019 (variable per site)	Turkey	Tertiary	Patients with candidaemia	127	161	Blood
You et al. [23]	2020	Retrospective cohort study	Multi-centre	01/2011–12/2018	China	Tertiary	Haematology patients with candidaemia	90	90	Blood
Zhou et al. [59]	2019	Retrospective cohort study	Single centre	01/2012–12/2017	China	Tertiary	Adult burns intensive care patients with candidiasis	Uncertain	68	Blood (6), Other including wound, intravascular catheter, respiratory tract and urine (64)
Castanheira et al. [26]	2020	Prospective cohort study	Multi-centre	01/2016–12/2017	25 countries	Tertiary	All patients	Uncertain	227	Blood, respiratory tract, wounds, urine and other
Chapman et al. [16]	2017	Prospective cohort study	Multi-centre	2014–2015	Australia	Mix	Patients with candidaemia	24	24	Blood
Chen et al. [31]	2019	Prospective cohort study	Single centre	03/2011–12/2017	Taiwan	Tertiary	Adult patients with candidaemia	344	344	Blood
Eliakim-Raz et al. [60]	2016	Retrospective cohort study	Single centre	01/2007–12/2014	Israel	Tertiary	Adult patients with candidaemia	16	16	Blood
Fan et al. [32]	2017	Retrospective cohort study	Multi-centre	08/2009 and 07/2014	China	Tertiary	Patients with invasive candidiasis	Uncertain	507	Blood (220), ascitic fluid (130), bronchoalveolar lavage (36), wounds (36), biliary fluid (27), other (65)
Fernández-Ruiz et al. [11]	2015	Retrospective cohort study	Multi-centre	05/2010–04/2011	Spain	Tertiary	Patients with candidaemia	59	59	Blood
Guinea et al. [48]	2014	Prospective cohort study	Multi-centre	05/2010–04/2011	Spain	Tertiary probably	Patients with candidaemia	Uncertain	59	Blood
Guo et al. [39]	2017	Prospective cohort study	Multi-centre	01/2012–12/2013	China	Tertiary	All patients with invasive candidiasis	Uncertain	160	61 Blood, 41 ascitic fluid, 18 BAL 12 CVC tips, 6 pus, 8 bile, 9 pleural fluid, 4 CSF, 1 tissue
Katsuragi et al. [35]	2014	Retrospective cohort study	Single centre	01/2007–12/2011	Japan	Tertiary	All patients	212	212	Sputum (123), Urogenital (49), Stool (17), Intra-body materials (11), Blood (11), Others (1)
Khadka et al. [33]	2017	Retrospective cohort study	Single centre	07/2014–01/2015	Nepal	Tertiary	All patients	20	20	Urine (12), Sputum (8)
Liu et al. [10]	2019	Retrospective cohort study	Multi-centre	07/2011–06/2014	Taiwan	Tertiary	Adults aged > 20 years with candidaemia	248	248	Blood

Table 3. Continued

Author	Year	Study design		Study period	Country	Level of care	Population description	Number of patients	Number of isolates	Samples collected from
Medeiros et al. [27]	2019	Retrospective cohort study	Single centre	01/2011–12/2016	Brazil	Tertiary	Patients with candidaemia	12	12	Blood
Megri et al. [4]	2020	Retrospective cohort study	Multi-centre	2016–2019	Algeria	Tertiary	All patients	16	19	Blood
Siopi et al. [28]	2020	Retrospective cohort study	Single centre	2009–2018	Greece	Tertiary	Patients with candidaemia	31	31	Blood
Tasneem et al. [29]	2017	Cross sectional study	Single centre	01/2014–02/2015	Pakistan	Tertiary	Patients with candida at any site	26	26	Urine (10), vaginal (6), sputum (4), tracheal lavage (3), pus (3)
Wang et al. [36]	2020	Retrospective cohort study	Single centre	12/2018–11/2019	China	Tertiary	Patients with C tropicalis urogenital infections	64	64	Urogenital
Wang et al. [37]	2020	Cross sectional study	Single centre	12/2018–11/2019	China	Tertiary	Patients with candida infection	84	87	Urine (43), vaginal swabs (22), blood (11), bile (4), sputum (4), catheter tips (2), ascites (1)
Xiao et al. [30]	2015	Prospective cohort study	Multi-centre	08/2009–07/2012	China	Tertiary	Patients with invasive candidiasis	Uncertain	379	Blood (148), ascitic fluid (100), central line catheter (12), pus (17), bronchoalveolar lavage (28), bile (28), pleural fluid (23), cerebrospinal fluid (13), tissue (9), peritoneal dialysate (1)
Yfsudhason et al. [38]	2015	Prospective cohort study	Single centre	01/2013–12/2013	India	Tertiary	Any isolates	Uncertain	61	urine (39), vaginal swabs (12), exudates (4), blood (6)
Toda [34]	2019	Retrospective cohort study	Multi-centre	2012–2016	USA	Tertiary	Patients with candidaemia	52	52	Blood

