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Sandra Cristina Santos Pinho

Rising Threat: A Systematic Review of the Global Epidemiology of Invasive Infections by Uncommon *Candida* Species

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Ciências médicas e da saúde

TÍTULO DISSERTAÇÃO

Rising Threat: A Systematic Review of the Global Epidemiology of Invasive Infections by uncommon Candida Species

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Eu, Sandra Cristina Santos Pinho, abaixo assinado, nº mecanográfico 201802347, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro que:

☒ Não procedi à utilização de ferramentas de *chatbox* generativo baseadas em *large language models* para nenhuma das tarefas no contexto do meu trabalho de Dissertação ou Monografia

☐ Procedi à utilização de ferramentas de *chatbox* generativo baseadas em *large language models* no contexto do meu trabalho de Dissertação ou Monografia, encontrando-se todas as interacções (*prompts* e respostas) transcritas em anexo bem como a indicação das aplicações utilizadas.

Neste sentido, confirmo que a eventual utilização de ferramentas de *chatbox* generativo baseadas em *large language models* no contexto do meu trabalho de Dissertação ou Monografia foi exclusivamente descrita na sequência de *prompts* e respostas transcritos em anexo e nas aplicações indicadas.

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obrigado pela oportunidade e apoio nesta fase.

Rising Threat: A Systematic Review of the Global Epidemiology of Invasive Infections by Uncommon *Candida* Species

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ABSTRACT

Emerging and atypical *Candida* species have been reported as an increasing cause of invasive fungal infections, especially in immunocompromised patients, leading to worldwide public health concerns. These infections are often associated with high mortality rates and with a reduced susceptibility to antifungal drugs.

We aim to systematize the global epidemiology associated with emergent uncommon *Candida* species responsible for invasive infections in adult patients.

A systematic review was carried out (from 1 January 2001 to 28 February 2023), following the search for articles in PubMed, SCOPUS, and Web of Science. Information regarding epidemiological, clinical, and microbiological data regarding patients with invasive *Candida* infections by uncommon *Candida* spp were collected.

One thousand five hundred and sixty-seven publications were identified, and 36 were selected according to inclusion criteria. The chosen studies covered the following *Candida* species: *C. auris* (n=21), *C. haemulonii* (n=6), *C. fermentati* (n=4, including *C. famata* detected in the same isolate), *C. kefyr* (n=4), *C. norvegensis* (n=3), *C. nivariensis* (n=3), *C. bracarensis* (n=1), *C. duobushaemulonii* (n=1), *C. blankie* (n=1), and *C. khanbai* (n=1). Candidemia was the most frequent ICI (86,9%). No data was obtained from Asia, Australia, and Antarctica. Identification with routine methods and susceptibility interpretation have been the most significant challenges encountered.

Therefore, it is crucial to focus on new and accessible microbiology techniques to make fast and accurate diagnostics and treatments.

Keywords: *Invasive infection; Candida spp.; Epidemiology; Uncommon yeast*

RESUMO

Espécies emergentes e atípicas de Candida têm sido relatadas como uma causa crescente de infeções fúngicas invasivas, especialmente em pacientes imunocomprometidos, levando a preocupações de saúde pública a nível mundial. Estas infeções estão frequentemente associadas a elevadas taxas de mortalidade e a uma reduzida suscetibilidade aos medicamentos antifúngicos.

O nosso objetivo é sistematizar a epidemiologia global associada a espécies emergentes e pouco comuns de Candida responsáveis por infeções invasivas em pacientes adultos. Foi realizada uma revisão sistemática (de 1 de janeiro de 2001 a 28 de fevereiro de 2023), após a pesquisa de artigos na PubMed, SCOPUS e Web of Science. Foram recolhidas informações relativas a dados epidemiológicos, clínicos e microbiológicos de pacientes com infeções invasivas por Candida spp incomuns.

Foram identificadas mil quinhentas e sessenta e sete publicações e 36 foram selecionadas de acordo com os critérios de inclusão. Os estudos selecionados abrangeram as seguintes espécies de Candida species: C. auris (n=21), C. haemulonii (n=6), C. fermentati (n=4, including C. famata detetado no mesmo isolado), C. kefyr (n=4), C. norvegensis (n=3), C. nivariensis (n=3), C. bracarensis (n=1), C. duobushaemulonii (n=1), C. blankie (n=1), and C. khanbai (n=1). A candidemia foi a infeção invasiva mais frequente (86,9%). Não foram obtidos dados da Ásia, Austrália e Antártida. A identificação com métodos de rotina e a interpretação da suscetibilidade foram os desafios mais significativos encontrados. Por conseguinte, é crucial focar em novas técnicas microbiológicas e acessíveis para efetuar diagnósticos e tratamentos rápidos e precisos.

Palavras-chave: Infeção invasiva; *Candida* spp; Epidemiologia; Fungos incomuns

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1. INTRODUCTION

Over the years, the enormous advances in science, including medicine, have allowed a remarkable increase in average life expectancy. However, the rise in longevity has been partly at the expense of better therapeutic options. Intensive care medicine, oncology and intensive care units, and oncology and intensive care units are some areas in which prophylaxis against bacteria and fungi has played a lead in preventing opportunistic infections in immunosuppressed individuals. In contrast, the increased use of broad-spectrum antibiotics has contributed to an increase in the incidence of opportunistic infections, particularly (but not exclusive) in immunocompromised patients, especially fungal infections.

The clinical manifestations of fungal infections include a broad spectrum ranging from superficial lesions to life-threatening invasive infections. Since the early 1980s, fungi have been leading in the etiology of invasive infections, with high mortality and morbidity rates. Over the last decade, there has been a dramatic increase in scientific studies associating sepsis with prior fungal infection [1]. According to a study developed by *Bassetti* and his colleagues in 2017, invasive infections in intensive care units are increasing, and 80% of these infections are caused by *Candida* species [2].*Candida* spp. are commonly distributed in the environment and are part of our normal microflora[3]. A transition from commensal to a pathogenic agent and evolution for invasive infections occur primarily in immunodepression situations or when barrier leakage occurs [4]. *Candida* infections can be classified as cutaneous (skin involvement), mucosal (infections affecting the oral cavity or vulvovaginal infections), or invasive when the infection reaches the bloodstream or other typically sterile sites [5]. *Candida albicans* is the most frequent species that causes invasive infections with severe repercussions not only on prognostic, morbidity, and mortality patients but also on the economic health system [3]. However, in the last decades, we have seen an increase in non-*albicans* invasive *Candida* infection (ICI) reports worldwide [6].

Although *Candida albicans* is still the most frequently isolated agent in invasive fungal infections, longitudinal studies indicate that there has been an increase in clinical isolates of uncommon *Candida* species in hospitals worldwide as causative agents of nosocomial invasive candidemias [7]. A recent ten-year analysis of the distribution of these species indicated that *C. glabrata* is the most common NAC species, and C*. parapsilosis, C. tropicalis, and C. krusei* are frequently isolated [8].

In 1991, the first case of *C. haemulonii* was reported in the USA and associated with a poor prognosis [9]. In 2009, *C. auris* was identified for the first time [10]. Since then, numerous studies have reported cases of invasive infections associated with high mortality and morbidity rates. These emerging pathogens have low susceptibility to antifungal drugs and affect mainly immunocompromised patients [11]. Consequently, ICI by uncommon *Candida* spp has led to a public health concern worldwide. This work aimed to systematically review the worldwide literature regarding the epidemiology, diagnostics, susceptibility profile, and clinical outcome of uncommon *Candida* species responsible for invasive infection.

2. METHODS

The systematic review was carried out in strict accordance with Cochrane Handbook for Systematic Reviews of Interventions[12] and reported following the preferred reporting items for systematic review and meta-analyses (PRISMA) guidelines [13] (Supplementary material, Appendix S1 PRISMA checklist).

2.1. Defining the problem and establishing the guiding question

To perform the guiding question, the PICO anagram (population; intervention, comparison, and outcome) was defined and represented in Table 1. According to the guiding question, the comparison element was not used in this work [14]. The guiding question of this research was: "What is the clinical information, diagnostics, susceptibility profile, and clinical outcome of patients with invasive infections by uncommon *Candida* species?"

Table 1: Description of the PICO anagram

PICO strategy	Elaboration of the study strategy
Population	Adults (age ≥ 18 years old) in the world diagnosed with uncommon candida non-albicans-related invasive infection
Intervention	Epidemiology of uncommon Candida species related invasive infection invasive infections
Comparison	Not applicable to this study
Outcome	Diagnosis, clinical, and geographic information

2.2. Data source and search strategy

An electronic literature search comprising keywords and MeSH (Supplementary material, Appendix S2) was carried out in databases Pubmed, Web of Science, and SCOPUS to identify case reports of patients with invasive infection caused by uncommon *Candida* species. The study was conducted from 1 January 2001 – 28 February 2023.
The search included all publication types except reviews or systematic reviews, and no language restrictions were applied.

2.3. Eligibility criteria

Studies were included in this review if they met the following criteria: (1) information reporting invasive infection by uncommon *Candida* spp in patients (≥18 years old) (2) predisposing factors/underlying medical conditions, (3) method(s) of diagnosis, susceptibility testing results, (4) information regarding treatment and other patient management strategies, and (5) patient outcome.
Uncommon *Candida* species were defined as all *Candida* spp. except *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, *C. lusitaniae* and *C. dubliniensis*.
Invasive *candida* infection, also known as invasive candidiasis or systematic candidiasis, involves the infection and dissemination of *Candida* through the bloodstream to multiple organs, such as the brain, kidney, heart, liver, and lungs [15]. Any studies without primary data or where the analysis was pooled without susceptibility testing information and clinical outcome was excluded.

2.4. Data extraction and synthesis

The screening of publications was carried out by two independently reviewers (SP and SCO), based on the eligibility criteria. The literature screening was based on a 2-step process. First, the extracted studies were uploaded to EndNote and Rayyan software[16] for duplicate removal a further selection according to the title and abstracts.
The second phase was the review of the full text of selected studies. Disagreements were resolved by consensus.
The PRISMA flowchart (figure 1) summarizes the literature search and screening strategies.

