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REVIEW ARTICLE

Candida haemulonii Species Complex: Emerging Fungal Pathogens of the Metschnikowiaceae Clade

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Abstract

Candida species, the most common fungal pathogens affecting humans, cause not only superficial infections but also life-threatening invasive infections, particularly in immunocompromised individuals. Although *Candida albicans* remains the most frequent cause of candidiasis, infections caused by non-*albicans Candida* species have been increasingly reported in clinical settings over the past two decades. Recently, species of the Metschnikowiaceae clade including the "superbug" *Candida auris* and other members of the *Candida haemulonii* species complex have attracted substantial attention for their multidrug resistance and high rates of transmission in clinical settings. In this review, we summarize the epidemiology, biology, virulence, and drug resistance of the *C. haemulonii* species complex and discuss potential reasons for the recent increase in the prevalence of infections caused by non-*albicans* species in clinical settings.

Key words: *Candida haemulonii* species complex, emerging pathogens, infectious diseases

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INTRODUCTION

Pathogenic fungi cause not only superficial infections but also life-threatening invasive infections, particularly in immunocompromised individuals [1]. According to estimates, 1.7 billion people experience superficial fungal infections, and 300 million people experience serious fungal infections annually worldwide [1,2]. Approximately 1.5 million people die from invasive fungal infections every year [1,3]. Fungal infections have recently gained worldwide attention because of the notable spikes in their incidence rates observed over the past several years; these spikes are probably a result of surges in the use of clinically invasive procedures, such as central venous catheters and shunts, the overuse of broad-spectrum antibiotics, the increase in prolonged hospital and intensive care unit stays, the prevalence of human immunodeficiency virus infections and other immunocompromised conditions, and a shift toward older populations [3-5]. In addition, the coronavirus disease 2019 pandemic, caused by severe acute respiratory syndrome coronavirus 2, has further exacerbated clinical situations [6]. Coinfection of *Aspergillus*, *Mucorales*, and *Candida* species, including *Candida auris*, for example, together with severe acute respiratory syndrome coronavirus 2, has been found to result in higher morbidity and mortality rates than observed with single infections with any of these pathogens alone [6].

Candida species are the most common fungal pathogens causing mucosal candidiasis, deep organ infections, and bloodstream infections [7]. Despite receiving treatment with antifungal drugs, more than 40% of patients with invasive *Candida* infections die [1,8,9]. *Candida albicans* is the most frequently isolated *Candida* species in clinical settings, and thus has received substantial research attention [3,10]. Over the past two decades, however, epidemiological surveillance has indicated a shift toward the isolation of non-*albicans Candida* species, probably because of an increase in the use of antifungal drugs in clinical practices [9,11]. Specially, non-*albicans Candida* species of the *Candida haemulonii* complex and the closely related species *C. auris*, which in some studies has been classified in the *C. haemulonii* complex [12,13], have garnered substantial attention among both clinical and basic research communities. Multidrug resistance is a notably common characteristic of the *C. haemulonii* species complex.

Most pathogenic *Candida* species (except for *Candida glabrata*) phylogenetically belong to the CTG clade; these species translate the CTG codon to serine rather than the canonical leucine [14]. The CTG clade is composed of the Metschnikowiaceae and Debaryomycetaceae clades [15]. *C. albicans*, *Candida tropicalis*, and *Candida parapsilosis* belong to the Debaryomycetaceae clade, whereas *C. auris* and the *C. haemulonii* species complex are classified into the Metschnikowiaceae clade. Species in the *C. haemulonii* complex are particularly concerning in hospital settings, owing to their rapidly increased emergence worldwide, and their intrinsic resistance to existing antifungal drugs [16,17]. Here, we review the past two decades of research progress in the epidemiology, biology, virulence, and drug resistance of the *C. haemulonii* species complex.