Table 4. Drug susceptibility to azoles

Author	Number of isolates	MIC method	Fluconazole	Voriconazole	Posaconazole	Itraconazole	Isavuconazole
Al-obaid et al. [58]	63	Vitek 2 YST AST/CLSI BPs	R: 0, 0% Range: 1–1 MIC50: 1 MIC90: 1	R: 0, 0% Range: 0.12–0.12 MIC50: 0.12 MIC90: 0.12	Not done	Not done	Not done
Arastehfar, Daneshnia, et al. [1]	64	CLSI M27-A3	R: 4, 6.25% [a] SDD: 7, 10.9% GM: 0.9 Range: 0.125–64 MIC50: 0.5 MIC90: 4	R: 7, 10.9% I: 18, 28.1% GM: 0.14 Range: 0.016–4 MIC50: 0.125 MIC90: 1	Not done	NWT: 2, 3.1% GM: 0.26 Range: 0.06–16 MIC50: 0.25 MIC90: 1	Not done
Arastehfar et al. [21]	161	CLSI M27-A3	R: 15, 9.3% [b] SDD: 1, 0.6%	R: 16, 9.9% I: 2, 1.2%	NWT: 25, 15.5%	NWT: 20, 12.4%	NWT: 22, 13.7%
Zhou et al. [59]	68	CLSI M44-A2	R or SDD: 34, 50%	R or I: 23, 33.3%	Not done	NWT: 34, 50%	Not done
Castanheira et al. [26]	227	CLSI M27-A3	R: 6, 2.6% [c] SDD: 1, 0.4%	R: 4, 1.8% I: 3, 1.3%	NWT: 17, 7.5%	Not done	Not done
Chapman et al. [16]	24	Sensititre YeastOne/CLSI BPs	R: 4, 16.7% SDD: 2, 8.3% GM: 2.6 Range: 0.5–256 MIC90: 64	R: 4, 16.7% I: 5, 19.3% GM: 0.2 Range: 0.008→8 MIC90: 3	NWT: 17, 71% GM: 0.18 Range: 0.0015–1 MIC90: 0.5	NWT: 17, 71% GM: 0.18 Range: 0.03–1 MIC90: 0.5	Not done
Chen et al. [31]	344	Sensititre YeastOne/CLSI BPs and EUCAST posaconazole BP	R: 48, 14% SDD: 10, 2.9% Range: 0.06–512 MIC50: 1 MIC90: 32	R or I: 75, 21.8% Range: 0.004–16 MIC50: 0.12 MIC90: 2	NWT: 285, 82.9% Range: 0.06–16 MIC50: 0.25 MIC90: 0.5	NWT: 20, 5.8% Range: 0.06–32 MIC50: 0.25 MIC90: 0.5	Not done
Fan et al. [32]	585	Sensititre YeastOne/CLSI BPs	R: 140, 12.8% SDD: 60, 10.3% GM: 2.59 MIC50: 2 MIC90: 32	R: 67, 11.4% I: 54, 9.3% GM: 0.13 MIC50: 0.12 MIC90: 1	NWT: 0, 0% GM: 0.17 MIC50: 0.12 MIC90: 0.5	NWT: 0, 0% GM: 0.21 MIC50: 0.25 MIC90: 0.5	Not done
Fernández-Ruiz et al. [11]	56	EUCAST broth microdilution	R: 13, 23.2% [d] GM: 1.83 MIC90: >64	R: 15, 26.8% GM: 0.13 MIC90: >8	R: 11, 19.6% GM: 0.047 MIC90: 8	Not done	Not done
Guinea et al. [48]	59	EUCAST and CLSI M27-A3	EUCAST R: 13, 22% GM: 1.83 Range: ≤0.12–≤64 MIC90: >64 CLSI R: 1, 1.7% SDD: 1, 1.7% GM: 0.71 Range: 0.12–8 MIC90: 1	EUCAST R: 15, 25.4% GM: 0.13 Range: ≤0.015–≤8 MIC90: >8 CLSI R: 0, 0% I: 1, 1.7% GM: 0.026 Range: 0.003–0.25 MIC90: 0.06	EUCAST R: 11, 18.6% GM: 0.047 Range: ≤0.015–≤8 MIC90: 8 CLSI R: 0, 0% GM: 0.023 Range: 0.0017–0.12 MIC90: 0.06	EUCAST GM: 0.057 Range: ≤0.015–≤8 MIC90: 8	Not done

Table 4. Continued

Author	Number of isolates	MIC method	Fluconazole	Voriconazole	Posaconazole	Itraconazole	Isavuconazole
Guo et al. [39]	160	CLSI M27-A3	R: 15, 9.4% [e] SDD: 13, 8.1% Range: 0.064–128 MIC50: 0.5 MIC90: 4	R: 15% I: 11, 6.9% Range: 0.016–8 MIC50: 0.032 MIC90: 0.25	Not done	NWT: 18, 11.2% Range: 0.032–32 MIC50: 0.25 MIC90: 1	Not done
Katsuragi et al. [35]	11	CLSI M27-A3	R: 4, 36.4% Range: 1→64 MIC50: 8 MIC90: >64	R: 0, 0% Range: 0.13–0.5 MIC50: 0.25 MIC90: 0.5	Not done	NWT: 8, 72.7% Range: 0.25→8 MIC50: 4 MIC90: >8	Not done
Khadka et al. [33]	20	CLSI M44-A disk diffusion	R: 4, 20% SDD 4, 20%	Not done	Not done	Not done	Not done
Liu et al. [10]	248	Sensititre YeastOne/CLSI BPs	R: 41, 16.5% [f] SDD 43, 17.3% [f] Range: 0.25→256 MIC50: 2 MIC90: 16	R: 32, 12.9% I: 109, 44% Range: 0.015–>8 MIC50: 0.25 MIC90: 1	NWT: 178, 71.8% Range: 0.015–2 MIC50: 0.25 MIC90: 0.5	NWT: 11, 4.4% Range: 0.06–1 MIC50: 0.25 MIC90: 0.5	Not done
Medeiros et al. [27]	12	CLSI M27-A3	R: 0, 0% SDD: 2, 16.7% Range: 0.125–4.0 MIC50: 0.5 MIC90: 4.0	Not done	Not done	R: 0, 0% SDD: 1, 8.3% Range: <0.03–0.125 MIC50: 0.03 MIC90: 0.06	Not done
Megri et al. [4]	19	CLSI M27-A3	R: 6, 31.6%	R: 9, 47.4%	Not done	NWT: 5, 26.3%	Not done
Siopi et al. [28]	23	Sensititre YeastOne/CLSI BPs	R: 0, 0% I: 1, 4% Range: 0.25–4 MIC50: 2 MIC90: 2	R: 0, 0% I: 1, 4% Range: 0.015–0.5 MIC50: 0.06 MIC90: 0.12	NWT: 0, 0% Range: 0.03–0.5 MIC50: 0.12 MIC90: 0.5	NWT: 0, 0% Range: 0.06–0.5 MIC50: 0.12 MIC90: 0.5	Not done
Tasneem et al. [29]	26	CLSI M44-A disk diffusion	R: 0, 0%	R: 2, 7.6%	Not done	Not done	Not done
Wang et al. [36]	64	CLSI M27-A4	R: 27, 42%	R: 28, 43.7%	Not done	NWT: 29, 45.3%	Not done
Wang et al. [37]	87	CLSI M27-A4	R: 36, 41.4% I, 2, 2.3% MIC50: 1 MIC90: >64	R: 36, 41.4% I: 12, 13.8% MIC50: 0.25 MIC90: 16	Not done	NWT: 36, 41.4% MIC50: 0.5 MIC90: 16	Not done
Xiao et al. [30]	379	Sensititre YeastOne/CLSI BPs	R: 31, 8.2% [g] SDD: 13, 3.4% GM: 1.9 Range: 0.25→256	R: 20, 5.3% I: 16, 4.2% GM: 0.08 Range: ≤0.008→8	NWT: 120, 31.7% GM: 0.13 Range: 0.008→8	NWT: 5, 98.7% GM: 0.18 Range: 0.015→16 NWT: 1.3%	Not done
Yfsudhason et al. [38]	61	Disk Diffusion	R: 23, 37.7%	Not done	Not done	R: 16, 26.2%	Not done
Toda [34]	52	CLSI M27-A3	R: 12, 4.2% [h]	R: 6, 2.1%	Not done	Not done	Not done