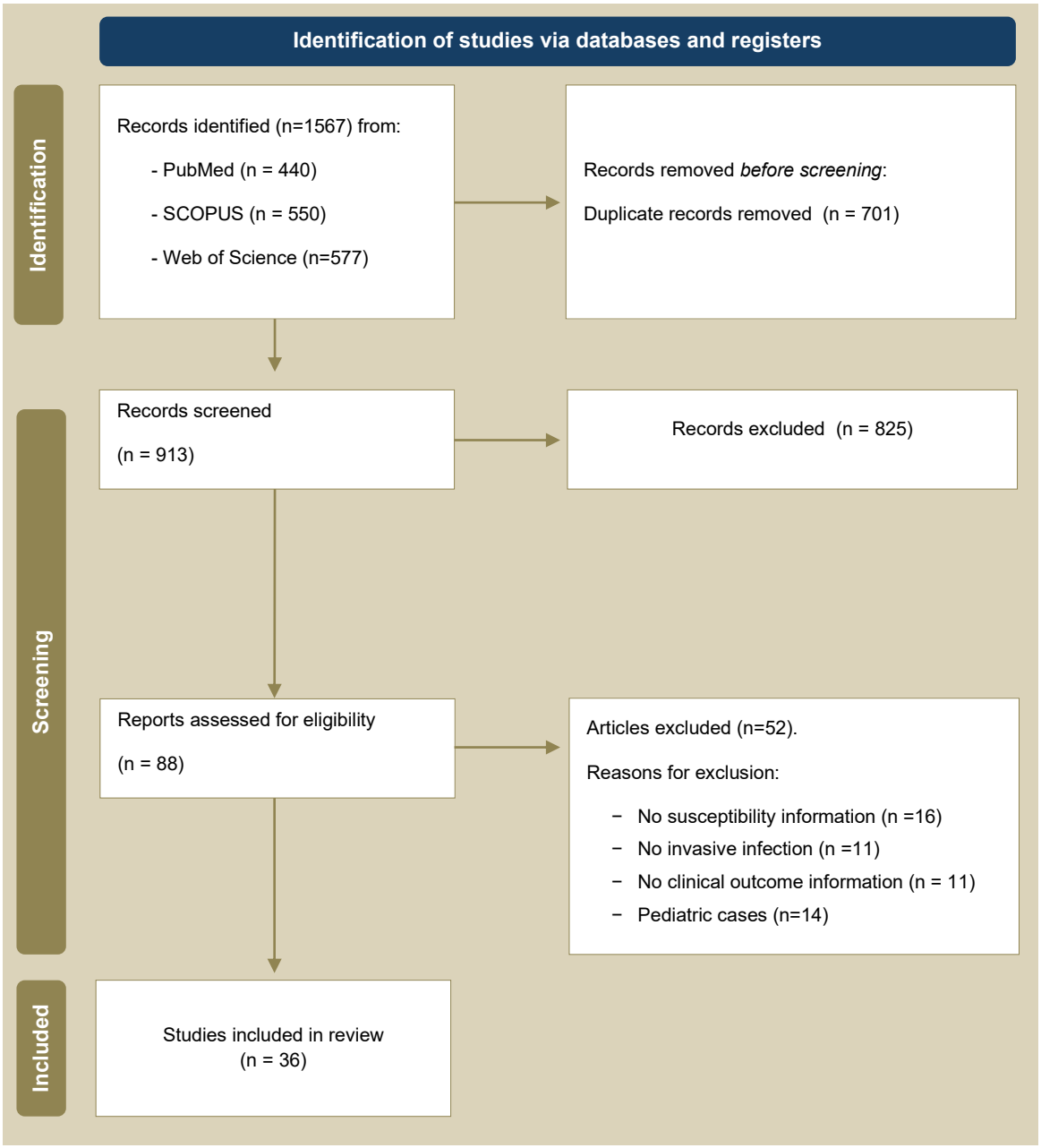

Figure 1: PRISMA flow diagram summarizing the search results.

A protocol was defined to synthesize the extracted data from the selected studies independently and compared. Data extracted included information about the publication date, country, age, gender, clinical history/underlying medical conditions, type of sample, *Candida* identification methods, susceptibility testing method and results, clinical outcome, microbiology identification method, and antifungal treatment or other management strategies.

Data were summarized using descriptive statistics, with means and standard deviations (for continuous variables) and standard deviations (for dichotomous variables).

2.5. Risk of bias (ROB) assessment

To evaluate the risk of bias in the studies included in this review, the National Institute of Health (NIH) Quality Assessment Tool for Case series Studies[17]. A 3-point scale was used to grade nine questions to evaluate the potential source of bias as good, fair, or poor. No studies were excluded based on quality. ROB assessment was performed independently by SP and IMM.

3. RESULTS

3.1. Publication characteristics

Detailed data on scientific papers included in this review are provided in Table 1.

We identified 1567 publications, including 440 from PubMed, 550 from Web of Science, 577 from SCOPUS, and 4 publications were later manually added from reference lists of identified papers. Seven hundred and one duplicates were removed using Endnote Web. After checking for duplicates, 866 studies were enrolled for the title and abstract screening were independently analyzed by two researchers. Seven hundred and seventy were excluded and 96 were enrolled for full-text screening and assessment. We excluded 47 multicentric studies, 7 pediatric publications, 2 publications in which the positive *candida* sample was not invasive, 5 publications in which treatment was not described, and 2 publications with no clinical outcome.

We included 36 publications reporting on 45 patients where clinical information of each case was reported separately. Bibliographic references for the case reports are included in Table 1. Included cases from Asia and Europe were the most common (n= 17, 37,8%; n=15 33,3% respectively), followed by America (n=8, 17,8%), and the Middle East (n=5, 11,1%).

3.2. Risk of Bias – quality assessment

Three studies were rated as Fair due to the lack of information regarding the study question[18], study population[19] and the type of intervention[20]. (Supplementary material, Appendix S2).

3.3. Patient characteristics

Among the 45 patients, 12 (median 26,7%) were female, and 33 cases (median 73,3%) were male patients. In Europe, the male proportion was significantly higher in comparison with females (male: 80%; female: 20%). In contrast, the Middle East had a major proportion of female patients (female: 80%; male: 20%). The age range was from 26 to 88 years, with a mean and standard deviation of 59,1±16.6 years.

3.4. Types of infection

The most common type of was candidemia with 40 cases in a total of 45 cases (median: 88,9%). In general, *C. auris* was the most frequent yeast reported to cause bloodstream infection (n=20, median 52,5%). *C. haemulonii* was presented in 5 cases of candidemia (12,5%); *C. fermentati* was isolated from 4 fungemia cases (10%), and *C. famata* was also isolated in one of these patients [21]. *C. norvegensis* and *C. nivariensis* were responsible for each one of the 3 cases of candidemia. One case had isolation of uncommon *candida* non-albicans related in blood, but no symptoms were associated with candidemia [22]. It also included one case of pyelonephritis, 1 case of endocarditis, 2 cases with uncommon *Candida spp.* related isolated from bronchoalveolar/pleural samples, and 2 cases of liver abscess and 1 case of bile specimen[23-29].

C. blankie, *C. duobushaemulonii*, *C. bracarensis,* and *C. khanbhai* invasive infections were less common, with only one case of each one of these [20,24,30,31]. However, atypical invasive infections were most common with these agents: endocarditis was associated with *C. blankii* invasive infection and *C. kefyr* was reported in a case of pyelonephritis [23,24].

Eighteen patients (40%) were reported to have more than one *candida* agent infection (bacterial and fungal). These cases were reported to have gastrointestinal, urinary, and upper respiratory tract infections, or other unspecified infections at the same time or recently.

Table 2: Characteristics of patients with invasive infection by uncommon *Candida* species.

	Author/Year	Country	*Candida* species	G	Age (years)	Hospital stay (days)	Death	Comorbilities	Site of isolation	Subsquent infection type	Antifungal treatment	MV	IC	Previous broad-spectrum ATB	PAT	Other infections	Microorganism
America	Biagi, M. J. et al., 2019[32]	USA	*C. auris*	M	54	≥100	No	Recurrent and recent SEPSIS Chronic tracheostomy Chronic indwelling Tubecolostomy	Blood	Candidemia	Micafungin Posaconazole Fluconazole	Yes	Yes	Yes	Yes	candiduria	*C. auris*
	Parra-Giraldo, C. M. et al., 2018[25]	Colombia	*C. auris*	M	74	17	Yes	Neuroleptic malignant syndrome Rhabdomyolysis Acute kidney failure Major depression Hypertension Mitral valve replacement Hypothyroidism	Blood	Candidemia	Anidulafungin	No	Yes	Yes	No	Nosocomial pneumonia	*Klebsiella pneumoniae*
	Kollu, V. S. et al., 2021[24]	USA	*C. blankii*	M	63	No information	No	Hypertension Dislipidemia Diabetes mellitus DRGE AVC SEPSIS recently	Blood	Endocarditis	Amphotericin Micafungin	No information	Yes	Yes	Yes	Bacteriemia	*Staphylococcus lugdunensis*
	Warren, T. A. et al., 2010[31]	Canada	*C. bracarensis*	M	50	53	Yes*	Chronic lymphocytic leukemia Bone marrow transplant 7 years previously Graft-versus-host disease	Blood	Candidemia	Caspofungin	No information	Yes	Yes	No information	Yes	*Klebsiella pneumoniae*
	Rodero, L. et al.,2002 [33]	Argentina	*C. haemulonii*	M	83	No information	No	Megaloblastic anemia	Blood	Catheter-related candidemia	No information	No	No	Yes	No	No	No
	Pérez-Lazo, G. et al., 2021[28]	Peru	*C. haemulonii*	F	72	43	No	Congenital polycystic kidney Liver disease End-stage renal disease on Hemodialysis	Purulent liver collection	Hepatic abscess	Caspofungin	No	Yes	Yes	No	No	No