EPIDEMIOLOGY

C. haemulonii was first isolated from seawater in the Atlantic Ocean and the intestines of *Haemulon sciurus* fish in 1962 [18]. The first clinical isolate of *C. haemulonii* was recovered from the blood of a patient with renal failure in 1984 [19]. In 2007, the first outbreak of *C. haemulonii* fungemia was reported in a neonatal intensive care unit in Kuwait, where seven isolates were identified from the blood of four neonates [20]. Fungemia caused by *C. haemulonii* was later reported in hospitalized patients in China and Korea in 2009 [21-23]. Other species of the *C. haemulonii* complex, including *Candida haemulonii* sensu stricto, *Candida duobushaemulonii*, *Candida pseudohaemulonii*, *Candida haemulonii* var. *vulnera*, and *Candida vulturna* have been sporadically identified from patients in hospital settings (Fig 1) [16,24-27].

C. duobushaemulonii was first isolated from a patient with a foot ulcer in 1990 [28]. A retrospective study

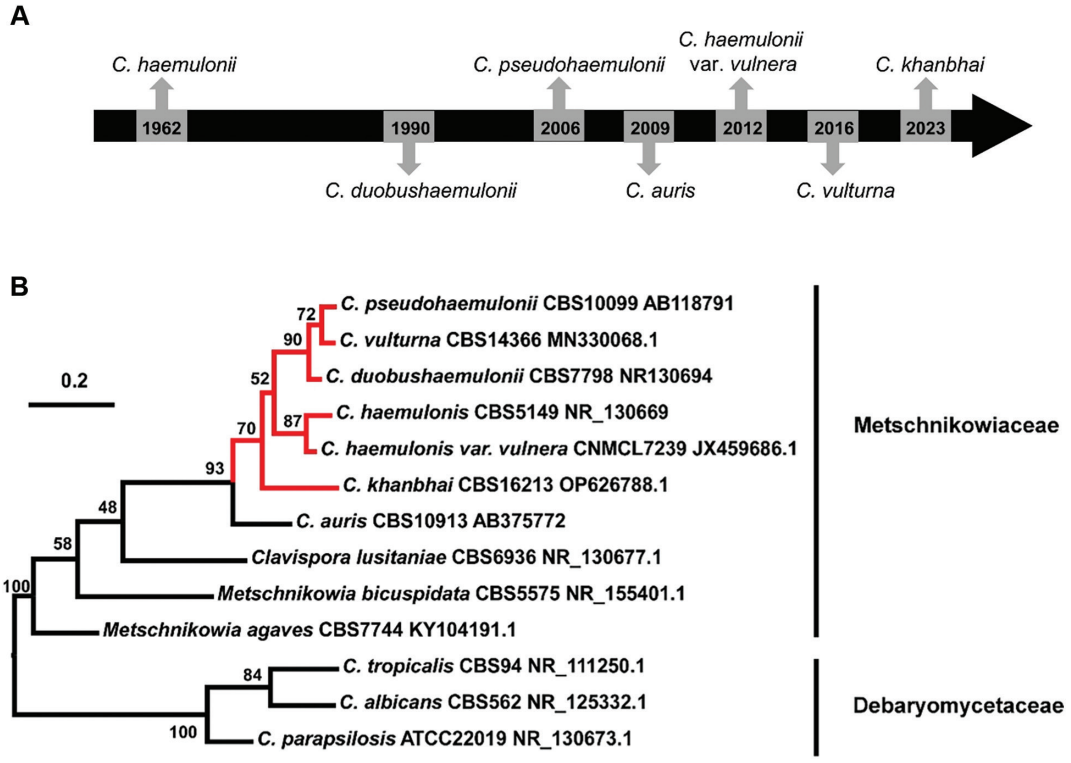

FIGURE 1 | Representative species of the *Candida* CTG clade.
A. Dates of the first reports of isolates of species in the *Candida haemulonii* complex. B. Maximum-likelihood phylogenetic tree of *C. haemulonii* species complex and closely related species, constructed on the basis of ITS sequences and 1,000 bootstrap replicates. All sequences were acquired from the NCBI GenBank database. General time reversible (GTR) and gamma distribution with invariant sites (G+I) models were used. Red lines indicate species of the *C. haemulonii* complex.

reported that a *C. duobushaemulonii* strain from the toenail of a patient in Spain was misidentified as *Candida intermedia* in 1996 [29]. Several invasive *C. duobushaemulonii* infections were reported in China by the China Hospital Invasive Fungal Surveillance Net between 2009 and 2017 [26,27]. Overall, although known cases of *C. duobushaemulonii* infection have been rare to date, occasional hospital outbreaks have been reported [28].

