Enfermedades Infecciosas y Microbiología Clínica 41 (2023) 67–69

Enfermedades Infecciosas y Microbiología Clínica

www.elsevier.es/eimc

Editorial

C. parapsilosis: The importance of an emerging pathogen

C. parapsilosis: la importancia de un patógeno emergente

Woolhouse defined an emerging pathogen as '*an infectious agent whose incidence is increasing following its first introduction into a new host population*'.[1] Emergence mainly applies to two particular situations: (a) the description of an entirely new species as a result of taxonomic changes; (b) the description of a previously unknown/rarely documented association between a known species and a host pathological state. A re-emerging pathogen, in contrast, is '*one whose incidence is increasing in an existing host population as a result of long-term changes in its underlying epidemiology*'. That evident increase in the number of cases caused by a particular species is usually linked to an evolutionary advantage newly developed by a known pathogen and/or to the expansion of the range of susceptible hosts.[1]

Contemporary Medical Mycology has witnessed a bloom of emergent and re-emergent fungal pathogens, with *Candida auris*, triazole-resistant *Aspergillus fumigatus*, or COVID-19 associated mucormycosis being only a few recent notorious examples all of us are familiar with. But, can we apply the adjective emergent/re-emergent to species within the *Candida parapsilosis* complex? To answer this question, let's take a few minutes for reflection.

Cryptic species of the *C. parapsilosis* complex

The first description of what we know today as *Candida parapsilosis* dates back to 1928. Seventy years would have to pass to recognize the existence of three separate species within the complex, namely *C. parapsilosis* sensu stricto, *C. metapsilosis*, and *C. orthopsilosis*.

Despite the interaction of *C. metapsilosis* and *C. orthopsilosis* with humans is thought to be mainly restricted to superficial colonization, they are able to cause invasive disease and candidemia. The rate of clinical infections, however, is considerably lower than *C. parapsilosis* sensu stricto and, according to published surveillance reports, these species may account for less than 9% of the *C. parapsilosis* complex infections.[2,3] Thus, by the time *C. metapsilosis* and *C. orthopsilosis* were described as separate entities, they merited to be considered emergent pathogens, but as no epidemiological changes have been noted since then, this may not hold true. Does this mean that they are no longer able to raise the interest of mycologists? The answer is no.

Until recently, microbiological methods commonly used in routine labs have not allowed the differentiation of the three species within the complex. This has hampered the precise identification of their epidemiology or the differences and similarities in their biology. However, as illustrated in the work Ruiz de Alegría and cols in this number of *Enfermedades Infecciosas y Microbiología Clínica*,[4] growing evidence points towards specific traits that justify the limited presence of *C. metapsilosis* and *C. orthopsilosis* in human pathology. As compared to *C. parapsilosis* sensu stricto, *C. metapsilosis* seems to present decreased virulence[5] and both *C. metapsilosis* and *C. orthospilosis* have reduced ability to produce biofilms. This reduced adherence may be one of the reasons why no nosocomial outbreaks have been related to the complex cryptic species.

Another interesting point is that the in vitro susceptibility behaviour of *C. metapsilosis* does not match that of *C. parapsilosis*, with fluconazole MICs moving in a slightly superior range. *C. orthopsilosis*, in turn, seems to be naturally susceptible to fluconazole. It should not be overlooked, however, that the Y132F mutation in the ERG11 gene (associated with fluconazole resistance), has been sporadically described in the latter.[6] To date, it is unknown whether the breakpoints defined for *C. parapsilosis* also apply to their two siblings in the complex or if the treatment recommendations given in clinical guidelines result in similar success rates for the three species.

Candida parapsilosis sensu stricto: what's up, old chap?

Initially considered to be non-pathogenic, decades of clinical experience have proven that, besides a common colonizer of the human skin, *Candida parapsilosis* sensu stricto is one of the major medically relevant fungal pathogens. It is of particular importance in warm-temperate areas, ranking as the second leading cause of bloodstream fungal infections in European countries of the Mediterranean Basin, Latin America, and Asia.[7]

One of the key features of this species is its ability to attach and persist on inert surfaces thanks to its capacity to develop biofilms. This trait is the basis for the increased risk of catheter-related infections in fragile patients, but also for the long-standing persistence of this yeast in the nosocomial environment. Persistence, coupled with easy cross-transmission via the skin of healthcare workers' hands or contaminated material, sets the scenario for a terrifying perfect storm: a long-standing hospital outbreak. In 1975, Plouffe et al. described a significant accumulation of *C. parapsilosis* can-