Note: Studies with a high risk of bias excluded from this table. Susceptibility values are expressed as minimum inhibitory concentrations (MICs) in mg/L. BPs, breakpoints, 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, wildtype; NWT, non-wild type. [a]2 cross-resistant to voriconazole; [b]9 cross-resistant to voriconazole; [c]4 cross-resistant to voriconazole; [d]resistance to fluconazole lower (1.7%) with CLSI method; [e]9.3% resistant/NWT to more than 2 azoles; [f]80 were R or I to voriconazole; [g]1 isolate cross-resistant to voriconazole; [h]No isolates cross-resistant. Data are given as provided in source documents.

Table 5. Drug susceptibility to other antifungal drugs

Author	Number of isolates	MIC method	Micafungin	Anidulafungin	Caspofungin	Amphotericin B	Flucytosine
Al-obaid et al. [58]	63	Vitek 2 YST AST/CLSI BPs	R: 0, 0% Range: 0.06–0.06 MIC50: 0.06 MIC90: 0.06	Not done	R: 0, 0% Range: 0.25–0.25 MIC50: 0.25 MIC90: 0.25	NWT: 0, 0% Range: 0.25–0.5 MIC50: 0.25 MIC90: 0.5	R: 1, 1.6% Range: 1.0–16 MIC50: 1 MIC90: 1
Arastehfar, Daneshnia, et al. [1]	64	CLSI M27-A3	R: 2, 3.1% GM: 0.05 Range: 0.008–1 MIC50: 0.06 MIC90: 0.25	R: 0, 0% GM: 0.04 Range: 0.008–0.5 MIC50: 0.025 MIC90: 0.125	Not done	NWT: 0, 0% GM 0.64 Range: 0.125–2 MIC50: 0.5 MIC90: 1	Not done
Arastehfar et al. [21]	161	CLSI M27-A3	R: 0, 0%	R: 0, 0%	Not done	NWT: 0, 0%	Not done
Castanheira et al. [26]	227	CLSI M27-A3	R: 2, 0.9%	R: 2, 0.9%	R: 2, 0.9%	NWT: 0, 0%	Not done
Chapman et al. [16]	24	Sensititre YeastOne/CLSI BPs	R: 0, 0% GM: 0.02 Range: <0.008–0.06 MIC90: 0.03	R: 0, 0% GM: 0.03 Range: <0.015–0.12 MIC90: 0.06	R: 0, 0% GM: 0.04 Range: 0.015–0.25 MIC90: 0.09	NWT: 0, 0% GM: 0.65 Range: <0.12–1 MIC90: 1	NWT: 1, 4% GM: 0.07 Range: <0.06–1 MIC90: 0.197
Chen et al. [31]	344	Sensititre YeastOne/CLSI BPs	R: 2, 0.6% Range: 0.015–2 MIC50: 0.03 MIC90: 0.03	R: 2, 0.6% Range: 0.008–1 MIC50: 0.06 MIC90: 0.12	R: 3, 0.9% Range: 0.015–8 MIC50: 0.06 MIC90: 0.12	NWT: 0, 0% Range: 0.25–1 MIC50: 1 MIC90: 1	NWT: 4, 1.2% Range: 0.03–64 MIC50: 0.03 MIC90: 0.06
Fan et al. [32]	585	Sensititre YeastOne/CLSI BPs	R: 2, 0.4% I: 0, 0% GM: 0.03 MIC50: 0.03 MIC90: 0.03	R: 2, 0.4% I: 2, 0.4% GM: 0.07 MIC50: 0.06 MIC90: 0.25	R: 2, 0.4% I: 0, 0% GM: 0.04 MIC50: 0.03 MIC90: 0.06	NWT: 0, 0% GM: 0.75 MIC50: 1 MIC90: 1	NWT: 3, 0.6% GM: 0.07 MIC50: 0.03 MIC90: 0.12
Fernández-Ruiz et al. [11]	56	EUCAST broth microdilution	GM: 0.034 MIC90: 0.03	R: 2, 3.6% GM: 0.034 MIC90: 0.03	GM: 0.41 MIC90: 0.5	R: 0, 0% GM: 0.079 MIC90: 0.12	Not done
Guinea et al. [48]	59	EUCAST and CLSI M27-A3	EUCAST GM: 0.034 MIC90: 0.03 Range: ≤0.03–2 CLSI R: 2, 3.4% GM: 0.021 MIC90: 0.06 Range: 0.03–1	EUCAST R: 2, 3.4% GM: 0.034 Range: ≤0.03–1 MIC90: 0.03 CLSI R: 2, 3.4% GM: 0.014 Range: 0.017–2 MIC90: 0.03	EUCAST GM: 0.41 Range:0.12–2 MIC90: 0.5 CLSI R: 0, 0% I: 1, 1.7% GM: 0.12 Range: 0.015–0.5 MIC90: 0.25	EUCAST GM: 0.079 Range: ≤0.03–0.5 MIC90: 0.12 CLSI GM: 0.22 Range: 0.03–1 MIC90: 0.5	EUCAST GM: 0.154 Range: ≤0.12–32 MIC90: 0.12
Guo et al. [39]	160	CLSI M27-A3	R: 0, 0% Range: 0.008–0.25 MIC50: 0.32 MIC90: 0.125	Not done	R: 0, 0% I: 9, 5.6% Range: 0.008-0.5 MIC50: 0.125 MIC90: 0.25	NWT: 0, 0% Range: 0.125–2 MIC50: 0.5 MIC90: 1	NWT: 0, 0% Range: 0.064–0.125 MIC50: 0.064 MIC90: 0.064
Katsuragi et al. [35]	11	CLSI M27-A3	Range: 0.06–2 MIC50: 0.06 MIC90: 0.13	Not done	Not done	Range: 0.13–1 MIC50: 0.25 MIC90: 0.5	NWT: 0, 0% Range: 0.13–4 MIC50: 0.25 MIC90: 0.25