C. pseudohaemulonii was first isolated in 2006 from the blood of a patient in Thailand [25]. Between 2004 and 2006, seven isolates of *C. pseudohaemulonii* were recovered from the blood of seven Korean patients [22]. Interestingly, however, hospital outbreaks caused by *C. pseudohaemulonii* have not yet been reported. *C. haemulonii* var. *vulnera*, which was first identified in 2012, is a rare variant of *C. haemulonii*. Infections caused by *C. haemulonii* var. *vulnera* have been reported in Brazil, India, Argentina, Peru, and China [30–34]. The first strain of *C. vulturna* was isolated from flowers in Cagayan de Oro in the Philippines in 2016; consequently, *C. vulturna* was believed to be associated with plants and the environment [24]. In the same year, a *C. vulturna* strain was isolated from the blood of a patient who died of pneumonia in Malaysia [24]. In 2022, a case of catheter-associated *C. vulturna* fungemia was identified from a patient with sepsis and an infected intractable retroperitoneal cyst in Malaysia [35]. *Candida khanbhai*, the newest member of the *C. haemulonii* complex, was isolated from clinical samples obtained from patients in Kuwait and Malaysia in a study published in 2023 [13]. The overall prevalence of infections caused by the *C. haemulonii* species complex has recently been increasing, and new reports of cases in China and Brazil have garnered considerable attention, because of the multidrug-resistance properties of the isolates involved [36,37]. Both clinical and basic research communities are urged to keep close watch on these globally emerging fungal pathogens.

BIOLOGY

Similarly to the major human fungal pathogen *C. albicans*, species of the *C. haemulonii* complex can undergo morphological transitions and form biofilms, which are important processes contributing to fungal pathogenesis [38–41]. Clinical isolates of *C. haemulonii* produce smooth, round colonies under standard laboratory culture conditions, and form colonies with light to dark violet coloration on CHROMagar, a chromogenic medium used to isolate and differentiate certain clinically relevant *Candida* species [42]. *C. haemulonii* phenotypic transitions have recently been characterized [40]. *C. haemulonii* displays different phenotypes (white, pink, or filamentous) in response to specific growth conditions. The transition between the white and pink phenotypes appears to be the primary switching system in *C. haemulonii*. Clinical isolates of *C. haemulonii* often form both white and pink colonies at 25°C on yeast peptone dextrose agar plates containing the red dye phloxine B. The cells from pink colonies are larger than those from white colonies. Similarly to the white-opaque switch of *C. albicans*, the white-pink switch of *C. haemulonii* appears to be heritable and reversible. Moreover, *C. haemulonii* pink cells can form wrinkled colonies containing elongated filaments at 25°C on yeast peptone glycerol agar plates. This *C. haemulonii* filamentous phenotype is relatively stable and therefore may be regulated through genetic or epigenetic mechanisms. These distinct *C. haemulonii* phenotypes also differ in gene expression profiles, metabolic profiles, production of secreted aspartyl proteases (Saps), and virulence [40].

Beyond morphological transitions, the ability to form biofilms is another important virulence factor for pathogenic *Candida* species [8,41], A fungal biofilm is a coordinated and functional community of fungal cells encased in an extracellular matrix. Fungal biofilms have greater drug resistance than free-floating fungal cells. Like *C. albicans*, species of the *C. haemulonii* complex can form biofilms on indwelling medical devices [8], thus significantly increasing morbidity and mortality among hospitalized patients [43,44]. For example, *C. haemulonii* has been shown to cause serious bloodstream infections originating from biofilms formed on the surfaces of indwelling intravascular catheters [41]. Proteins and carbohydrates are the main components of the extracellular matrix of biofilms formed by clinical isolates of the *C. haemulonii* species complex [41]. Interestingly, species of the *C. haemulonii* complex can form biofilms of different biomasses on several types of catheter surfaces, including vascular (polystyrene), urinary (siliconized latex), nasoenteric (polyurethane), and nasogastric (polyvinyl chloride) catheters [41]. Although the structure and function of biofilms formed by the *C. haemulonii* species complex have been described, the underlying mechanisms of biofilm formation in these species remain unclear [23,41,45,46]. In general, the abilities to undergo phenotypic transitions and to form biofilms are important in the environmental adaptation and virulence of the *C. haemulonii* species complex. Future exploration of the regulatory mechanisms involved in these processes will provide new insights into the development of novel strategies for the prevention and treatment of fungal infections.