	Almeida-Jr, J. N. et al., 2012[34]	Brazil	*C. haemulonii*	M	64	8	Yes	Ovarian carcinoma	Blood	Candidemia	No information	No information	Yes	Yes	No	No	No
	Corpus, K. et al., 2004 [26]	USA	*C. kefyr*	M	64	24	No	Colon cancer	Pleural fluid	Pulmonary infection	Fluconazole Amphotericin B Voriconazole	No information	Yes	Yes	Yes	Yes	*Vancomycin-resistant enterococcus faecium*
Asia	Tsai, Y. T. et al., 2022 [35]	Taiwan	*C. auris*	M	64	42	No	Diabetes mellitus Ischaemic stroke	Blood	Candidemia	Anidulafungin	yes	yes	yes	yes	Nosocomial infection	No information
	Das, S. et al., 2018[36]	India	*C. auris*	F	58	46	No	Hypertension Left ventricular failure Bronchitis Acute renal failure Spinal muscular dystrophy	Blood	Candidemia	Fluconazole	Yes	Yes	Yes	No	Yes	*Acinetobacter species*
			C. auris	M	50	25	No	Alcoholic Chronic smoker	Blood	Candidemia	Fluconazole	Yes	No	Yes	No	Tracheal aspirate	*Acinetobacter species*
			C. auris	F	26	25	No	Puerperal sepsis Acute kidney injury Multiple organ dysfunction syndrome	Blood	Candidemia	No information	Yes	Yes	Yes	No	Yes	*Klebsiella pneumoniae*
	Barantsevich, N. E. et al., 2019 [19]	Russia	*C. auris*	F	88	43	Yes	acute stroke	Blood	Candidemia	anidulafungin	Yes	Yes	Yes	No information	No information	
	Lee, W. G. et al., 2011[37]	South Korean	*C. auris*	M	74	79	Yes	Laryngeal squamous cell carcinoma Laryngectomy	Blood Catheter tip	Fungemia	Fluconazole Amphotericin	No information	yes	No information	No information	no	No
	Xie, O. et al., 2020[20]	Vietnam	*C. duobushaemulonii*	M	85	9	Yes	Non-insulin dependent diabetes IgA nephropathy	Blood	Candidemia	No information	No information	Yes	Yes	No information	Yes	*carbapenem resistant Klebsiella pneumoniae*
	Konuma, T. et al., 2017[38]	Japan	*C. fermentati*	M	68	100+	No	Leukaemia Allogeneic hematopoietic cell transplant	Blood	Candidemia	Amphotericin 5-fluorocytosine	No information	Yes	Yes	Yes	No	N/A

Morita, K. et al., 2018[21]	Japan	*C. fermentati*	M	59	35	No	Leukaemia Cord blood transplantation	Blood Bronchial lavage fluid	Candidemia	Amphotericin	No	Yes	Yes	Yes	No	No
		C. fermentati	F	63	45	Yes	Leukaemia Cord blood transplantation	Blood	Candidemia	Micafungin Amphotericin	No	Yes	Yes	Yes	No	No
		C. fermentati *C. famata*	M	70	24	Yes	Leukaemia Cord blood transplantation	Blood Bronchial lavage fluid	Candidemia	Amphotericin Micafungin Amphotericin	Yes	Yes	Yes	Yes	No	No
Ruan, S. Y. et al., 2010[39]	Taiwan	*C. haemulonii*	M	79	No information	No	Hypertension Pneumonia with respiratory failure Pneumothorax	Blood	Candidemia	Fluconazole	Yes	No	No	No	No	No
		C. haemulonii	M	85	25	No	Advanced rectal adenocarcinoma Surgery	Blood	Candidemia	Fluconazole Micafungin	Yes	Yes	No information	No information	No	No
Kim, S. et al., 2011[40]	South Korean	*C. haemulonii*	M	67	55	No	Cerebral Infarction Tracheostomy	Blood Catheter tip	Candidemia	Fluconazole Caspofungin	No	No	No	No	No	No
Jyothi, L. et al., 2021[41]	India	*C. Kefyr*	M	51	No information	No	Diabetes mellitus Hypertension Diabetic retinopathy CVA Rhabdomyolysis Acute kidney injury	Blood	Candidemia	Fluconazole	No information	Yes	Yes	No information	urinary tract infection	*Enterococcus faecalis*
de Jong, A. W. et al., 2023 [30]	Malysia	*C. khanbhai*	M	55	14	Yes	New-onset hospital-acquired pneumonia	Blood	Candidemia	NA Died before TSA	No information	No	No	No	No	No

	Fujita, S. et al., 2007[18]	Japan	*C. nivariensis*	F	70	≥100	No	Rheumatic arthritis Nutritional disorder	Blood	Candidemia	Voriconazole Micafungin	No information	No	No	Yes	No	No
Europe	Ruiz Gaitán, A. C. et al., 2017[42]	Spain	*C. auris*	M	26	56	No	Decompressive craniectomy and maxillo-facial emergencysurgery	Blood Catheter tip	Candidemia	Anidulafungin	No	No information	No	No	No	No
			C. auris	M	48	44	No	Emergent decompressive craniectomy	Blood Catheter tip	Candidemia	micafungin	Yes	No information	No	No	No	No
			C. auris	M	66	84	Yes	Hepatocellular carcinoma Liver resection	Blood Catheter tip peritoneal fluid	Candidemia	Amphotericin Anidulafungin	Yes	Yes	No information	No information	No	No
			C. auris	F	39	91	Yes	Severe ventricular dysfunction	Blood Catheter tip	Candidemia	Fluconazole	No information	No	Yes	Yes	No	No
	Vogelzang, E. H. et al., 2019[22]	Netherlands	*C. auris*	M	middle-aged	No information	No	SEPSIS recently due to pneumonia	Catheter tip	No symptoms	No	Yes	Yes	Yes	Yes	No	No
	Dewaele, K. et al., 2020 [43]	Belgium	*C. auris*	F	middle-aged	≥100	No	Bariatric surgery	Blood	Catheter-related candidemia	Anidulafungin	Yes	No	Yes	No	ITU	*Klebsiella pneumoniae Escherichia coli*
	Katsiari, M. et al., 2023 [44]	Greece	*C. auris*	M	78	20	Yes	Diabetes mellitus Arterial hypertension Stent in the common bile duct	Blood	Candidemia	Caspofungin Amphotericin B	No information	Yes	No	No	No	No

	Levy, Y. etr al., 2021[27]	France	*C. auris*	M	36	19	Yes	Paroxysmal nocturnal hemoglobinuria Cerebral thrombophlebitis	Blood Catheter tip	Candidemia	Caspofungin Amphotericin	No information	Yes	No	No	Endocarditis	*C. auris*
	Desnos-Ollivier, M. et al., 2021[45]	Greece	*C. auris*	M	54	50	Yes	Hepatitis C Liver transplantation Cholestasis	Hepatic drainage	Hepatic abcess	Caspofungin Posaconazole	No information	Yes	Yes	No	No	No
	Seth-Smith, H. M. B. et al., 2020 [46]	Switzerland	*C. Kefyr*	M	61	No information	No	Leukaemia Allogeneic haematopoietic stem cell transplantation	Blood	Candidemia	Fluconazole Posaconazol	No information	Yes	Yes	Yes	No	N/A
	Spiliopoulou, A. et al., 2022 [23]	Greece	*C. Kefyr*	M	41	50	No	Bronchial asthma Severe Covid 19	Urine (+) Blood (-)	Pyelonephritis	Amphotericin Fluconazole	Yes	No	No information	No information	No	No
	Cartier, N. et al., [47]	France	*C. nivariensis*	M	77	51	No	Urothelial carcinoma Cystoprostectomy Primary pulmonary adenocarcinoma	Blood	Candidemia	Caspofungin Voriconazole	No information	Yes	Yes	Yes	No	No
	Lopez-Soria, L. M. et al., 2013[48]	Spain	*C. nivariensis*	M	81	56	No	Jejunocolic fistula Severe malnutrition Secondary anemia bilateral Pulmonary thromboembolism	Blood	Catheter-related candidemia	Fluconazole Caspofungin	No information	No	Yes	No	No	No
	Musso, M. et al., 2014[49]	Italy	*C. norvegensis*	M	47	30	No	HCV Hepatocarcinoma Transplant	Blood Bile specimens	Candidemia Intrabdominal abscesses	Anidulafungin	Yes	Yes	Yes	Yes	Candidemia Bilateral pneumonia	*Enterococcus faecalis* *Klebsiella pneumoniae*
	Sanclemente, G. et al., 2015[29]	Spain	*C. norvegensis*	M	61	40	Yes	Hepatocellular carcinoma Liver transplantation	Blood	Candidemia	Anidulafungin	No information	Yes	Yes	Yes	no	no
Middle East	Mohsin, J. et al., 2017[50]	Oman	*C. auris*	M	77	40	No	Diabetes mellitus Hypertension Osteomyelitis	Blood	Candidemia	Caspofungin	Yes	Yes	Yes	No	Candidemia	*Escherichia coli*

		C. auris	F	70	35	Yes	Diabetes mellitus Arterial hypertension	Blood	Candidemia	Anidulafungin	No information	Yes	Yes	No	Candidemia Gastric infection	*Enterococcus faecium* *Helicobacter pylori*
	Al-Obaid, I. et al., 2022[51]	Kuwait	*C. auris*	F	32	79	Yes	Bilateral lung transplant Diabetes mellitus type 1 Chronic transplant rejection Respiratory failure	Blood Tracheal aspirate	Candidemia	Amphotericin Caspofungin Voriconazole	Yes	Yes	Yes	No	Colitis	*Cytomegalovirus*
	Alatoom, A. et al., 2018[52]	United Arab Emirates	*C. auris*	F	84	92	Yes	Chronic renal failure Hemodialysis Severe psoriasis Chronic atrial fibrillation Hypertension	Blood	Candidemia	Caspofungin Amphotericin	No information	Yes	Yes	No information	No	No
	Kiraz, N. et al., 2009[53]	Turkey	*C. norvegensis*	F	53	23	Yes	Leukaemia	Blood	Candidemia	Amphotericin	No information	Yes	Yes	Yes	No	No

Legend: Gender (G); Female (F); Male (M); Mechanical ventilation (MV); Imunocompromised (IC); Previous Antifungal therapy (PAT).

3.5. Identification method

In this work, 45 cases of uncommon *Candida* species were documented as causative agents of invasive infection. Most of the authors reported that the identification of uncommon species was not initially correct. One case mentioned that the samples went to an external laboratory without further information [24,26]. Table 3 represents the misidentification present in our cases. Among the 44 cases with information regardless of identification methods, only 11 cases had corrected *Candida* identification in the first tentative (25%) through VITEK2, API32, or MicroScan Method. In 24 cases (54,5%), the infectious agent was misidentified for the first time or not clearly identified with conventional methods. Confirmation was performed through MALDI-TOF and some cases also PCR sequencing (ITS and D1/D2 domain). Important to mention that misidentification was also performed with MALDI-TOF: one case of *C. auris* candidemia was initially identified as *C. haemulonii* and identification of one case of *C. kefyr* and one case of C. *duoshaemulonii* candidemia failed [20,32,46].

The VITEK system was one of the most used identification routinely techniques, in 19 of 44 cases (43,2%). However, *C. auris* misidentification was common, with 8 in total of 21 isolates with VITEK2. *C. haemulonii* was the most frequent agent identified as *C. auris* (n=4).

Fourteen cases were initially identified through the API AUX model and five cases with the MicroScan Model. Thirteen cases performed identification agents with only one method and PCR sequencing was the most used in these cases (n=5). *C. auris* clades identification was performed in 6 cases [22,35,43,44,50] and was identified in South Asia (n=4) and East Asian clade (n=2). Noted that although 2 *C. auris* isolates nested into two distinct clusters (Indian and UK) the authors concluded that both isolates belonged to East Asian clade [50].