Table 5. Continued

Author	Number of isolates	MIC method	Micafungin	Anidulafungin	Caspofungin	Amphotericin B	Flucytosine
Liu et al. [10]	248	Sensititre YeastOne/CLSI BPs	R: 4, 1.6% I: 2, 0.8% Range: 0.015–2 MIC50: 0.03 MIC90: 0.03	R: 4, 1.6% I: 1, 0.4% Range: 0.03–2 MIC50: 0.12 MIC90: 0.25	R: 4, 1.6% I: 2, 0.8% Range: 0.015–>8 MIC50: 0.06 MIC90: 0.25	NWT: 0, 0% Range: 0.12–2 MIC50: 0.5 MIC90: 1	NWT: 3, 1.2% Range: <0.06–64 MIC50: 0.06 MIC90: 0.12
Medeiros et al. [27]	12	CLSI M27-A3	R: 0, 0% Range: <0.015–1.0 MIC50: <0.015 MIC90: 0.03	Not done	Not done	R: 0, 0% Range: 0.06–1.0 MIC50: 0.25 MIC90: 1.0	Not done
Megri et al. [4]	19	CLSI M27-A3	R: 0, 0%	R: 0, 0%	Not done	NWT: 0, 0%	Not done
Siopi et al. [28]	23	Sensititre YeastOne/CLSI BPs	R: 0, 0% Range: 0.015–0.06 MIC50: 0.03 MIC90: 0.06	R: 0, 0% Range: ≤0.015–0.12 MIC50: ≤0.015 MIC90: 0.06	R: 0, 0% Range: 0.015–0.12 MIC50: 0.03 MIC90: 0.06	Not done	NWT: 0, 0% Range: ≤0.06–0.12 MIC50: ≤0.06 MIC90: 0.12
Tasneem et al. [29]	26	CLSI M44-A disk diffusion	Not done	Not done	Not done	NWT: 0, 0%	Not done
Xiao et al. [30]	379	Sensititre YeastOne/CLSI BPs	R: 0, 0% GM: 0.03 Range: ≤0.008–0.06	R: 0, 0% I: 11, 0.3% GM: 0.05 Range: ≤0.015–0.5	R: 0, 0% GM: 0.04 Range: 0.15–0.25	NWT: 0, 0% GM: 0.68 Range: 0.25–1	NWT: 3, 1.1% GM: 0.04 Range: ≤0.06→64

Note: Susceptibility values are expressed as minimum inhibitory concentrations (MICs) in mg/L. BPs, breakpoints, 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, wildtype; NWT, non-wild type. Data are given as provided in source documents.

Table 6. Risk factors

Author	Year	Study design		Study period	Country	Level of care	Population description	Number of patients	Risk factors
Fernández-Ruiz et al.[11]	2015	Retrospective cohort study	Multi-center	05/2010–04/2011	Spain	Tertiary	Patients with candidaemia	59	Bloodstream infections due to *Candida tropicalis* vs. other *Candida* species: Age [OR 1.01 (95% CI 1.00–1.02)], leukaemia [OR 4.77 (95% CI 1.96–11.6)], chronic lung disease [OR 2.62 (95% CI 1.44–4.77)]
Jordan et al.[24]	2014	Retrospective cohort study	Multi-center	01/2008–12/2009	Spain	Tertiary	Paediatric intensive care patients with invasive candidiasis	19	Neutropenia in 3/19 *C. tropicalis* vs. 5/125 any *Candida* species
Ko et al.[2]	2019	Retrospective cohort study	Multi-center	01/2010–02/2016	Korea	Tertiary	>16 years old with non-albicans candidaemia	263	Renal disease associated with *C. tropicalis* compared with other non-albicans species ($P < .001$), APACHE II scores were highest in *C. tropicalis* ($P < .001$)