VIRULENCE

Saps, phospholipases, and esterases are important virulence factors that facilitate the colonization and survival of pathogenic *Candida* species in their hosts [47]. The genomes of the *C. haemulonii* species complex genomes contain multiple genes encoding Sap-like conserved domains, and the production of Saps by both clinical and environmental *C. haemulonii* species complex isolates has been reported [33,48–51]. In fact, polyclonal antibodies specific to *C. albicans* Sap1, Sap2, and Sap3 recognize *C. haemulonii* Sap-like proteins [49]. Other hydrolytic enzymes, including serine proteases, phospholipases, and esterases, have

also been found in species of the *C. haemulonii* complex [33,48,50,52,53].

Compared with other pathogenic *Candida* species, in species of the *C. haemulonii* complex, the dose-dependent virulence has been reported to be relatively low in an immunocompetent murine model of disseminated infection [54]. In this model, all mice inoculated with *C. haemulonii* survived; however, half the mice died when the inoculum of *C. haemulonii* cells increased by 1 to 2 log. *C. haemulonii* yeast cells were recovered from various organs of infected mice on days 5 and 10 post-infection, regardless of the inoculum size [54]. Another study has indicated that *C. haemulonii* is completely nonvirulent in an immunosuppressed mouse model of disseminated infection: no viable yeast cells were recovered from the kidneys of infected mice 12 days post-infection [55]. In a *Galleria mellonella* infection model, diminished fungal burdens and prolonged host survival have been observed for species of the *C. haemulonii* complex compared with *C. auris* [56]. Indeed, in both the mouse and *G. mellonella* infection models, host survival rates after infection with species of the *C. haemulonii* complex have been found to be higher than those after infection with *C. auris* or *C. albicans* [56]. Future virulence studies will be important to shed new light on the mechanisms of pathogenesis of the *C. haemulonii* species complex compared with other *Candida* species.

DRUG RESISTANCE

Species of the *C. haemulonii* complex are often resistant to multiple antifungal drugs, and this resistance is a common reason for treatment failure [17]. Most clinical isolates of the *C. haemulonii* complex exhibit limited susceptibility to the triazoles and to amphotericin B, with elevated minimum inhibitory concentrations [20,22,26,30,42,57,58]. Several clinical isolates of the *C. haemulonii* complex also exhibit resistance to the echinocandins and to flucytosine [16,26,27,31,33,34,59,60].

Mutations in the lanosterol 14α-demethylase-encoding gene *ERG11* and upregulation of the efflux pump-encoding genes, such as *CDR1*, are associated with azole resistance in the *C. haemulonii* species complex [28,61,62]. Interestingly, efflux pump inhibitors have been shown to reverse the observed azole resistance caused by these mutations [62]. The mechanisms of echinocandins and amphotericin B resistance in the *C. haemulonii* species complex remain to be investigated. Given the common multidrug resistance characteristics of *C. haemulonii* complex species, the associated mechanisms are likely to be complex, and substantial research efforts should be focused on this area in the future.

PERSPECTIVES

Infections with historically "rare" fungal pathogens, such as *C. auris* and the *C. haemulonii* species complex, have been increasingly observed in clinical settings over the past two decades. Given the difficulties in accurately identifying these species through conventional phenotypic methods or standard biochemical methods, the prevalence of infections caused by these species is likely to be underestimated. The more widespread use of molecular identification techniques, such as metagenomic next-generation sequencing and matrix-assisted laser desorption/ionization-time of flight mass spectrometry in clinical settings is expected to greatly improve the accuracy of identification and the characterization of these fungal species.

The emergence of new fungal pathogens and the increased reports of multidrug resistant *C. auris* and species of the *C. haemulonii* complex from different countries may have several potential explanations. First, the widespread use of antifungal drugs in clinical settings and of fungicides in the environment (for example, in agriculture and wood preservation) may promote the evolution and emergence of drug resistant fungal species. Second, the increase in immunocompromised and older populations, combined with the use of clinical antifungal drug treatment regimens, provides an additional avenue for the evolution of antifungal drug resistance. Third, ecological factors, including climate change, combined with exposure to fungicides in the environment, provide yet another avenue for new emerging multidrug resistant fungal pathogens to infect human hosts.