DOI of original article: https://doi.org/10.1016/j.eimc.2021.08.001

https://doi.org/10.1016/j.eimce.2022.09.010

didemia cases linked to the use of contaminated hyperalimentation and albumin solutions in Michigan,[8] earning on its own merit the title of "emerging pathogen" and heralding the increasing number of genotypically related nosocomial cases that we can trace back in the literature nowadays. Outbreaks have mainly occurred in neonatal and adult intensive care units,[9] but have also been associated with surgical procedures after exposure to contaminated environmental reservoirs.[10] Of interest, cross-transmission has been documented to occur not only among patients admitted to a particular hospital ward, but also between hospitals.[11] Under the light of the currently existing body of evidence, why put back the focus on *C. parapsilosis*? Because many recent reports of *C. parapsilosis* nosocomial outbreaks have been caused by fluconazole non-susceptible clones.

Wildtype *C. parapsilosis* sensu stricto strains are characterized by an exquisite susceptibility to triazoles whereas, as compared to other important *Candida* species, it displays a reduced in vitro susceptibility to echinocandins. In Spain, as in other worldwide surveillance reports, the prevalence of fluconazole-resistant strains has been traditionally lower than 5%.[12] In Europe, however, this panorama has started to change with the sudden rise of fluconazole non-susceptible strains noted in 2015 at the expense of outbreaks involving centres from northern Italy.[13] Since then, outbreaks have been reported in France, Greece, Turkey, Brazil, Mexico, South Korea, and now, also in Spain.[11,14] Spanish isolates were first detected in Palma de Mallorca in 2015.[14] Since then, more than 10 hospitals in different geographical areas (Barcelona, Madrid, Burgos, Santander) have identified this new threat so far.[15] Such epidemiological global shift makes *C. parapsilosis* meet the definition of a re-emergent pathogen meriting the consideration of a priority species to keep under surveillance.

The emergence of fluconazole non-susceptible *C. parapsilosis* sensu stricto resembles *Candida auris* in different aspects. First, it has the potential for silent dissemination. In centres without well-implemented screening policies, the spreading of non-susceptible strains goes undetected until the first cases of invasive infection develop. Second, once it is established in the environment, it is very difficult to eradicate, leading to long-lasting endemic situations. Data regarding the efficacy of common disinfectants are scarce and evidence on the most effective cleaning and disinfection procedures is lacking,[16] which hampers the design and implementation of appropriate policies aimed at the eradication of this species from the environment. And third, in case of infection, the antifungal treatment of choice is under debate. Guidelines recommend fluconazole as the preferred treatment for *C. parapsilosis* infections when the isolate is reported as susceptible. However, they fail to offer advice in cases of non-susceptible isolates due to the absence of solid scientific evidence to guide the proper management of these cases. At present, both liposomal amphotericin B and echinocandins might be options of treatment.

In vivo studies with the *Galleria melonella* model suggest that fluconazole-non susceptible *C. parapsilosis* isolates carrying the Y132F mutation (the most frequently found in outbreaks) are not necessarily more virulent and that amphotericin B might be an effective treatment,[17] albeit its potential risk for toxicity. As an alternative, echinocandins might be considered a safer option. Some clinicians might be concerned by the reduced in vitro activity of *C. parapsilosis* complex isolates against echinocandins and its theoretically decreased response to therapy. A limited number of randomized controlled trials have shown that echinocandin use is more frequently associated with persistent candidemia and microbiological failure when compared to fluconazole or amphotericin B in the subgroup of susceptible *C. parapsilosis* isolates.[18,19] However, observational studies have failed to link the use of echinocandins with increased clinical failure or 30-day mortality.[20]

Setting aside the in vitro susceptibility profile, other major factors must be carefully balanced before deciding on the treatment: potential and severe side-effects should be considered when administering amphotericin B and the risk of clinical failure should be monitored when administering echinocandins, especially if the source of infection cannot be controlled. As for today, we lack scientific evidence to recommend which antifungal treatment is the best therapeutic option for fluconazole-non susceptible isolates.

Relevance of the *C. parapsilosis* complex from a Public Health perspective

In light of previously presented data, *C. parapsilosis* has re-emerged as a pathogen of public health importance that has captured the attention of the scientific community. Similar to *C. auris*, it is of nosocomial relevance and infection prevention strategies are essential to control the worldwide spread of fluconazole non-susceptible *C. parapsilosis* strains. Not surprisingly, the World Health Organization has listed azole-resistant *Candida* species as a priority fungal pathogen to keep under surveillance and in need of more research. Gaps in knowledge remain for optimal treatment options and critical infection control interventions.

