Revista Argentina de Microbiología 55 (2023) 201–203

asociación argentina de microbiología

REVISTA ARGENTINA DE MICROBIOLOGÍA

www.elsevier.es/ram

EDITORIAL

# The rising threat of intrinsically resistant *Candida* species in Argentina

## El creciente riesgo de *Candida* spp. intrínsicamente resistentes en Argentina

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In recent years, the medical community has faced a growing concern: the emergence of *Candida* species that exhibit intrinsic resistance to commonly used antifungal drugs. This alarming trend poses a significant challenge in the management of fungal infections and demands immediate attention and action. In this editorial, we shed light on the implications of intrinsic resistance in *Candida* species and emphasize the urgent need for enhanced strategies to combat this threat.

## Understanding intrinsic resistance

The 2022 document M27M44SEd3E from the Clinical and Laboratory Standards Institute (CLSI) defines intrinsic resistance (IR) as the ''inherent or innate (not acquired) resistance to an antifungal, which is reflected in the non-wild-type susceptibility patterns of all or almost all representatives of a species''. This characterization implies that a correct taxonomical identification would be enough to classify an isolate as intrinsically resistant or not. As an important achievement, the first list of intrinsically resistant species was published in the same document. This list includes *Candida krusei* (also recognized under the taxonomic name *Pichia kudriavzevii*), showing intrinsic resistance (IR) to fluconazole, and three basidiomycetous fungi (*Cryptococcus* spp., *Rhodotorula* spp., and *Trichosporon* spp.)[2] that should be considered intrinsically resistant to echinocandins, with *Rhodotorula* also being resistant to fluconazole. In this list has disappointed a part of the scientific community since intrinsic resistance limits the effectiveness of standard treatment options from the onset.

## Implications for Public Health

The impact of intrinsic resistance in *Candida* species on public health cannot be overstated. Infections caused by these resistant species often result in prolonged hospital stays, increased healthcare costs, and elevated mortality rates. Deep-seated *Candida* spp. infections are associated with mortality rates of ∼50% and these ratios are higher in the context of infections with drug-resistant *Candida* spp. Patients with compromised immune systems, such as those with HIV/AIDS or undergoing chemotherapy, are particularly vulnerable to these infections. In addition, the limited arsenal of effective antifungal drugs against these resistant Candida strains leaves healthcare providers with few treatment options, making it challenging to achieve successful outcomes.

## Contributing factors

Several factors contribute to the emergence of intrinsic antifungal-resistant *Candida* spp. One key factor is the

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https://doi.org/10.1016/j.ram.2023.09.001

overuse and misuse of antifungal agents. Inappropriate prescribing practices, inadequate dosing, and failure to complete treatment regimens have fueled the selection pressure of *Candida* spp. populations, leading to the development and propagation of resistant species. Furthermore, it was proposed that the extensive use of antifungals in agriculture and animal husbandry has contributed to the creation of reservoirs of resistant strains, which can be transmitted to humans.

## The rise of *Candida auris* and the *Candida haemulonii* species complex

*Candida auris* has rapidly gained attention as an emerging global health threat and has recently been included as one of the four fungal pathogens of the critical priority group of the WHOś fungal priority pathogens list due to its morbidity and mortality rate, antifungal resistance and major knowledge gaps on its global burden[1]. Although *C. auris* was proposed to be included as a fluconazole IR species in the aforementioned CLSI document, it does not strictly meet the inclusion criteria since not all but more than 93% of the studied *C. auris* strains show high fluconazole MICs (and some high voriconazole MICs). Moreover, more than 35% of the strains showed high MIC values for amphotericin B and over 10% of the strains exhibited high MIC values for echinocandins (multidrug resistant: non-susceptible to one or more drugs of two or more antifungal classes). Their antifungal susceptibilities, resistance mechanisms and other characteristics are linked to different clonal populations that were partially kept geographically restricted[3]. In Argentina, the first two *C. auris* isolates reported in October 2022 were classified as clade III (known as the South African clade) and showed high azole, polyene and echinocandin MICs. These strains were clonal, demonstrating that they were transmitted among patients[5,6].

The *Candida haemulonii* complex comprises four species that are considered human pathogens: *C. haemulonii*, *C. duobushaemulonii*, *C. pseudohaemulonii* and *C. vulturna*. These species showed high MIC values for multiple antifungals. In many cases, those MICs are higher than the ones shown by *C. auris*. For instance, the susceptibility profile of 25 Argentinian strains of this complex showed that all but two strains had high fluconazole MIC values, 13 strains exhibited cross-high MICs for all tested azole and echinocandin drugs, while 8 strains displayed pan-resistance (resistance to amphotericin B, echinocandins and azole drugs)[4].

## Transmission and clinical impact of *C. auris* and the *C. haemulonii* species complex

*C. auris* has been associated with nosocomial outbreaks, as well as the potential for rapid dissemination and high mortality rates among affected patients. In addition, *C. auris* has the ability to persist better than other *Candida* spp. on environmental surfaces. These facts have led the CDC to recommend the isolation of the affected patients. In order to comply with these recommendations, the correct identification of this species in clinical laboratories is essential. However, both *C. auris* and the *C. haemulonii* species complex pose challenges to accurate species identification, which can hinder appropriate treatment and surveillance efforts. There are two unique recommended methods for unequivocal identification: molecular-based procedures and/or MALDI-TOF, since most of the phenotype-based methods misidentify these species.

The ability of the *C. haemulonii* species complex to persist and cause outbreaks has not been thoroughly studied as in the case of *C. auris*. Nevertheless, the fact that they are taxonomically related −they all belong to the yeast family *Metshnikowiaceae*− allows to infer that something similar could happen. In Argentina, the isolation of yeasts from the *C. haemulonii* species complex is relatively common. Taking into account only the published data from the Malbrán Institute group -25 strains- and the autochthonous isolates that we keep in our laboratory, we can count more than 40 strains in the last six years. This leads us to ponder why there is such an alarm for two *C. auris* isolates and not such a stir for the regular and constant isolation of multi- and pan-resistant yeast strains that have the potential to cause outbreaks.

## Addressing the Challenge

Addressing the emergence of yeasts of the *Metshnikowiaceae* family requires a multi-pronged approach. Enhanced surveillance and rapid identification methods are crucial for the early detection and containment of outbreaks. Constant training is needed in the techniques necessary for the identification of these species, including strict adherence to hand hygiene protocols and environmental decontamination procedures. Interdisciplinary collaboration among healthcare professionals, mycologists and other members of the infection control teams is vital to prevent and manage infections caused by these resistant species. Furthermore, research efforts should focus on exploring alternative treatment options.

## Conclusion

The emergence of these intrinsically resistant species represents a significant threat to global health. Immediate action is needed to prevent the further spread of these pathogens and mitigate their impact. Strengthened surveillance, including improving identification and antifungal susceptibility testing capability, is key to addressing this escalating challenge.

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