Although the global prevalence of the *C. haemulonii* species complex remains relatively low with respect to that of other fungal pathogens, nosocomial outbreaks have been reported with increasing frequency in many countries. To limit infections caused by the *C. haemulonii* species complex, future studies should focus on understanding the epidemiology, pathogenesis, and drug resistance of these important emerging fungal pathogens. In particular, the transmission of the *C. haemulonii* species complex is a notable area for future research, because how transmission to the host occurs is not clearly understood. Given the increase in reported cases and the multidrug resistance of the associated isolates, the *C. haemulonii* species complex should be considered a serious public health threat worldwide.

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CONFLICTS OF INTEREST

Clarissa J. Nobile is a cofounder of BioSynesis, Inc., a company developing diagnostics and therapeutics for biofilm infections. All other authors have no competing interests to disclose.

REFERENCES

1. Brown GD, Denning DW, Gow NA, Levitz SM, Netea MG, White TC. Hidden killers: human fungal infections. Sci Transl Med. 2012;4:165rv113.
2. Rodrigues ML, Nosanchuk JD. Fungal diseases as neglected pathogens: a wake-up call to public health officials. PLoS Negl Trop Dis. 2020;14:e0007964.
3. Bongomin F, Gago S, Oladele RO, Denning DW. Global and multi-national prevalence of fungal diseases-estimate precision. J Fungi (Basel). 2017;3:57.
4. Ortega M, Marco F, Soriano A, Almela M, Martínez JA, López J, et al. *Candida* species bloodstream infection: epidemiology and outcome in a single institution from 1991 to 2008. J Hosp Infect. 2011;77:157-161.
5. Kullberg BJ, Arendrup MC. Invasive candidiasis. N Engl J Med. 2015;373:1445-1456.
6. Hoenigl M, Seidel D, Sprute R, Cunha C, Oliverio M, Goldman GH, et al. COVID-19-associated fungal infections. Nat Microbiol. 2022;7:1127-1140.
7. Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis. 2004;39:309-317.
8. Sardi JCO, Scorzoni L, Bernardi T, Fusco-Almeida AM, Mendes Giannini MJS. *Candida* species: current epidemiology, pathogenicity, biofilm formation, natural antifungal products and new therapeutic options. J Med Microbiol. 2013;62:10-24.
9. Stavrou AA, Lackner M, Lass-Florl C, Boekhout T. The changing spectrum of Saccharomycotina yeasts causing candidemia: phylogeny mirrors antifungal susceptibility patterns for azole drugs and amphothericin B. Fems Yeast Res. 2019;19.
10. Guinea J. Global trends in the distribution of *Candida* species causing candidemia. Clin Microbiol Infect. 2014;20(Suppl 6):5-10.
11. Deorukhkar SC, Saini S, Mathew S. Non-albicans Candida infection: an emerging threat. Interdiscip Perspect Infect Dis. 2014;2014:615958.
12. Satoh K, Makimura K, Hasumi Y, Nishiyama Y, Uchida K, Yamaguchi H. *Candida auris* sp. nov., a novel ascomycetous yeast isolated from the external ear canal of an inpatient in a Japanese hospital. Microbiol Immunol. 2009;53:41-44.
13. de Jong AW, Al-Obaid K, Mohd Tap R, Gerrits van den Ende B, Groenewald M, Joseph L, et al. *Candida khanbhai* sp. nov., a new clinically relevant yeast within the *Candida haemulonii* species complex. Med Mycol. 2023;61:myad009.
14. Santos MA, Gomes AC, Santos MC, Carreto LC, Moura GR. The genetic code of the fungal CTG clade. C R Biol. 2011;334:607-611.
15. O'Brien CE, McCarthy CGP, Walshe AE, Shaw DR, Sumski DA, Krassowski T, et al. Genome analysis of the yeast Diutina catenulata, a member of the Debaryomycetaceae/ Metschnikowiaceae (CTG-Ser) clade. PLoS One. 2018;13:e0198957.
16. Cendejas-Bueno E, Kolecka A, Alastruey-Izquierdo A, Theelen B, Groenewald M, Kostrzewa M, et al. Reclassification of the *Candida haemulonii* complex as *Candida haemulonii* (*C. haemulonii* group I), *C. duobushaemulonii* sp. nov. (*C. haemulonii* group II), and *C. haemulonii* var. *vulnera* var. nov.: three multiresistant human pathogenic yeasts. J Clin Microbiol. 2012;50:3641-3651.
17. Gomez-Gaviria M, Martinez-Alvarez JA, Chavez-Santiago JO, Mora-Montes HM. *Candida haemulonii* complex and *Candida auris*: biology, virulence factors, immune response, and multidrug resistance. Infect Drug Resist. 2023;16:1455-1470.