Table 3: Identification results from uncommon *Candida* species isolates from patients with invasive infection.

Author/Year	Microorganism	VITEK		API AUX		Microscan	MALDI-TOF	DNA sequencing
		Model	Result (% ID)	Model	Result			
Biagi, M. J. et al., 2019[32]	*C. auris*						*C. haemulonii*	*C. auris*
Parra-Giraldo, C. M. et al., 2018[25]	*C. auris*					*C. albicans*	*C. auris*	*C. auris*
Das, S. et al., 2018[36]	*C. auris*					*C. famata*		*C. auris*
	C. auris					*C. famata*		*C. auris*
	C. auris					*C. famata*		*C. auris*
Lee, W. G. et al., 2011[37]	*C. auris*	VITEK2 system	*C. haemulonii*	API20 C	*R. glutinis*			*C. auris*
Tsai, Y. T. et al., 2022[35]	*C. auris*						*C. auris*	*C. auris*
Barantsevich, N. E. et al., 2019[19]	*C. auris*						*C. auris*	*C. auris*
Levy, Y. et al., 2021[27]	*C. auris*						*C. auris*	
Desnos-Ollivier, M. et al., 2021[45]	*C. auris*							*C. haemulonii* *C. auris*
Katsiari, M. et al., 2023[44]	*C. auris*						*C. auris*	*C. auris*
Dewaele, K et al., 2020[43]	*C. auris*	VITEK2 system	*C. haemulonii*				*C. auris*	*C. auris*
Ruiz Gaitán, A. C. et al., 2017[42]	*C. auris*	VITEK MS	*C. lusitaniae (78%)*	API 20C AUX	*C. sake (99.8%)*			*C. auris*
	C. auris	VITEK MS	*C. haemulonii (99.9)*	API 20C AUX	*C. sake (99.8%)*			*C. auris*
	C. auris	VITEK MS	*No identification*	API 20C AUX	*C. sake (99.8%)*			*C. auris*
	C. auris	VITEK MS	*No identification*	API 20C AUX	*C. sake (99.8%)*			*C. auris*
Vogelzang, E. H. et al., 2019[22]	*C. auris*						*C. auris*	*C. auris*
Al-Obaid, I. et al., 2022[51]	*C. auris*	VITEK2 system	*C. haemulonii*					*C. auris*
Alatoom, A. et al., 2018[52]	*C. auris*	VITEK2 system	*C. haemulonii*				*C. auris*	
Mohsin, J. et al., 2017[50]	*C. auris*			API 20C AUX	C. haemulonii		*C. auris*	C. auris
	C. auris			API 20C AUX	C. haemulonii		*C. auris*	C. auris
Kollu, V. S. et al., 2021[24]	*C. blankii*	No information	No information	No information	No information	No information	No information	No information
Warren, T. A. Et al., 2010[31]	*C. bracarensis*			API 20C AUX	C. glabrata			
Xie, O. et al., 2020[20]	*C. duobushaemulonii*	Vitek MS MALDI	*C. duobushaemulonii (99%)*				no result in any	C. duobushaemulonii (86)

							matched patterns	
	C. duobushaemulonii	Vitek2 system	*C. duobushaemulonii (97%)*					
Konuma, T. et al., 2017[38]	*C. fermentati*	VITEK2 system	*C. famata*					*C. fermentati*
Morita, K. et al., 2018[21]	*C. fermentati*							*C. fermentati*
	C. fermentati							*C. fermentati*
	C. fermentati C. famata							*C. fermentati*
Kim, S. et al., 2011[40]	*C. haemulonii*	VITEK2 system	*C. haemulonii*					*C. haemulonii*
Ruan, S. Y. et al., 2010[39]	*C. haemulonii*	VITEK2 system	*C. haemulonii (98.5)*	API 32C system	*C. intermedia* or *C. sake* or *C. globosa* or *C. melibiosica* or *Saccharomyces kluyveri*			*C. haemulonii*
	C. haemulonii	VITEK2 system	*C. haemulonii (95)*	API 32C system	*C. sake*			*C. haemulonii*
Pérez-Lazo G. et al., 2021[28]	*C. haemulonii*	VITEK2 system	*C. haemulonii*					
Almeida-Jr, J. N. et al., 2012[34]	*C. haemulonii*	VITEK2 system	*C. haemulonii (97%)*					*C. haemulonii*
Rodero, L. et al., 2002[33]	*C. haemulonii*	VITEK system	*Pichia ohmeri (86%)*	API 32C system	No identification		*C. haemulonii*	
Seth-Smith, H. M. B. et al., 2019[46]	*C. Kefyr*						*No identification*	*C. kefyr*
Jyothi, L. et al., 2021[41]	*C. Kefyr*					*C. kefyr (99.99)*		
Corpus, K. et al., 2004[26]	*C- kefyr*	No information	No information	No information	No information	No information	No information	No information
Spiliopoulou, A. et al., 2021[23]	*C. Kefyr*			API 20C AUX	C. kefyr		*C. kefyr*	
de Jong, A. W. et al., 2022[30]	*C. khanbhai*						*C. khanbhai*	
Fujita, S. et al., 2007[18]	*C. nivariensis*							*C. nivariensis*
Cartier, N. et al., 2020[47]	*C. nivariensis*			API 20C AUX	*C. glabrata*		*C. nivariensis*	*C. nivariensis*
Lopez-Soria, L. M. et al., 2013[48]	*C. nivariensis*	VITEK2 system	No conclusive indetification					*C. nivariensis*
Sanclemente, G. et al., 2015[29]	*C. norvegensis*						*C. norvegensis*	
Musso, M. et al., 2014[49]	*C. norvegensis*	VITEK2 system	*C. norvegensis*					
Kiraz, N. et al., 2009[53]	*C. norvegensis*			API 20C AUX	*C. norvegensis*			

3.6. Susceptibility methods and results

The susceptibility tests of the reported cases included in the present work are summarized in the Table 4.

To evaluate the susceptibility of the isolated agents, a variety of methods were used, such as the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) broth microdilution, Etest, and automated VITEK2 yeast susceptibility system. CLSI broth microdilution was the most used method (n=14, 33,3%), however, the recent reported cases use more often in last year's automatized method VITEK2 and Etest. Information related to susceptibility determination method(s) was absent in 4 articles [24,38,52,54]. In 10 cases, the Sensititre Yeast One colorimetric method (23,8%), 6 cases used the Etest susceptibility test (14,2%) including one case that also used EUCAST broth microdilution to compare with Etest results in *C. nivariensis* candidemia [47]. Another paper also performed two distinct susceptibility tests to the same isolate: Sensititre YeastOne and EUCAST broth microdilution [43]. In one case of *C. kefyr* invasive infection in 2004, CLSI broth microdilution was performed [26]. Automated VITEK2 was applied only in 1 case reported in Italy [49]. Another distinct colorimetric microdilution antifungal susceptibility test, MICRONAUT was recently performed in 1 fatal case of *C. auris* [51].

C. auris

Regarding the susceptibility profile, *C. auris* had in general high values for fluconazole with a range between 2 and ≥256 mg/L; 17 of 22 *C. auris* cases had high MICs to fluconazole, according to CDC breakpoints (77.2%)[55]. One case did not have information regarding fluconazole. Europe had de high incidence of *C. auris* high MICs of fluconazole, 10 of 22 cases (45.4%). Susceptibility testing for amphotericin was performed in all cases and the results revealed 5 of 23 *C. auris* cases had high MICs to this antifungal (21.7%). Curiously, 4 of the 5 *C. auris* with cases elevated amphotericin MICs, also showed high values for fluconazole[36,44]

The susceptibility testing results for other azoles showed only 3 cases with voriconazole resistance, 2 cases of itraconazole, and 1 case of posaconazole resistance. There's no register of high MICs for micafungin or caspofungin. Sensitive Yeast One assay performance was evaluated in parallel with EUCAST broth microdilution assay (that is considered the reference technique) for *C. auris* isolate for the first time in 2018 [43]. The obtained results are represented in Table 3.

C. haemulonii

One reported case of *C. haemulonii* invasive infection although the isolate susceptibility results don´t have any information related to the method used [40]. In this case, the authors mention that the isolate is susceptible to echinocandins such as caspofungin or micafungin and it isn't resistant to new triazoles (e.g. Voriconazole). Cutoff of CLSI was used in 4 of 5 cases of *C. haemulonii* isolate cases (Table 4). In these cases, the interpretation results were performed according to the susceptibility breakpoints established by the CLSI: ≤8mg/L for fluconazole, ≤0.125 mg/L for itraconazole and ketoconazole, ≤4mg/L for flucytosine, ≤1mg/L for voriconazole, posaconazole and amphotericin B and ≤2mg/L for caspofungin, anidulafungin and micafungin (Table 4).

A case report of *C. fermentati* published in 2018 demonstrated a discrepancy between in vitro and in vivo susceptibility to antifungal drugs, particularly in echinocandins [21]; A patient with low MICs for amphotericin and micafungin, was initially treated with amphotericin and micafungin; however, blood cultures were persistent positive and ultimately, the patient died [21].

According to these breakpoints, all the isolates had low MICs to itraconazole (0.25 mg/L). Three isolates showed elevated MICs to amphotericin with results between 2 and 4 mg/L [34,39] and the other 3 isolates were also non-susceptible to fluconazole (16 - > 64 mg/L).

C. nivariensis

There are three cases reported of *C. nivariensis* invasive infection in the present work. All the cases had defined the method used for susceptibility testing. Regarding this agent and contrary to other cases non used broth microdilution CLSI. *Cartier N. et al.* performed two different susceptibilities testing in the same *C. nivariensis* isolate: Etest and broth microdilution according to EUCAST [47]. The results presented in Table 3 showed distinct MICs for azoles (fluconazole, voriconazole and posaconazole), amphotericin B and micafungin. A reported case documented in Kuwait in 2021, concluded that the *C. nivariensis* isolate exhibited high MIC for fluconazole (6 mg/L) [56].

C. norvegensis

A few cases have been reported of *C. norvegensis* associated with invasive infection and mostly of of the cases are associated with acute comorbilities such as solid and liquid malignance or immunosuppression[57]. In fact, *C. norvegensis* was reported only in

three included cases and all of the patients were imunossupressed[29,49] and with leukemia[53].

Susceptibility *C. norvengensis* profile indicates high MICs for fluconazole in two included cases[29,53]. Echinocandins susceptibility profile was performed in only one case, through caspofungin MICs which showed low values (0.047mg/L)[29] (Table 4).