Table 7. Annual incidence

Author	Publication year	Study design	Study design	Study period	Country	Level of care	Population description	Number of patients	Annual incidence
Chapman et al.[16]	2017	Prospective cohort study	Multi-center	2014–2015	Australia	Mix	Patients with candidaemia	24	0.11/100 000/year based on *Candida tropicalis* comprising around 4%–5% of candidaemia (24 isolates of 548 episodes/526 patients) and population based on annual incidence of 2.41/100 000/year (for all candidaemia)
Fernández-Ruiz et al.[11]	2015	Retrospective cohort study	Multi-center	05/2010–04/2011	Spain	Tertiary	59	59	Annual incidence 0.62 cases per 100 000 population

ble 7),[11,16] a single-center study conducted in Taiwan between 2009 and 2012 reported 52 *C. tropicalis* cases out of 242 candidaemia episodes in cancer patients, with an estimated incidence of 0.38 cases per 1000 hospital admissions (Table 8).[40]

Trends in last 10 years

Trends in the last 10 years for *C. tropicalis* could not be assessed due to a lack of data from the included studies.

Discussion

This systematic review synthesizes the available data on *Candida tropicalis*. Data specific to *C. tropicalis* is scarce with only 30 studies included in the final analysis over the 10 years. High-quality studies with low risk of bias represented just under half of these. However, the data available supports *C. tropicalis* as an important pathogen due to its increasing prevalence, high mortality, morbidity, and drug resistance.

The mortality of *C. tropicalis* infections appears to be higher than that of other *Candida* species. Overall mortality

Table 8. Distribution

Author	Publication year	Study design	Study period	Country	Level of care	Population description	Number of patients	Prevalence
Tang et al.[40]	2014	Retrospective Single-center cohort study	2009–2012	Taiwan	Tertiary	Adult patients with cancer	52	0.38 per 1000 admissions (52 tropicalis out of 242 episodes of candidaemia with an incidence of 1.77 episode per 1000 admissions)

was as high as 55%–60% and was 26%–40% in paediatric patients, with the 30-day mortality of bloodstream infection between 32% and 52%. This compares poorly to the 30-day mortality of candidaemia overall (30%–40%).[6–9,12] Virulence factors of *C. tropicalis* include biofilm formation which may contribute to worse outcomes along with higher rates of resistance.[41,42] *Candida tropicalis* pathogenicity is likely to be related to characteristics it shares with *C. albicans* of true pseudohyphae formation which aids adhesion, tissue penetration, biofilm formation and immune cell evasion, with data suggesting higher protease activity, host cell damage and biofilm formation than *C. albicans*,[43–45] contributing to high mortality.[43,46]

Morbidity may also be greater for *C. tropicalis* though the impact on inpatient care, complications or sequelae could not be assessed due to lack of data. For other *Candida* species, hospital length of stay is 2–8 weeks, and the rate of complications or sequelae is considered 'low' as survivors are seldom left with disability.

Of concern, and related to worse outcomes, are the increasing resistance rates to azoles. Resistance or non-wild type rates varied, with higher rates of resistance noted from non-sterile sites, where susceptibility testing may only be done because of lack of clinical response. It should also be noted that *C. tropicalis* is renowned for the phenomenon of producing trailing endpoints in susceptibility tests, with unclear clinical significance.[47] Few studies were noted to account for trailing,[1,16,48] and user differences between reading endpoints by eye with CLSI methodology and reading of 51% inhibition being recorded as resistant by EUCAST methodology may also lead to differences in interpretation of the trailing phenomenon, as noted with the higher rates of azole resistance with EUCAST methodology compared to CLSI in Guinea *et al.*[48] Nonetheless, the increasing reports of *ERG11* gene mutations in *C. tropicalis* associated with high-level and pan-azole resistance indicates that true azole resistance is increasing in *C. tropicalis*, and support reports of around 15%–20% resistance which is increased from previous (7%).[16,49] When examining studies with a low risk of bias, using CLSI methodology on blood culture isolates, the highest rate of fluconazole resistance was 16.7%.[16] Low resistance or non-wild type rates to echinocandins, amphotericin B and flucytosine were reassuring. Data assessing whether decreased susceptibility of *C. tropicalis* to azoles is leading to breakthrough infections or failure of therapy are needed. Whilst azole prophylaxis in haematology patients is one factor associated with breakthrough azole-resistant *C. tropicalis* infection, other risk factors play a significant role.[1,50] Azole use in the environment may select for azole-resistant *C. tropicalis* prevalent in enriched soil and be transferred into the food chain.[41,51,52]

Factors associated with the development of infection with *C. tropicalis* included immunosuppressive conditions such as leukaemia and organ dysfunction such as renal impairment and chronic lung disease. Preventative measures were not described in the retrieved articles. It remains to be seen whether measures that are relevant differ from those for other non-*albicans Candida* species and is an area for further research. Should colonization via the food chain prove important,[41,51,52] reduction in environmental use of azoles as well as close attention to cleaning food and preparation may help. Antifungal stewardship in clinical medicine is also likely to be beneficial.[53]

The extent to which the incidence of *C. tropicalis* infections has increased also warrants further study. Annual incidence rates of *C. tropicalis* infections were reported in Spain (0.62/100 000 population)[11] and in Australia (estimated to be 0.11/100 000 population).[16] Infection with *C. tropicalis* is noted globally. Several reports have shown *C. tropicalis* increasing as a proportion of all candidaemia episodes in various locations especially Brazil[14] and the Asia Pacific where it is reported as the most common species isolated.[13]

Limitations of this study include the relatively small number of studies eligible for inclusion, and the fact that many of these included substantial risk of bias. Conference abstracts were not assessed, and bias introduced by this could not be assessed, acknowledging that research from poorly resourced countries is less likely to progress to publication. Conclusions were limited by the high level of heterogeneity in the format of reporting outcome measures.