18. van U, Kolipinski MC. *Torulopsis haemulonii* nov. spec., a yeast from the Atlantic Ocean. Antonie Van Leeuwenhoek. 1962;28:78-80.
19. Lavarde V. Peritonite mycosique a *Torulopsis haemulonii*. Bull Soc Fr Mycol. Med. 1984;13:173-176.
20. Khan ZU, Al-Sweih NA, Ahmad S, Al-Kazemi N, Khan S, Joseph L, et al. Outbreak of fungemia among neonates caused by *Candida haemulonii* resistant to amphotericin B, itraconazole, and fluconazole. J Clin Microbiol. 2007;45:2025-2027.
21. Ruan SY, Kuo YW, Huang CT, Hsiue HC, Hsueh PR. Infections due to *Candida haemulonii*: species identification, antifungal susceptibility and outcomes. Int J Antimicrob Agents. 2010;35:85-88.
22. Kim MN, Shin JH, Sung H, Lee K, Kim EC, Ryoo N, et al. *Candida haemulonii* and closely related species at 5 university hospitals in Korea: identification, antifungal susceptibility, and clinical features. Clin Infect Dis. 2009;48:e57-e61.
23. Oh BJ, Shin JH, Kim MN, Sung H, Lee K, Joo MY, et al. Biofilm formation and genotyping of *Candida haemulonii*, *Candida pseudohaemulonii*, and a proposed new species (*Candida auris*) isolates from Korea. Med Mycol. 2011;49:98-102.
24. Sipiczki M, Tap RM. *Candida vulturna* pro tempore sp. nov., a dimorphic yeast species related to the *Candida haemulonis* species complex isolated from flowers and clinical sample. Int J Syst Evol Microbiol. 2016;66:4009-4015.
25. Sugita T, Takashima M, Poonwan N, Mekha N. Candida pseudohaemulonii Sp. Nov., an amphotericin B-and azole-resistant yeast species, isolated from the blood of a patient from Thailand. Microbiol Immunol. 2006;50:469-473.
26. Hou X, Xiao M, Chen SC, Wang H, Cheng JW, Chen XX, et al. Identification and antifungal susceptibility profiles of *Candida haemulonii* species complex clinical isolates from a multicenter study in China. J Clin Microbiol. 2016;54:2676-2680.
27. Chen XF, Zhang H, Jia XM, Cao J, Li L, Hu XL, et al. Antifungal susceptibility profiles and drug resistance mechanisms of clinical *Candida duobushaemulonii* isolates from China. Front Microbiol. 2022;13:1001845.
28. Gade L, Muñoz JF, Sheth M, Wagner D, Berkow EL, Forsberg K, et al. Understanding the emergence of multidrug-resistant *Candida*: using whole-genome sequencing to describe the population structure of *Candida haemulonii* species complex. Front Genet. 2020;11:554.
29. Jurado-Martin I, Marcos-Arias C, Tamayo E, Guridi A, de Groot PWJ, Quindós G, et al. *Candida duobushaemulonii*: an old but unreported pathogen. J Fungi (Basel). 2020;6.
30. de Almeida JN Jr, Assy JG, Levin AS, Del Negro GM, Giudice MC, Tringoni MP, et al. *Candida haemulonii* complex species, Brazil, January 2010-March 2015. Emerg Infect Dis. 2016;22:561-563.
31. Kumar A, Prakash A, Singh A, Kumar H, Hagen F, Meis JF, et al. *Candida haemulonii* species complex: an emerging species in India and its genetic diversity assessed with multilocus sequence and amplified fragment-length polymorphism analyses. Emerg Microbes Infect. 2016;5:e49.
32. Perez-Lazo G, Morales-Moreno A, Soto-Febres F, Hidalgo JA, Neyra E, Bustamante B. Liver abscess caused by *Candida haemulonii* var. *vulnera*. First case report in Peru. Rev Iberoam Micol. 2021;38:138-140.
33. Ramos LS, Figueiredo-Carvalho MHG, Silva LN, Siqueira NLM, Lima JC, Oliveira SS, et al. The threat called *Candida haemulonii* species complex in Rio de Janeiro State, Brazil: focus on antifungal resistance and virulence attributes. J Fungi (Basel). 2022;8:574.
34. Chen XF, Hou X, Zhang H, Jia XM, Ning LP, Cao W, et al. First two fungemia cases caused by *Candida haemulonii* var. *vulnera* in China with emerged antifungal resistance. Front Microbiol. 2022;13:1036351.
35. Muthusamy A, Rao M, Chakrabarti A, Velayuthan RD. Case report: catheter related blood stream infection caused by *Candida vulturna*. Med Mycol Case Rep. 2022;36:27-30.
36. Xiao M, Chen SC, Kong F, Xu XL, Yan L, Kong HS, et al. Distribution and antifungal susceptibility of *Candida* species causing candidemia in China: an update from the CHIF-NET study. J Infect Dis. 2020;221:S139-S147.