In Spain, the National Centre for Microbiology from the Instituto de Salud Carlos III acts as a national reference centre for clinically isolated fungi. However, it is not mandatory to surveil all *Candida* isolates and detecting real-time epidemiological changes at a national level is challenging. These limitations hamper our capacity of response to fungal outbreaks and our ability to detect and prevent cross-transmission between hospitals. However, local initiatives are also important and offer a front-line surveillance response to *Candida* infections/outbreaks. At a hospital level, laboratories can track a new resistant pattern in yeasts or an unexpected cluster of candidemia cases in a specific unit. In this line, every effort to strengthen the lab capacity to correctly identify *Candida* species should be encouraged, as this is the first step to improving our health system.[4] Finally, we should not forget that stewardship strategies aimed at optimizing antifungal use are of special relevance to address the growing concern of antifungal resistance.

In conclusion, is *C. parapsilosis* an emergent/re-emergent pathogen? The answer is yes. Spain is experiencing a worrying rise of fluconazole non-susceptible *C. parapsilosis* strains capable of causing long-lasting outbreaks. Global awareness of this new threat is key to surveil this re-emerging pathogen we cannot let go under-recognized.

Funding

None.

Conflict of interest

M. Martín-Gómez and M. Puig-Asensio have received honoraria on behalf of Gilead and Pfizer.

References

1. Woolhouse ME. Population biology of emerging and re-emerging pathogens. Trends Microbiol. 2002;10 Suppl.:3–7, http://dx.doi.org/10.1016/s0966-842x(02)02428-9.
2. Arastehfar A, Khodavaisy S, Daneshnia F, Najafzadeh MJ, Mahmoudi S, Charsizadeh A, et al. Molecular identification, genotypic diversity, antifungal susceptibility, and clinical outcomes of infections caused by clinically underrated yeasts, candida orthopsilosis, and candida metapsilosis: an Iranian multicenter study (2014–2019). Front Cell Infect Microbiol. 2019;9:264, http://dx.doi.org/10.3389/fcimb.2019.00264.
3. de Toro Crespo M, Torres MJ, Maite R, Aznar J. Characterization of Candida parapsilosis complex isolates. Clin Microbiol Infect. 2011;17:418–24, http://dx.doi.org/10.1111/j.1469-0691.2010.03302.x.