Cohort studies and sub-analysis evaluating morbidity outcome measures such as length of stay and long-term complications for invasive *C. tropicalis* infections are needed. *Candida* bloodstream infection is complicated by endocarditis in 2%–15% of cases and endophthalmitis in 1%–20% of cases, both of which are likely to have long-term morbidity though this is rarely measured.[53–56] Whilst *C. tropicalis* is the causative agent in a minority of these complications,[54–56] quantifying the long-term burden of illness on the healthcare system including cost analyses would help inform the need for preventative measures. Evaluation of potential *in vitro* and *in vivo* synergy between antifungal drugs could allow optimization of the current treatment regimens for *C. tropicalis*. Global surveillance studies could better inform the annual incidence rates, distribution and trends in other countries and regions.

Conclusion

Candida tropicalis is an important fungal pathogen associated with infection that carries a high mortality. Available data suggest increasing incidence and rates of resistance to azoles,

though these as well as risk factor analysis are poorly quantified. There is a need for high-quality studies focused on *C. tropicalis*.

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 do not necessarily represent the decisions, policies, or views of the World Health Organization.

Author contributions

Caitlin Keighley (Data curation, Formal analysis, Writing – original draft), Hannah Yejin Kim (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft), Sarah Kidd (Writing – review & editing), Sharon C-A. Chen (Writing – review & editing), Ana Alastruey (Conceptualization, Methodology, Writing – review & editing), Aiken Dao (Data curation, Investigation, Writing – review & editing), Felix Bongomin (Writing – review & editing), Tom Chiller (Writing – review & editing), Retno Wahyuningsih (Writing – review & editing), Agustina Forastiero (Writing – review & editing), Adi Al-Nuseirat (Writing – review & editing), Peter Beyer (Conceptualization, Writing – review & editing), Valeria Gigante (Writing – review & editing), Justin Beardsley (Conceptualization, Formal analysis, Methodology, Writing – review & editing), Hatim Sati (Conceptualization, Methodology, Writing – review & editing), C. Orla Morrissey (Conceptualization, Formal analysis, Methodology, Writing – review & editing), and Jan-Willem Alffenaar (Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft)

Declaration of interest

The authors have no conflicts of interest to declare.

References

1. Arastehfar A, Daneshnia F, Hafez A et al. Antifungal susceptibility, genotyping, resistance mechanism, and clinical profile of *Candida tropicalis* blood isolates. *Med Mycol*. 2020; 58: 766–773.
2. Ko JH, Jung DS, Lee JY et al. Poor prognosis of *Candida tropicalis* among non-albicans candidemia: a retrospective multicenter cohort study, Korea. *Diagn Microbiol Infect Dis*. 2019; 95: 195–200.
3. Liu WL, Huang YT, Hsieh MH et al. Clinical characteristics of *Candida tropicalis* fungaemia with reduced triazole susceptibility in Taiwan: a multicentre study. *Int J Antimicrob Agents*. 2019; 53: 185–189.
4. Megri Y, Arastehfar A, Boekhout T et al. *Candida tropicalis* is the most prevalent yeast species causing candidemia in Algeria: the urgent need for antifungal stewardship and infection control measures. *Antimicrobial Resistance Infection Control*. 2020;9: 50. https://doi.org/10.1186/s13756-020-00710-z
5. Munoz P, Giannella M, Fanciulli C et al. *Candida tropicalis* fungaemia: incidence, risk factors and mortality in a general hospital. *Clin Microbiol Infect*. 2011; 17: 1538–1545.
6. Keighley C, Chen SC, Marriott D et al. Candidaemia and a risk predictive model for overall mortality: a prospective multicentre study. *BMC Infect Dis*. 2019; 19: 445.
7. Kofteridis DP, Valachis A, Dimopoulou D et al. Factors influencing non-albicans candidemia: a case-case-control study. *Mycopathologia*. 2017; 182: 665–672.
8. Magill SS, Edwards JR, Bamberg W et al. Multistate point-prevalence survey of health care-associated infections. *N Engl J Med*. 2014; 370: 1198–1208.
9. Lockhart SR, Iqbal N, Cleveland AA et al. Species identification and antifungal susceptibility testing of *Candida* bloodstream isolates from population-based surveillance studies in two U.S. cities from 2008 to 2011. *J Clin Microbiol*. 2012; 50: 3435–3442.
10. Liu WL, Huang YT, Hsieh MH et al. Clinical characteristics of *Candida tropicalis* fungaemia with reduced triazole susceptibility in Taiwan: a multicentre study. *Int J Antimicrob Agents*. 2019; 53: 185–189.
11. Fernández-Ruiz M, Puig-Asensio M, Guinea J et al. *Candida tropicalis* bloodstream infection: incidence, risk factors and outcome in a population-based surveillance. *J Infect*. 2015; 71: 385–394.
12. Keighley CL, Pope A, Marriott DJE et al. Risk factors for candidaemia: a prospective multi-centre case-control study. *Mycoses*. 2020; 64: 257–263.
13. Chakrabarti A, Sood P, Rudramurthy SM et al. Incidence, characteristics and outcome of ICU-acquired candidemia in India. *Intensive Care Med*. 2015; 41: 285–295.
14. Pfaller MA, Diekema DJ, Gibbs DL et al. Results from the ARTEMIS DISK Global Antifungal Surveillance Study, 1997 to 2007: a 10.5-year analysis of susceptibilities of *Candida* apecies to fluconazole and voriconazole as determined by CLSI standardized disk diffusion. *J Clin Microbiol*. 2010; 48: 1366–1377.
15. McTaggart LR, Cabrera A, Cronin K, Kus JA-O. Antifungal susceptibility of clinical yeast isolates from a large Canadian reference laboratory and application of whole-genome sequence analysis to elucidate mechanisms of acquired resistance. LID - 10.1128/AAC.00402-20 [doi] LID - e00402-20. (1098-6596 (Electronic)).
16. Chapman B, Slavin M, Marriott D et al. Changing epidemiology of candidaemia in Australia. *J Antimicrob Chemother*. 2017; 72: 1103–1108.
17. Chen S, Slavin M, Nguyen Q et al. Active surveillance for candidemia, Australia. *Emerg Infect Dis*. 2006; 12: 1508–1516.
18. Page MJ, McKenzie JE, Bossuyt PM et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021; 372: n71.
19. Sterne JAC, Savović J, Page MJ et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019; 366: l4898.
20. Kim SY, Park JE, Lee YJ et al. Testing a tool for assessing the risk of bias for nonrandomized studies showed moderate reliability and promising validity. *J Clin Epidemiol*. 2013; 66: 408–414.
21. Arastehfar A, Polat SH, Daneshnia F et al. Recent increase in the prevalence of fluconazole-non-susceptible *Candida tropicalis* blood isolates in Turkey: clinical implication of azole-non-susceptible and fluconazole tolerant phenotypes and genotyping. *Front Microbiol*. 2020; 11: 587278. https://doi.org/10.3389/fmicb.2020.587278
22. Kang SJ, Kim SE, Kim UJ et al. Clinical characteristics and risk factors for mortality in adult patients with persistent candidemia. *J Infect*. 2017; 75: 246–253.
23. You LS, Yao CY, Yang F et al. Echinocandins versus amphotericin B against *Candida tropicalis* fungemia in adult hematological patients with neutropenia: a multicenter retrospective cohort study. *Infect Drug Resist*. 2020; 13: 2229–2235.