37. Lima SL, Francisco EC, de Almeida Júnior JN, Santos DWCL, Carlesse F, Queiroz-Telles F, et al. Increasing prevalence of multidrug-resistant *Candida haemulonii* species complex among all yeast cultures collected by a reference laboratory over the past 11 years. J Fungi (Basel). 2020;6:110.
38. Huang G. Regulation of phenotypic transitions in the fungal pathogen *Candida albicans*. Virulence. 2012;3:251-261.
39. Fanning S, Mitchell AP. Fungal biofilms. Plos Pathog. 2012;8:e1002585.
40. Deng Y, Li S, Bing J, Liao W, Tao L. Phenotypic switching and filamentation in *Candida haemulonii*, an emerging opportunistic pathogen of humans. Microbiol Spectr. 2021;9:e0077921.
41. Ramos LS, Mello TP, Branquinha MH, Santos ALS. Biofilm formed by *Candida haemulonii* species complex: structural analysis and extracellular matrix composition. J Fungi (Basel). 2020;6:46.
42. Ramos LS, Figueiredo-Carvalho MH, Barbedo LS, Ziccardi M, Chaves AL, Zancopé-Oliveira RM, et al. *Candida haemulonii* complex: species identification and antifungal susceptibility profiles of clinical isolates from Brazil. J Antimicrob Chemother. 2015;70:111-115.
43. Rajendran R, Sherry L, Nile CJ, Sherriff A, Johnson EM, Hanson MF, et al. Biofilm formation is a risk factor for mortality in patients with *Candida albicans* bloodstream infection-Scotland, 2012-2013. Clin Microbiol Infect. 2016;22:87-93.
44. Rajendran R, Sherry L, Deshpande A, Johnson EM, Hanson MF, Williams C, et al. A prospective surveillance study of candidaemia: epidemiology, risk factors, antifungal treatment and outcome in hospitalized patients. Front Microbiol. 2016;7:915.
45. Ramos LS, Oliveira SSC, Souto XM, Branquinha MH, Santos ALS. Planktonic growth and biofilm formation profiles in *Candida haemulonii* species complex. Med Mycol. 2017;55:785-789.
46. Ramos LS, Silva LN, Branquinha MH, Santos ALS. Susceptibility of the *Candida haemulonii* complex to echinocandins: focus on both planktonic and biofilm life styles and a literature review. J Fungi (Basel). 2020;6:201.
47. Schaller M, Borelli C, Korting HC, Hube B. Hydrolytic enzymes as virulence factors of *Candida albicans*. Mycoses. 2005;48:365-377.
48. Ramos LS, Branquinha MH, Santos AL. Different classes of hydrolytic enzymes produced by multidrug-resistant yeasts comprising the *Candida haemulonii* complex. Med Mycol. 2017;55:228-232.
49. Ramos LS, Oliveira SSC, Braga-Silva LA, Branquinha MH, Santos ALS. Secreted aspartyl peptidases by the emerging, opportunistic and multidrug-resistant fungal pathogens comprising the *Candida haemulonii* complex. Fungal Biol. 2020;124:700-707.
50. Pagani DM, Heidrich D, Paulino GV, de Oliveira Alves K, Dalbem PT, de Oliveira CF, et al. Susceptibility to antifungal agents and enzymatic activity of *Candida haemulonii* and Cutaneotrichosporon dermatis isolated from soft corals on the Brazilian reefs. Arch Microbiol. 2016;198:963-971.