C. kefyr

In recent years, the number *C. kefyr* invasive infections reports increased[57]. In our work, 4 cases were included, and all showed susceptibility to amphotericin B, fluconazole and itraconazole[23,26,41,46]. One case don´t reported numerical MICs, however, the authors mentioned that the isolate were susceptible to amphotericin and azoles [41].

C. famata, C. bracarensis, C. khanbhai, C. blankii and C. duobushaemulonii

All of these species were reported in only one case each with exception of *C. famata* which was documented in two studies involving a total of 4 patients (Table 2). The susceptibility testing results of *C. duobushaemulonii* and *C. khanbhai* revealed high MIC for fluconazole[20,41].

C. famata susceptibility profile was documented in four cases (Table 4) and results suggested susceptibility to both polyenes and azoles antifungal classes[21,38]. On the contrary, *C. blankii* isolate susceptibility profile showed high MICs for both amphotericin and azoles (Table 4).

The susceptibility profile of the only case of *C. bracarensis* candidemia was performed with the YeastOne method and results showed susceptibility to all antifungals tested (Table 4) except for itraconazole, which susceptibility was classified as “susceptible dose dependent”[31].

Table 4: Minimal inhibitory concentrations (MIC; mg/L) and mutations of uncommon *Candida* spp. Isolated from patients with invasive infections.

Author/Year	Microorganisms	TSA Method	Breakpoints	Units	AMP	FCZ	VCZ	ICZ	PCZ	5-FC	CFG	AFG	MFG	Mutation
Biagi, M. J. et al., 2019[32]	*C. auris*	Broth microdilution CLSI YestOne	CLSI (AMP and ICZ) YestOne (all the others)	mg/L	1	2	0.015	≤0.03	ND	ND	0.06	0.12	0.12	FKS1
Parra-Giraldo, C. M. et al., 2018[25]	*C. auris*	Etest	No information	mg/L	0.75	24	0.64	0.25	0.023	ND	0.47	0.12	0.19	
Das, S. et al., 2018[36]	*C. auris*	Etest	CLSI	mg/L	1	8	0.125	0.064	0,047	ND	0,25	ND	ND	
	C. auris	Etest	CLSI	mg/L	8	64	0,094	0,064	0,125	ND	0,023	ND	ND	
	C. auris	Etest	CLSI	mg/L	16	8	0.19	0.047	0,064	ND	0,25	ND	ND	
Al-Obaid, I. et al., 2022[51]	*C. auris*	MICRONAUT-AM	CDC breakpoints	mg/L	1	≥128	0.5	0.5	0.063	ND	ND	0.25	0.125	FKS1 ERG11
Lee, W. G. et al., 2011[37]	*C. auris*	Broth microdilution CLSI	CLSI	mg/L	1	8	0.06	0.25	ND	ND	0.06	ND	0.03	

Tsai, Y. T. et al., 2022[35]	*C. auris*	Broth microdilution CLSI	CLSI	mg/L	1	8	0.12	ND	0.12	≤ 0.06	ND	0.12	0.06	ERG11 and FKS1 not detected
Barantsevich, N. E. et al., 2019[19]	*C. auris*	Broth microdilution CLSI	CLSI	mg/L	0.5	≥ 128	≥ 8	ND	≥ 2	ND	≥ 4	ND	ND	
Levy, Y. et al., 2021[27]	*C. auris*	Broth microdilution EUCAST	EUCAST	mg/L	0.25	≥64	1	ND	≤0.014	≥64	0.015	ND	0.03	
Desnos-Ollivier, M. et al., 2021[45]	*C. auris*	Broth microdilution EUCAST	EUCAST	mg/L	0.5	≥64	0.5	ND	0.125	NA	0.06	ND	0.5	
Katsiari, M. et al., 2023[44]	*C. auris*	broth microdilution EUCAST	CDC breakpoints**	mg/L	2	>128	0.12	0.06	0.12	0.12	ND	0.25	0.25	
Dewaele, K et al., 2020[43]	*C. auris*	broth microdilution EUCAST	EUCAST	mg/L	0.5	>64	> 4	> 4	> 4	0.25	ND	0.125	≤0.03	
2020	*C. auris*	Sensititre® YeastOne®	No information	mg/L	1	256	8	16	8	0,125	NA	0,125	0,125	
Ruiz Gaitán, A. C. et al., 2017[42]	*C. auris*	Sensititre® YeastOne®	No information	mg/L	0.5	≥256 mg/L	2	ND	ND	≤0.06	ND	ND	ND	
	C. auris	Sensititre® YeastOne®	No information	mg/L	0.5	≥256 mg/L	2	ND	ND	≤0.06	ND	ND	ND	

	C. auris	Sensititre® YeastOne®	No information	mg/L	0.5	≥256 mg/L	2	ND	ND	≤0.06	ND	ND	ND	
	C. auris	Sensititre® YeastOne®	No information	mg/L	0.5	≥256 mg/L	2	ND	ND	≤0.06	ND	ND	ND	
Vogelzang, E. H. et al., 2019[22]	*C. auris*	Broth microdilution CLSI	CLSI	mg/L	0.5	> 64	4	ND	ND	ND	ND	< 0.016-0.063	0.063	
Alatoom, A. et al., 2018[52]	*C. auris*	No information	No information	mg/L	1	ND	1	ND	ND	ND	0.25	NA	NA	
Mohsin, J. et al., 2017[50]	*C. auris*	Broth microdilution CLSI	CLSI	mg/L	2	64	0.125	0.031	<0.016	ND	ND	0.031	0.063	
	C. auris	Broth microdilution CLSI	CLSI	mg/L	1	>64	1	0.0125	0.063	ND	ND	0.125	0.125	
Kollu, V. S. et al., 2021[24]	*C. blankii*	No information	No information	mg/L	0.500	16	0.250	0.500	1	≤0.060	1	0.250	0.120	
Warren, T. A. Et al., 2010[31]	*C. bracarensis*	YeastOne®	No information	mg/L	0.25	8	0.12	0.25	0.5	≤ 0.06	0.06	0.03	≤ 0.008	
Xie, O. et al., 2020[20]	*C. duobushaemulonii*	Sensititre® YeastOne®	No information	mg/L	0.5	64	ND	ND	ND	ND	ND	ND	0.06	
Konuma, T. et al., 2017[38]	*C. fermentati*	No information	No information	mg/dL	1	4	0.12	1	NA	≤ 0.12	NA	NA	1	FKS1

Morita, K. et al., 2018[21]	*C. fermentati*	Broth microdilution CLSI	CLSI	mg/L	0.5	8	ND	1	ND	≤ 0.12	ND	ND	0.5
	C. fermentati	Broth microdilution CLSI	CLSI	mg/L	0.25	4	ND	1	ND	≤ 0.12	ND	ND	1
	C. fermentati *C. famata*	Broth microdilution CLSI	CLSI	mg/L	0.25	8	ND	0.5	ND	≤ 0.12	ND	ND	0.5
Almeida-Jr, J. N. et al., 2012[34]	*C. haemulonii*	Sensititre® YeastOne®	CLSI	mg/L	4	8	0.064	0.25	0.125	64	0.25	ND	ND
Pérez-Lazo G. et al., 2021[28]	*C. haemulonii*	Broth microdilution CLSI	CLSI	mg/L	1	> 64	ND	ND	ND	ND	ND	0.06	ND
Rodero, L. et al., 2002[33]	*C. haemulonii*	Broth microdilution CLSI with EUCAST modification Time-kill curve	No information	mg/L	4	32	0.12	ND	ND	0.12	ND	ND	ND
Kim, S. et al., 2011[40]	*C. haemulonii*	No information	No information	mg/L	0.5	8	0.5	0.25	ND	ND	0.125	ND	ND

Ruan, S. Y. et al., 2010[39]	*C. haemulonii*	Broth microdilution CLSI	CLSI	mg/L	2	16	0.25	0.25	0.12	0.06	1	0.25	0.12
	C. haemulonii	Broth microdilution CLSI	CLSI	mg/L	2	16	0.25	0.25	0.12	0.12	1	0.12	0.12
Corpus, K. et al., 2004[26]	*C. kefyr*	Broth macrodilution CLSI 24h	CLSI	mg/L	0.125	0,25	0.03	0.06	ND	ND	≤ 0.125	ND	ND
	C. kefyr	Broth macrodilution CLSI 48h	CLSI	mg/L	0,25	0,5	0,03	0,06	ND	ND	≤ 0.125	ND	ND
Jyothi, L. et al., 2021[41]	*C. Kefyr*	Etest	No information	No information	S	S	S	S	ND	ND	ND	ND	ND
Seth-Smith, H. M. B. et al., 2019[46]	*C. Kefyr*	Sensititre® YeastOne®	No information	mg/dL	1	0.12	≤0.008	0.12	0.06	0.5	≤ 0.08	0.03	0.03
Spiliopoulou, A. et al., 2021[23]	*C. Kefyr*	Broth microdilution EUCAST	EUCAST	mg/L	2	0.12	0.008	0.06	0.06	1	0.03	0.12	0.12
	C. Kefyr	Etest	No information	mg/L	>32	0.38	0.023	0.125	0.126	2	0.25	0.064	0.047
	C. khanbhai	Broth dilution EUCAST 24h	EUCAST	mg/L	2	>64	0,5	1	2	4	ND	0,5	0,25

de Jong, A. W. et al., 2022[30]	*C. khanbhai*	Broth dilution EUCAST 48h	EUCAST	mg/L	4	>64	16	16	4	16	ND	1	0,5
Fujita, S. et al., 2007[18]	*C. nivariensis*	ASTY colorimetric microdilution	No information	mg/L	0.5	ND	4	≥128	ND	2	ND	ND	0.06
Cartier, N. et al., 2020[47]	*C. nivariensis*	Broth microdilution EUCAST	EUCAST	mg/L	0,06	4	0,25	NA	0,125	ND	ND	ND	≤0.08
	C. nivariensis	Etest	CLSI	mg/L	0,75	6	0,047	NA	0,38	ND	ND	ND	0,012
Lopez-Soria, L. M. et al., 2013[48]	*C. nivariensis*	Sensititre® YeastOne®	No information	mg/L	1	4	0.03	0.25	0.25	0.125	0.125	0.015	0.015
Sanclemente, G. et al., 2015[29]	*C. norvegensis*	Broth microdilution CLSI	CLSI	mg/L	0,5	64	0,75	4	ND	64	0,047	ND	ND
Musso, M. et al., 2014[49]	*C. norvegensis*	Vitek2	EUCAST	mg/L	NA	8 mg/L	0.25 mg/L	ND	ND	ND	ND	ND	ND
Kiraz, N. et al., 2009[53]	*C. norvegensis*	broth microdilution CLSI	CLSI	mg/L	0.25	128	ND	0,5	ND	ND	ND	ND	ND

Legend: Amphotericin B (AMP); Fluconazole (FCZ); Voriconazole (VCZ); Itraconazole (ICZ); Posaconazole (PCZ); 5-Flucytosine (5-FC); Caspofungin (CFG); Anidulafungin (AFG); Micafungin (MFG); European Committee on Antimicrobial Susceptibility Testing (EUCAST); Clinical & Laboratory Standards Institute (CLSI); Not determinated (ND); Susceptible (S)

3.7. Global epidemiology

All the cases included in this systematic review were documented in 3 continents: Europe, Asia, and America (Figure 2).