4. Ruiz de Alegría Puig C, Merino M, del SG, Fonseca ADMP, Balbín JA. Characterization, antifungal susceptibility and virulence of Candida parapsilosis complex isolates in a tertiary hospital in Cantabria, Northern Spain. Enferm Infecc Microbiol Clin. 2023;41:99–102.
5. Bertini A, De Bernardis F, Hensgens LAM, Sandini S, Senesi S, Tavanti A. Comparison of *Candida parapsilosis*, *Candida orthopsilosis*, and *Candida metapsilosis* adhesive properties and pathogenicity. Int J Med Microbiol. 2013;303:98–103, http://dx.doi.org/10.1016/j.ijmm.2012.12.006.
6. Rizzato C, Poma N, Zoppo M, Posteraro B, Mello E, Bottai D, et al. CoERG11 A395T mutation confers azole resistance in *Candida orthopsilosis* clinical isolates. J Antimicrob Chemother. 2018;73:1815–22, http://dx.doi.org/10.1093/jac/dky122.
7. Tóth R, Nosek J, Mora-Montes HM, Gabaldon T, Bliss JM, Nosanchuk JD, et al. Candida parapsilosis: from genes to the bedside. Clin Microbiol Rev. 2019;32:1–38, http://dx.doi.org/10.1128/CMR.00111-18.
8. Plouffe JF, Brown DG, Silva J Jr, Eck T, Stricof RL, Fekety FR. Nosocomial outbreak of *Candida parapsilosis* fungemia related to intravenous infusions. Arch Intern Med. 1977;137:1686–9.
9. Qi L, Fan W, Xia X, Yao L, Liu L, Zhao H, et al. Nosocomial outbreak of Candida parapsilosis sensu stricto fungaemia in a neonatal intensive care unit in China. J Hosp Infect. 2018;100:e246–52, http://dx.doi.org/10.1016/j.jhin.2018.06.009.
10. Johnston BL, Schlech WF 3rd, Marrie TJ. An outbreak of *Candida parapsilosis* prosthetic valve endocarditis following cardiac surgery. J Hosp Infect. 1994;28:103–12, http://dx.doi.org/10.1016/0195-6701(94)90137-6.
11. Thomaz DY, Del Negro GMB, Ribeiro LB, da Silva M, Carvalho GOMH, Camargo CH, et al. A Brazilian inter-hospital candidemia outbreak caused by fluconazole-resistant candida parapsilosis in the COVID-19 era. J Fungi. 2022;8:100, http://dx.doi.org/10.3390/jof8020100.
12. Puig-Asensio M, Padilla B, Garnacho-Montero J, Zaragoza O, Aguado JM, Zaragoza R, et al. Epidemiology and predictive factors for early and late mortality in Candida bloodstream infections: a population-based surveillance in Spain. Clin Microbiol Infect. 2014;20:O245–54, http://dx.doi.org/10.1111/1469-0691.12380.
13. Pfaller MA, Diekema DJ, Turnidge JD, Castanheira M, Jones RN. Twenty years of the SENTRY antifungal surveillance program: results for Candida species from 1997–2016. Open Forum Infect Dis. 2019;6 Suppl. 1:S79–94, http://dx.doi.org/10.1093/ofid/ofy358.
14. Alcoceba E, Gómez A, Lara-Esbrí P, Oliver A, Beltrán AF, Ayestarán I, et al. Fluconazole-resistant *Candida parapsilosis* clonally related genotypes: first report proving the presence of endemic isolates harbouring the Y132F ERG11 gene substitution in Spain. Clin Microbiol Infect. 2022;28:1113–9, http://dx.doi.org/10.1016/j.cmi.2022.02.025.
15. Zaragoza O, Alcázar-Fuoli L, Trevijano-Contador N, Torres-Cano A, Carballo-González C, Puig-Asensio M, et al. Global emergence of resistance to fluconazole and voriconazole in *Candida parapsilosis* in tertiary hospitals in Spain during the COVID-19 pandemic. 2022; Available from: https://medrxiv.org/cgi/content/short/2022.06.06.22275514.
16. Fu L, Le T, Liu Z, Wang L, Guo H, Yang J, et al. Different efficacies of common disinfection methods against candida auris and other candida species. J Infect Public Health. 2020;13:730–6, http://dx.doi.org/10.1016/j.jiph.2020.01.008.
17. Binder U, Arastehfar A, Schnegg L, Hörtnagl C, Hilmioğlu-Polat S, Perlin DS, et al. Efficacy of LAMB against emerging azole-and multidrug-resistant candida parapsilosis isolates in the galleria mellonella model. J Fungi. 2020;6:1–11, http://dx.doi.org/10.3390/jof6040377.
18. Reboli AC, Rotstein C, Pappas PG, Chapman SW, Kett DH, Kumar D, et al. Anidulafungin versus fluconazole for invasive Candidiasis. N Engl J Med. 2007;356:2472–82, http://dx.doi.org/10.1056/NEJMoa066906.
19. Mora-Duarte J, Betts R, Rotstein C, Colombo AL, Thompson-Moya L, Smietana J, et al. Comparison of caspofungin and amphotericin B for invasive candidiasis. N Engl J Med. 2002;347:2020–9, http://dx.doi.org/10.1056/NEJMoa021585.
20. Fernández-Ruiz M, Aguado JM, Almirante B, Lora-Pablos D, Padilla B, Puig-Asensio M, et al. Initial use of echinocandins does not negatively influence outcome in Candida parapsilosis bloodstream infection: a propensity score analysis. Clin Infect Dis. 2014;58:1413–21, http://dx.doi.org/10.1093/cid/ciu158.

María Teresa Martín-Gómez [a,*], Mireia Puig-Asensio [b,c,*]

[a] *Microbiology Department, Hospital Universitari Vall d'Hebron, Barcelona, Spain*

[b] *Department of Infectious Diseases, Hospital Universitari de Bellvitge, Institute for Biomedical Research (IDIBELL), l'Hospitalet de Llobregat, Barcelona, Spain*

[c] *Center for Biomedical Research in Infectious Diseases Network (CIBERINFEC; CB21/13/00009), Instituto de Salud Carlos III, Madrid, Spain*

* Corresponding author.
E-mail address: mariateresa.martin@vallhebron.cat (M.T. Martín-Gómez), mpuiga@bellvitgehospital.cat (M. Puig-Asensio).