51. Parra-Ortega B, Cruz-Torres H, Villa-Tanaca L, Hernandez-Rodriguez C. Phylogeny and evolution of the aspartyl protease family from clinically relevant *Candida* species. Mem Inst Oswaldo Cruz. 2009;104:505-512.
52. Souto XM, Ramos LS, Branquinha MH, Santos ALS. Identification of cell-associated and secreted serine-type peptidases in multidrug-resistant emergent pathogens belonging to the *Candida haemulonii* complex. Folia Microbiol (Praha). 2019;64:245-255.
53. Souto XM, Branquinha MH, Santos ALS. Chymotrypsin- and trypsin-like activities secreted by the multidrug-resistant yeasts forming the *Candida haemulonii* complex. An Acad Bras Cienc. 2019;91:e20180735.
54. Fakhim H, Vaezi A, Dannaoui E, Chowdhary A, Nasiry D, Faeli L, et al. Comparative virulence of *Candida auris* with *Candida haemulonii*, *Candida glabrata* and *Candida albicans* in a murine model. Mycoses. 2018;61:377-382.
55. Ben-Ami R, Berman J, Novikov A, Bash E, Shachor-Meyouhas Y, Zakin S, et al. Multidrug-resistant *Candida haemulonii* and *C. auris*, Tel Aviv, Israel. Emerg Infect Dis. 2017;23:195-203.
56. Munoz JE, Ramirez LM, Dias LDS, Rivas LA, Ramos LS, Santos ALS, et al. Pathogenicity levels of colombian strains of *Candida auris* and Brazilian strains of *Candida haemulonii* species complex in both murine and *Galleria mellonella* experimental models. J Fungi (Basel). 2020;6:104.
57. Frias-De-Leon MG, Martinez-Herrera E, Acosta-Altamirano G, Arenas R, Rodriguez-Cerdeira C. Superficial candidosis by *Candida duobushaemulonii*: an emerging microorganism. Infect Genet Evol. 2019;75:103960.
58. Ramos R, Caceres DH, Perez M, Garcia N, Castillo W, Santiago E, et al. Emerging multidrug-resistant *Candida duobushaemulonii* Infections in Panama hospitals: importance of laboratory surveillance and accurate identification. J Clin Microbiol. 2018;56:e00371-18.
59. de Barros Rodrigues DK, Lockhart SR, Berkow EL, Gade L, Bonfietti LX, Mazo Fávero Gimenes V, et al. Whole-genome sequencing of *Candida haemulonii* species complex from Brazil and the United States: genetic diversity and antifungal susceptibility. Med Mycol. 2023;61:myad030.
60. Muro MD, Motta Fde A, Burger M, Melo AS, Dalla-Costa LM. Echinocandin resistance in two *Candida haemulonii* isolates from pediatric patients. J Clin Microbiol. 2012;50:3783-3785.
61. Rodrigues LS, Gazara RK, Passarelli-Araujo H, Valengo AE, Pontes PVM, Nunes-da-Fonseca R, et al. First genome sequences of two multidrug-resistant *Candida haemulonii* var. *vulnera* isolates from pediatric patients with candidemia. Front Microbiol. 2020;11:1535.
62. Silva LN, Ramos LS, Oliveira SSC, Magalhães LB, Squizani ED, Kmetzsch L, et al. Insights into the multi-azole resistance profile in *Candida haemulonii* species complex. J Fungi (Basel). 2020;6:215.

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