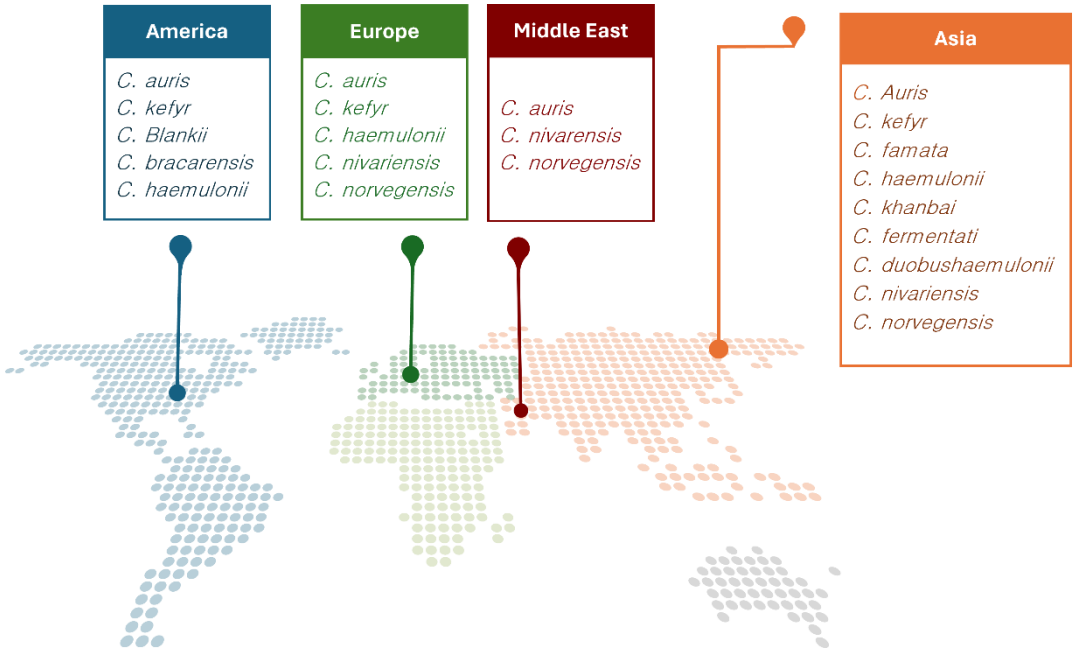

Figure 2: Global epidemiology of uncommon *Candida* species invasive infections.

3.7.1. EUROPE

It is notary of the incidence of emerging infections in Europe in the last decade. Our review included 16 cases of invasive infection in Europe reported from distinct European countries: 7 cases in Spain[29,42,48], 3 in Greece[23,44,45], 3 in France[27,47], and one in Belgium[43], Netherlands, Switzerland[46], and Italy[49] (Table 2 and Figure 3).

C. auris was the most reported agent (n=9). *C. norvegensis* and *C. nivariensis* were documented in France, Spain, and Italy. Candidemia was the most frequent invasive infection although pyelonephritis and hepatic infection were also reported (Table 2).

Figure 3: Epidemiology of uncommon *Candida* species invasive infections in Europe.
Legend: Invasive *Candida* Infection (ICI).

3.7.2. ASIA

Asia was the second continent with the most cases included in the present work, with a total of 15 cases. Just like Europe, *C. auris* was the most isolated agent (n=5), all related to candidemia. *C. fermentati* was the second most reported agent associated with invasive infection with 4 cases including one case in which *C. famata* was also identified in the same isolate [21]. It was also reported two cases of *C. haemulonii* candidemia in Taiwan[39] and South Korea[40] in 2010 and 2011 respectively (Table 2 and Figure 4).

C. kefyr, *C. nivariensis,* and C. duoshaemulonii were documented in 1 case each, all related to candidemia (Table 2). A new *candida* species was reported in 2022 in blood isolate, *C. khanbhai* [30].

3.7.3. MIDDLE EAST

The present work included 5 invasive infection cases which were reported from 2009 to 2022 in four countries Kuwait[51], United Arab Emirates[52], Oman[50], and Turkey[53]. *C. auris* was documented in 4 cases and 1 case of *C. norvegensis* was also included (Table 2 and Figure 4). Candidemia was present in all the cases and peritonitis was diagnosed in one patient with *C. auris* isolated (Table 2).

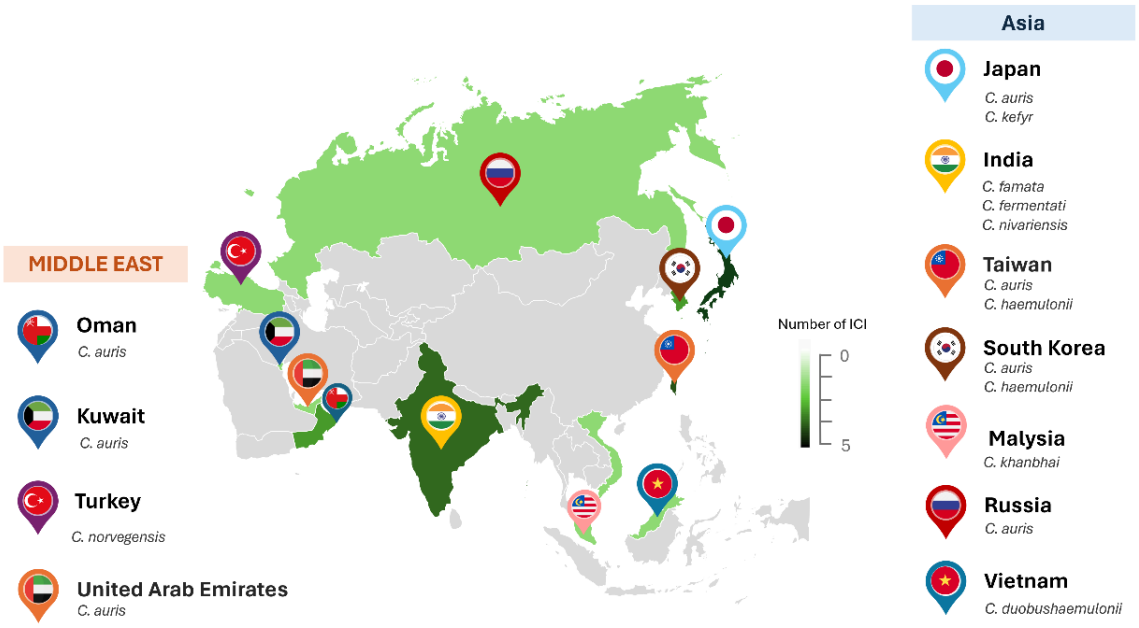

Figure 4: Epidemiology of uncommon *Candida* species invasive infections in Asia and Middle East countries. Legend: Invasive *Candida* Infection (ICI).

3.7.4. AMERICA

A total of 8 cases reported in the American continent were included: 3 cases of *C. auris* candidemia, 2 cases of *C. haemulonii*[28,34], and 1 case of *C. kefyr*[26], *C. blankii*[24], and *C. bracarensis* [31](Table 2 and Figure 5). All the cases were associated with candidemia, except one case. *C. haemulonii* which was isolated from the purulent liver collection and *C. kefyr* reported case, which was identified in pleural fluid isolated, in 2004.

Figure 5: Epidemiology of uncommon *Candida* species invasive infections invasive infections in America countries.

3.8. Underlying conditions, hospitalization time, treatment, and clinical outcome

Malignancy diseases were the most common underlying condition, present in 16 cases among a total of 45 cases. Diabetes mellitus was noted in 8 patients[20,24,35,41,44,50,51] and transplantation was documented in 10 cases[21,29,31,38,45,46,49,51]. Hospitalization time information was absent in 6 cases[22,24,33,39,41,46]; however, the remaining 42 cases had a minimum hospitalization time of 8 days and a maximum of more than 100 days. Only 21 cases had information related to mechanical ventilation: 17 patients needed intubation/ventilation. In 34 cases, prior exposure to antibiotics belonging to the broth spectrum was recorded; in 4 cases, this information was not provided. The antifungal agents used for the treatment of invasive candidemia were also documented in Table 2. In a total of 45 patients, 5 cases had no information related to antifungal treatment[20,22,33,34,36].

A patient with *C. khanbhai* isolated in blood culture died before starting treatment [30]. Fluconazole and amphotericin were the most common antifungals used, documented in 14 cases. Caspofungin was the echinocandin most documented (n=11) followed by anidulafungin and micafungin, 9 and 8 cases respectively (Table 2). Fluconazole was also the antifungal agent most used in prophylaxis and empirical treatment (Table 2).

Two different mutations, *FKS*1 and *ERG*11, associated with antifungal drug resistance were documented in four and two studies respectively [32,35,38,51]. *FKS*1 was presented in 2 *C. auris* invasive infection cases and 1 *C. fermentation* candidemia, and *ERG*11 was detected in 1 immunocompromised patient with a *C. auris* fatal infection. In another study, *FKS*1 and *ERG*11 were not detected [35].

Mortality caused by *Candida* uncommon species related invasive infection was documented in 18 patients (40%). Another patient succumbed but his death was not attributed to *C.* bracarensis invasive infection [31]. Mortality specified for each *candida* species was: 52,4% for *C. auris* (11 of 21 cases), 50% for *C. fermentati* (2 of 4 cases), 16,7% for *C. haemulonii* (1 of 6 patients), 66,6% for *C. norvegensis* (2 of 3 cases), 0% for *C. kefyr* and *C. nivariensis*. There is only one case of *C. khanbhai* and the patient had an unfavorable clinical outcome [30]. In the case of *C. duobushaemulonii* candidemia, the patient also died because the treatment was withdrawn due to poor neurological recovery [20].

4. DISCUSSION

Invasive infections by uncommon *Candida* species present a significant and complex challenge in clinical microbiology and infectious disease management. These uncommon species are of particular concern due to their potential for resistance to standard antifungal treatments and their varying virulence profiles, being a great challenge for patients and clinicians.