24. Jordan I, Hernandez L, Balaguer M et al. *C. albicans*, *C. parapsilosis* and *C. tropicalis* invasive infections in the PICU: clinical features, prognosis and mortality. *Rev Esp Quimioter*. 2014; 27: 56–62.
25. Karadag-Oncel E, Kara A, Ozsurekci Y et al. Candidaemia in a paediatric centre and importance of central venous catheter removal. *Mycoses*. 2015; 58: 140–148.
26. Castanheira M, Deshpande LM, Messer SA, Rhomberg PR, Pfaller MA. Analysis of global antifungal surveillance results reveals predominance of Erg11 Y132F alteration among azole-resistant *Candida parapsilosis* and *Candida tropicalis* and country-specific isolate dissemination. *Int J Antimicrob Agents*. 2020; 55: 105799.
27. Medeiros MAP, Melo APV, Bento AO et al. Epidemiology and prognostic factors of nosocomial candidemia in Northeast Brazil: a six-year retrospective study. *PLoS One*. 2019; 14: e0221033.
28. Siopi M, Tarpatzi A, Kalogeropoulou E et al. Epidemiological trends of fungemia in Greece with a focus on candidemia during the recent financial crisis: a 10-year survey in a tertiary care academic hospital and review of literature. *Antimicrob Agents Chemother*. 2020; 64: e01516–19. https://doi.org/10.1128/aac.01516-19
29. Tasneem U, Siddiqui MT, Faryal R, Shah AA. Prevalence and antifungal susceptibility of *Candida* species in a tertiary care hospital in Islamabad, Pakistan. *J Pak Med Assoc*. 2017; 67: 986–991.
30. Xiao M, Fan X, Chen SCA et al. Antifungal susceptibilities of *Candida glabrata* species complex, *Candida krusei*, *Candida parapsilosis* species complex and *Candida tropicalis* causing invasive candidiasis in China: 3 year national surveillance. *J Antimicrob Chemother*. 2015; 70: 802–810.
31. Chen PY, Chuang YC, Wu UI et al. Clonality of fluconazole-nonsusceptible *Candida tropicalis* in bloodstream infections, Taiwan, 2011–2017. *Emerg Infect Dis*. 2019; 25: 1660–1667.
32. Fan X, Xiao M, Liao K et al. Notable increasing trend in azole non-susceptible *Candida tropicalis* causing invasive candidiasis in China (August 2009 to July 2014): molecular epidemiology and clinical azole consumption. *Front Microbiol*. 2017;8: 464. https://doi.org/10.3389/fmicb.2017.00464
33. Khadka S, Sherchand JB, Pokhrel BM et al. Isolation, speciation and antifungal susceptibility testing of *Candida* isolates from various clinical specimens at a tertiary care hospital, Nepal. *BMC Res Notes*. 2017; 10: 218.
34. Toda M, Williams SR, Berkow EL et al. Population-based active surveillance for culture-confirmed candidemia - four sites, United States, 2012–2016. *MMWR Surveill Summ*. 2019; 68: 1–15.
35. Katsuragi S, Sata M, Kobayashi Y et al. Antifungal susceptibility of *Candida* isolates at one institution. *Med Mycol J*. 2014; 55: E1–7.
36. Wang QY, Li CR, Tang DL, Tang KW. Molecular epidemiology of *Candida tropicalis* isolated from urogenital tract infections. *Microbiologyopen*. 2020;9: e1121. https://doi.org/10.1002/mbo3.1121.
37. Wang QY, Tang DL, Tang KW, Guo J, Huang Y, Li CR. Multilocus sequence typing reveals clonality of fluconazole-nonsusceptible *Candida tropicalis*: a study from Wuhan to the global. *Front Microbiol*. 2020; 11: 11554249.
38. Yfsudhason BL, Mohanrani K. *Candida tropicalis* as a predominant isolate from clinical specimens and its antifungal susceptibility pattern in a tertiary care hospital in Southern India. *J Clin Diagnos Res*. 2015;9: DC14–6. https://doi.org/10.7860/jcdr/2015/13460.6208.
39. Guo LN, Xiao M, Cao B et al. Epidemiology and antifungal susceptibilities of yeast isolates causing invasive infections across urban Beijing, China. *Future Microbiol*. 2017; 12: 1075–1086.
40. Tang HJ, Liu WL, Lin HL, Lai CC. Epidemiology and prognostic factors of candidemia in cancer patients. *PLoS One*. 2014;9: e99103.
41. Cordeiro Rde A, de Oliveira JS, Castelo-Branco Dde S et al. *Candida tropicalis* isolates obtained from veterinary sources show resistance to azoles and produce virulence factors. *Med Mycol*. 2015; 53: 145–152.