4.1. Population and comorbidities

According to numerous studies, male gender has been identified as a risk factor for ICI, with a prevalence of between 52% and 60% [58,59]. A recent study developed by Egger M. *et al*. have shown the gender as a risk factor for ICI [60] where females represent 51,2% of ICI, which was not in concordance with the studies enrolled in this systematic review. However, there are few case reports of invasive infections by uncommon *Candida* species when comparing with the most prevalent *Candida* species.

Other risk factors for ICI beyond demographic factors and gender, also include comorbidities and medical interventions [4]. Immunosuppression conditions such as transplantation or HIV, solid and hematological malignancies, corticoid therapy, kidney diseases, and neutropenia are known major risk factors for ICI [4]. The mechanisms involved in each condition have been studied, noticing that destabilization of the immune system is the theory basis [61,62]. In our review, it is a notary of the high proportion of transplanted and oncology patients. Diabetes was also a common comorbidity in the studies included. It is known that *Candida* species are capable of growing in biofilm forms, exhibiting enhanced resistance against most antifungal agents [63]. High levels of glucose in the blood (common in diabetes) promote an increase of *Candida* biofilm formation and consequently develop pathogenicity mechanisms [4]. Other important predisposing factors leading to ICI include recent antifungal treatments, previous broad-spectrum antibiotic therapy, and mechanical ventilation [64]. All these risk factors were presented in several patients in our study associated with unfavorable clinical outcome.

4.2. Uncommon Candida spp. identification challenging

It is known that difficulties with *Candida* species identification especially the emergence of new *Candida* species and the lack of awareness has resulted in transmission and several outbreaks which has remained unnoticed [65]. The development of rapid and precise methods for identifying uncommon *Candida* invasive agents is a challenge, but it is imperative for patient care and to certify the appropriate implementation of measures to ensure the prevention of infection [66].

Among the conventional methods that traditionally identify pathogenic yeast based on biochemical and morphological characteristics at the species level that are commercially available, the VITEK 2 systems, API ID32c and AUX Color are the most routinely used systems in clinical microbiology [67]. Unfortunately, the databases of these methods are limited, time consuming, require high experience in this area and generally identified only the most common pathogens yeasts [68]. In the last few years evolution in molecular biology has provided increasingly used of DNA techniques as tools for yeast identification and characterization with high accuracy [69]. Recently, MALDI-TOF and DNA sequencing (ITS and D1/D2 regions) have been discussing as accurate identification methods for *C. auris* [70].

An included study in this systematic review developed by *Ruan, S. Y. et al.* reported that VITEK 2 system, in comparation with VITEK 1 and API32C system, is a better solution

to *C. haemulonii* identification. VITEK 2 system results were high consistent with molecular methods for sequence analysis of the rRNA [39]. In fact, these conclusions are in concordance with the other five included cases in which *C. haemulonii* was correct identified with VITEK 2 (Table 3).

Identification of in 1 of 3 *C. fermentati* was successfully performed with VITEK 2 system. DNA sequencing was performed, identifying *C. fermentati* in all the 3 cases. *Konuma, T.* and colleagues documented the VITEK 2 system misidentification of *C. fermentati* in a fungemia case [38]. The authors confirmed that this result is consistent with recent publications: *C. fermentati* is commonly misidentified as *C. famata* by VITEK 2 system [71-73]. Since it is a cryptic species of C. *guilliermondii, C. fermentati* misidentification as *C. guilliermondii* consequently leads to underreported of infections due to this pathogenic yeast [21]. For this reason, it is crucial the implementation of accurate and rapid PCR method for *C. fermentati* identification.

C. nivariensis identification it's another challenge in mycology laboratories since is routinely misidentified as *C. glabrata* [74]. Poorly identification with conventional methods is common. In the present work, all the isolates identified with VITEK or API AUX systems were misidentified or identification was not conclusive [47,48]. Fortunately, in order to distinguish *C. nivariensis* from *C. glabrata*, several molecular methods such as multiplex PCR, a fast, cost-effective and reliable tool can be used [75].

Currently, five different genetic Clades have been found related to *C. auris* species [76]: South-Asian (Clade I), East-Asia (Clade II), Africa (Clade III) and South America (Clade IV) [77]. In our work, only 4 cases had results from genetic analysis related to clade identification. Clade I was founded in three cases reported in Europe (Netherland, Greece, and Belgium) [22,43,44]. Two patients recently had history of hospitalization in Asia and the other case (isolated in Greece) had no travel information, but the authors suggest a horizontal transmission since *C. auris* with identical sequences was detected from environmental screening.

4.3. Susceptibility interpretation and treatment challenges

Antifungal susceptibility testing are increasingly vital tools for understanding the local and worldwide disease epidemiology, considered by clinicians to guide their treatment decision-making process, the treatment of fungal illnesses, and identifying antifungal

resistance [78].Distinct methods are currently available for evaluating the susceptibility of fungi to different antifungals. Broth microdilution is one of the most common susceptibility methods used in clinical and research microbiology laboratories.

Over the years, several commercial susceptibility methods have been available, with the advantage of easier interpretation and effective MICs such as Etest and YeasOne [79]. Broth microdilution from CLSI and EUCAST, Etest, YEAST were the most used methods in our cases. In a study reported in 2022, *C. auris* isolate susceptibility was assessed using the MICRONAUT colorimetric method [51]. Another work used VITEK 2 to test susceptibility of *C. norvegensis* isolate [49]. ASTY colorimetric microdilution panel was used in susceptibility testing of *C. nivariensis* isolate [18].

Regarding to susceptibility testing, there are two different approved reference procedures based on microdilution techniques for antifungal susceptibility testing: firstly CLSI and later EUCAST [80]. CLSI and EUCAST define breakpoints for C. *albicans* and other common *candida* non-albicans pathogenic yeasts, such as C. *glabrata*, C. *parapsilosis* and C.*tropicalis* [81]. However, none of the *Candida* species discuss in our work has these breakpoints demarked. In 2020, CDC suggested tentative MIC breakpoints for *C. auris* [55] and it was applied in most recent published cases included in this systematic review [44,51]. Recently CLSI also suggested breakpoints for some uncommon *Candida* non-albicans unrelated, including species included in the present study, such us *C. haemulonii*, *C. duobushaemulonii* and *C. kefyr* [82]. Although these new breakpoints for uncommon species, most of the studies included in the present work, emphasize the challenges regarding to interpretation of susceptibility results. Several papers revealed that due the absence of clinical breakpoints for the majority of uncommon *Candida* species, MICs obtained have been compared to the susceptibility cutoffs determined for common *Candida* species by CLSI or EUCAST [21,26,48,49]. Nonetheless, it has been reported that susceptibility varies significantly among *Candida* species [38]. Morita k. *et al.* used CLSI cutoffs values of *C. guilliermondii* for interpretation of susceptibility results of *C. fermentati* isolated from a case of candidemia. In regard to *C. guilliermondii* and *C. fermentati* susceptibility profile, there seems to be no much difference, with echinocandins good antifungal activity in both species [83]. One the other hand, *C. fermentati* micafungin resistance has been documented and associated with *FSK*1P mutation [38].

Multidrug resistance *Candida spp* species are increasingly reported [84]. It was also observed in the present work, several isolates of distinct *Candida* spp. with high MICs for azoles, polyenes and echinocandins, mainly fluconazole.

Candida spp. antifungal resistance mechanisms can be conferred through gain-of-functions mutations in different target pathway genes or in their transcriptional regulators [85]. In the present work, were included some *C. auris* and *C. fermentati* cases which analyzed the presence of the most knew mutations associated with reduced susceptibility to fluconazole and echinocandins: ergosterol biosynthesis pathways mutations (*ERG*11) and cell wall biosynthesis mutation (*FKS*1) respectively [32,35,38,51].

4.4. Global epidemiology

Asia was the epicenter of several uncommon *Candida* species[10,86]. It was a notary high incidence of reported cases documenting high MICs for distinct classes of antifungal agents. Due to this emergence of uncommon *Candida* species antifungal resistance, susceptibility testing is crucial to guide the management of ICI in Asian countries[37].

Over the last few years, numerous hospitals have reported a significant and progressive shift in the etiology of invasive candidiasis in diverse patient populations and distinct hospital settings [87]. European countries have reported several of these patients; in our included cases were documented diagnostic delays and aggravating related to difficulty in fast and accurate identification and the absence of breakpoints for these uncommon species [42,47].

Evidence of included cases from American countries seems to suggest that although uncommon species are rare, they are becoming pathogens namely in immunosuppressed patients with high mortality rates [25,34]. It was also reported in several studies the challenges associated with the lack of economic, rapid, and accurate identification and susceptibility methods [32,33].

With the present work, it was possible to understand the concordance in the challenges related to the emergence of uncommon invasives *Candida* species. It was also possible to understand that some species are most related to specific comorbidities, for example: in included cases, *C. norvegensis* were majority presented in transplanted patients [29,49]. It was also observed resistance to fluconazole of distinct uncommon *Candida* species independently of geographical localization [20,36].

5. LIMITATIONS

There are several studies reporting ICI due to uncommon *Candida* species, however, the exclusion of studies with no information regarding clinical outcome or susceptibility results may have led to a bias of selection and results.

Our findings are limited nevertheless by the quality and breadth of the low number of cases and data in the reports, which were not uniform (for example: distinct identification and susceptibility methods; different comorbidities). The low number of studies related to some of the uncommon species may limit us from reaching conclusions.

6. CONCLUSION

It's undeniable that in the last years, uncommon *Candida* species have worldwide emerged. Early and accurate identification and tailored antifungal therapy are essential for effective management and improving patient outcomes. Ongoing research into the pathogenesis, diagnosis, and treatment of these infections is critical to address the challenges they present in the clinical setting worldwide.

7. AUTHOR CONTRIBUTIONS:

Conceptualization, SP and SCO; Methodology, SP and SCO; Validation, SP, IMM and SCO; Data Analysis, SP and SCO; Original Draft Preparation, SP; Review & Editing, SCO and IMM; Supervision, SCO.

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9. CONFLICTS OF INTEREST:

The authors declare no conflicts of interest.