42. Moralez AT, Franca EJ, Furlaneto-Maia L, Quesada RM, Furlaneto MC. Phenotypic switching in *Candida tropicalis*: association with modification of putative virulence attributes and antifungal drug sensitivity. *Med Mycol*. 2014; 52: 106–114.
43. Yang B, Wei Z, Wu M, Lai Y, Zhao W. A clinical analysis of *Candida tropicalis* bloodstream infections associated with hematological diseases, and antifungal susceptibility: a retrospective survey. Original research. *Front Microbiol*. 2023; 14: 1092175. https://doi.org/10.3389/fmicb.2023.1092175
44. Saiprom N, Wongsuk T, Oonanant W, Sukphopetch P, Chantratita N, Boonsilp S. Characterization of virulence factors in *Candida* species causing candidemia in a Tertiary Care hospital in Bangkok, Thailand. *J Fungi (Basel)*. 2023;9: 353.
45. dos Santos MM, Ishida K. We need to talk about *Candida tropicalis*: virulence factors and survival mechanisms. *Med Mycol*. 2023; 61: myad075. https://doi.org/10.1093/mmy/myad075
46. Keighley C, Pope AL, Marriott D, Chen SC, Slavin MA., Group AaNZMI. Time-to-positivity in bloodstream infection for *Candida* species as a prognostic marker for mortality. *Med Mycol*. 2023; 61: myad028.
47. Marcos-Zambrano LJ, Escribano P, Sánchez-Carrillo C, Bouza E, Guinea J. Scope and frequency of fluconazole trailing assessed using EUCAST in invasive Candida spp. Isolates. *Med Mycol*. 2016; 54: 733–739.
48. Guinea J, Zaragoza Ó, Escribano P et al. Molecular identification and antifungal susceptibility of yeast isolates causing fungemia collected in a population-based study in Spain in 2010 and 2011. *Antimicrob Agents Chemother*. 2014; 58: 1529–1537.
49. Keighley C, Gall M, van Hal S et al. Whole genome sequencing shows genetic diversity, as well as clonal complex and gene polymorphisms associated with fluconazole non-susceptible isolates of *Candida tropicalis*. *J Fungi*. 2022;8: 896.
50. Kontoyiannis DP, Vaziri I, Hanna HA et al. Risk factors for *Candida tropicalis* fungemia in patients with cancer. *Clin Infect Dis*. 2001; 33: 1676–1681.
51. Lo HJ, Tsai SH, Chu WL et al. Fruits as the vehicle of drug resistant pathogenic yeasts. *J Infect*. 2017; 75: 254–262.
52. Yang YL, Lin CC, Chang TP et al. Comparison of human and soil *Candida tropicalis* isolates with reduced susceptibility to fluconazole. *PLoS One*. 2012;7: e34609.
53. Keighley C, Cooley L, Morris AJ et al. Consensus guidelines for the diagnosis and management of invasive candidiasis in haematology, oncology and intensive care settings, 2021. *Intern Med J*. 2021; 51 Suppl 7: 89–117.
54. Prabhudas-Strycker KK, Butt S, Reddy MT. *Candida tropicalis* endocarditis successfully treated with AngioVac and micafungin followed by long-term isavuconazole suppression. *IDCases*. 2020; 21: e00889.
55. Tanaka H, Ishida K, Yamada W, Nishida T, Mochizuki K, Kawakami H. Study of ocular candidiasis during nine-year period. *J Infect Chemother*. 2016; 22: 149–156.
56. Ueda T, Takesue Y, Tokimatsu I et al. The incidence of endophthalmitis or macular involvement and the necessity of a routine ophthalmic examination in patients with candidemia. *PLoS One*. 2019; 14: e0216956.
57. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6: e1000097.
58. Al-Obaid K, Asadzadeh M, Ahmad S, Khan Z. Population structure and molecular genetic characterization of clinical *Candida tropicalis* isolates from a tertiary-care hospital in Kuwait reveal infections with unique strains. *PLoS One*. 2017; 12: e0182292.
59. Zhou J, Tan J, Gong Y, Li N, Luo G. Candidemia in major burn patients and its possible risk factors: a 6-year period retrospective study at a burn ICU. *Burns*. 2019; 45: 1164–1171.

60. Eliakim-Raz N, Babaoff R, Yahav D, Yanai S, Shaked H, Bishara J. Epidemiology, microbiology, clinical characteristics, and outcomes of candidemia in internal medicine wards—a retrospective study. *Int J Infect Dis*. 2016; 52: 49–54.

61. Wang Y, Shi C, Liu JY, Li WJ, Zhao Y, Xiang MJ. Multilocus sequence typing of *Candida tropicalis* shows clonal cluster enrichment in azole-resistant isolates from patients in Shanghai, China. *Infect Genet Evol*. 2016; 44: 418–424.

Received: September 9, 2023. **Revised:** January 14, 2024. **Accepted:** April 29, 2024