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Appendix

Appendix S1: *Reporting guidelines checklist*

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1: “Rising Threat: A Systematic Review of the Global Epidemiology of Invasive Infections by Uncommon Candida Species”
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 7: Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 13: “Consequently, ICI by uncommon Candida spp has led to a public health concern worldwide.”
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 13: “What is the clinical information, diagnostics, susceptibility profile, and clinical outcome of patients with invasive infections by uncommon Candida species?”
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 14: “Eligibility criteria“
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 15: “PRISMA flow diagram summarizing”
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 15: “Page 15: “PRISMA flow diagram”
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 14: “The screening of publications was carried out by two independently reviewers (SP and SCO), based on the eligibility criteria”
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 15: “A protocol was defined to synthesize the extracted data from the selected studies”
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 15: “A protocol was defined to synthesize the extracted data from the selected studies”
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 15: “[…]microbiology identification method, and antifungal treatment or other management strategies.”
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 16: “Risk of bias (ROB) assessment“
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Not applied in the present work
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 14: “Eligibility criteria“
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Not applied in the present work

Section and Topic	Item #	Checklist item	Location where item is reported
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Not applied in the present work
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Not applied in the present work
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Not applied in the present work
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Not applied in the present work
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Not applied in the present work
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Not applied in the present work
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 16: “Publication characteristics “
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 15: “PRISMA flow diagram summarizing”
Study characteristics	17	Cite each included study and present its characteristics.	Page 18: Table 2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 16: “Risk of Bias – quality assessment “
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Not applied in the present work
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Appendix S2
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Not applied in the present work
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Not applied in the present work
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Not applied in the present work
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 16: Risk of Bias – quality assessment
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 16: Risk of Bias – quality assessment
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 42: “Uncommon Candida spp. identification challenging “

Section and Topic	Item #	Checklist item	Location where item is reported
	23b	Discuss any limitations of the evidence included in the review.	Page 45: “LIMITATIONS”
	23c	Discuss any limitations of the review processes used.	Page 45: “LIMITATIONS”
	23d	Discuss implications of the results for practice, policy, and future research.	Page 45: “With the present work, it was possible to understand the concordance in the challenges […]”
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	The review was not registered
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Protocol was not prepared
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Not applied in the present work
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 45: “Fundings”
Competing interests	26	Declare any competing interests of review authors.	Not applied in the present work
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Not applied in the present work

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Appendix S2: ***Risk of Bias – quality assessment***

Study	Was the study question or objective clearly stated?	Was the study population clearly and fully described, including a case definition?	Were the cases consecutive?	Were the subjects comparable?	Was the intervention clearly described?	Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	Was the length of follow-up adequate?	Were the statistical methods well-described?	Were the results well-described?	Quality Rating
A Report of Candida blankii Fungemia and Possible Endocarditis in an Immunocompetent Individual and the Review of Literature	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes	Good (7)
An Unusual Case of Candida kefyr Fungemia in an Immunocompromised Patient	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes	Good (7)
Bloodstream infection with Candida kefyr/Kluyveromyces marxianus: case report and draft genome	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes	Good (7)
Breakthrough fungemia due to Candida fermentati with fks1p mutation under micafungin treatment in a cord blood transplant recipient	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes	Good (7)
Candida auris in critically ill patients: Emerging threat in intensive care unit of hospitals	Yes	Yes	No	Yes	Yes	Yes	Yes	NA	Yes	Good (7)
Candida bracarensis bloodstream infection in an immunocompromised patient	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes	Good (7)
Candida duobushaemulonii sepsis and Candida auris co-isolation following hospitalisation in Vietnam	Yes	Yes	NA	Yes	Yes	Yes	No	NA	Yes	Fair (6)
Candida kefyr, an uncommon but emerging fungal pathogen: Report of two cases	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes	Good (7)
Candida khanbhai sp. nov., a new clinically relevant yeast within the Candida haemulonii species complex	Yes	Yes	No	Yes	Yes	Yes	Yes	NA	Yes	Good (7)
Candida nivariensis: Identification strategy in mycological laboratories	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes	Good (7)
Candida norvegensis fungaemia in a neutropenic patient with acute non-lymphoblastic leukaemia	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes	Good (7)
Candida norvegensis fungemia in a liver transplant recipient	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes	Good (7)
Case Report: Emergence of Candida auris in the Indian Ocean Region	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	Good (8)
Catheter-related candidemia caused by Candida haemulonii in a patient in long-term hospital care	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes	Good (7)
Catheter-related fungemia due to fluconazole-resistant Candida nivariensis	No	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes	Fair (6)
Development of High-Level Echinocandin Resistance in a Patient With Recurrent Candida auris Candidemia Secondary to Chronic Candiduria [1]	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes	Good (7)
Earliest case of Candida auris infection imported in 2007 in Europe from India prior to the 2009 description in Japan	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes	Good (7)
Emergence of Clonally-Related South Asian Clade I Clinical Isolates of Candida auris in a Greek COVID-19 Intensive Care Unit	Yes	Yes	No	Yes	Yes	Yes	Yes	NA	Yes	Good (7)

Fatal Breakthrough Candidemia in an Immunocompromised Patient in Kuwait Due to Candida auris Exhibiting Reduced Susceptibility to Echinocandins and Carrying a Novel Mutation in Hotspot-1 of FKS1	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes	Good (7)
First case of Candida auris infection in Belgium in a surgical patient from Kuwait	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes	Good (7)
First case report of catheter-related fungemia by Candida nivariensis in the Iberian Peninsula	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes	Good (7)
First report of a clinical isolate of Candida haemulonii in Brazil	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes	Good (7)
First report of sporadic cases of Candida auris in Colombia	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes	Good (7)
First three reported cases of nosocomial fungemia caused by Candida auris	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	Good (8)
Infections due to Candida haemulonii: species identification, antifungal susceptibility and outcomes	Yes	Yes	No	Yes	Yes	Yes	Yes	NA	Yes	Good (7)
Invasive Candida kefyr infection presenting as pyelonephritis in an ICU hospitalized COVID-19 patient: Case report and review of the literature	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes	Good (7)
Invasive Candidiasis due to Candida Norvegensis in a Liver Transplant Patient: Case Report and Literature Review	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes	Good (7)
Liver abscess caused by Candida haemulonii var. vulnera. First case report in Peru	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes	Good (7)
Nosocomial fungemia by Candida auris: First four reported cases in continental Europe	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	Good (8)
Persistent candidemia despite appropriate fungal therapy: First case of Candida auris from the United Arab Emirates	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes	Good (7)
The first cases of Candida auris candidaemia in Oman	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	Good (8)
The first invasive Candida auris infection in Taiwan	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes	Good (7)
The first Russian case of candidaemia due to Candida auris	Yes	No	NA	Yes	No	Yes	Yes	NA	Yes	Fair (5)
The first two cases of candida auris in the Netherlands	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	Good (8)
Three cases of Candida fermentati fungemia following hematopoietic stem cell transplantation	Yes	Yes	No	Yes	Yes	Yes	Yes	NA	Yes	Good (7)
Transient fungemia caused by an amphotericin B-resistant isolate of Candida haemulonii	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	Good (8)

Appendix S3: MYCOSIS journal (formation)

Parts of the Manuscript

The manuscript should be submitted in separate files: main text file; figures.

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The text file should be presented in the following order:

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v. Acknowledgments;
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acknowledgement footnote. In addition to collaborator names, their institution and address should be entered, as with authors proper. This enables transfer of the set of collaborators in Medline, where they can be retrieved. Financial and material support should also be mentioned. Thanks to anonymous reviewers are not appropriate.

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Abstract

Normally in less than 250 words, this should indicate clearly the scope and main conclusions of the paper. Original articles should have a structured abstract, comprising the five headings: Background, Objectives, Patients/Methods, Results and Conclusions. For Review Articles, abstracts are not required to be structured.

Keywords

Please provide eight keywords. Keywords should preferably be taken from those recommended by the US National Library of Medicine's Medical Subject Headings (MeSH) browser list at www.nlm.nih.gov/mesh.

Main Text

- Authors should aim for a concise readable style. Spelling should follow the *Concise Oxford Dictionary, and The Oxford Dictionary for Writers and Editors*. The Editors reserve the right to make corrections, both literary and technical, to the papers.
- The introduction should explain why the work was done and briefly introduce the scope and contents of the paper. Essential details should be included in materials and methods, including experimental design and statistical analysis. Results should be recorded in the past tense. The discussion should present the author's results in the broader context of other work on the subject. Acknowledgements should be as brief as possible.

References

All references should be numbered consecutively in order of appearance and should be as complete as possible. In text citations should cite references in consecutive order using Arabic superscript numerals. For more information about AMA reference style please consult the AMA Manual of Style

Tables

Tables should be self-contained and complement, not duplicate, information contained in the text. They should be supplied as editable files, not pasted as images. Legends should be concise but comprehensive – the table, legend, and footnotes must be understandable without reference to the text. All abbreviations must be defined in footnotes. Footnote symbols: †, ‡, §, ¶, should be used (in that order) and *, **, *** should be reserved for P-values. Statistical measures such as SD or SEM should be identified in the headings.

Numerical results should be expressed as means with the relevant standard errors and/or statistically significant differences, quoting probability levels (P-values). Three significant figures are usually sufficient for mean values and standard errors should be quoted two or three more decimals than the mean.

The only lines appearing in the table should be horizontal and all decimals should be aligned in columns. The placement of all tables should be indicated in the text, being referred to as Table 1 or Tables 2 and 3.

Figure Legends

Legends should consist of a short title together with a brief explanatory paragraph. They should be concise but comprehensive – the figure and its legend must be understandable without reference to the text. Include definitions of any symbols used and define/explain all abbreviations and units of measurement.

Acceptable symbols for experimental points are ¡, r, o, ˜, p, ¢. The symbols + and × will not be accepted.

Photomicrographs should state the original magnification.

The position of all figures should be indicated in the text and should be referred to as Fig. 1 or Figs 1 and 3. Figure 1 should be written out in full if at the beginning of a sentence.

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The following points provide general advice on formatting and style.

- **Abbreviations:** When first mentioned, cumbersome medical names should be abbreviated for later reference in the text. Latin bi-nominals should abbreviate the genera to the initial letter after the first mention unless it begins a sentence.
- **Units of measurement:** Measurements should be given in SI or SI-derived units. Visit the Bureau International des Poids et Mesures (BIPM) website for more information about SI units.
- **Numbers:** numbers under 10 are spelt out, except for: measurements with a unit (8mmol/l); age (6 weeks old), or lists with other numbers (11 dogs, 9 cats, 4 gerbils). The 24-hour clock, e.g. 21.00 hours, should be used.
- **Doses and Concentrations:** Doses of drugs should be given as unit weight per body weight, e.g. mmol kg-1. Rates should be expressed with negative indices. Concentrations should be given in terms of molarity, e.g. mmol l-1, not mM.
- **Trade Names:** Chemical substances and drugs should be referred to by the generic name only. Trade names should not be used. If proprietary drugs have been used in the study, refer to these by their generic name, mentioning the proprietary name and the name and location of the manufacturer in parentheses.

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