https://doi.org/10.1038/s44259-025-00173-5

Emerging antifungal resistance in *Candida parapsilosis*: the end of the innocence

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Candida parapsilosis is an opportunistic yeast that was recently deemed a high- importance fungal pathogen by the World Health Organization. In fact, *C. parapsilosis* poses an escalating threat in healthcare settings due to its ability to adapt to diverse environments, propensity for human-to-human transmission, and capacity to develop antifungal resistance. Recent studies emphasize its rising clinical importance, particularly with the increasing resistance to antifungals and the emergence of clonal outbreaks, making it a serious threat to public health. This review provides an up-to-date synthesis of our current knowledge on this yeast, addressing its epidemiology, environmental adaptability, and the molecular mechanisms driving resistance to azoles and echinocandins. In particular, it provides a comprehensive overview of the resistome of *C. parapsilosis*, offering insights into the genetic determinants associated with antifungal resistance. We also identify key unresolved questions and emphasize the need for further research to mitigate its impact on healthcare systems.

Candida parapsilosis is a diploid ascomycetous yeast and a member of the Debaryomycetaceae. Like other medically relevant yeasts such as *Candida albicans*, *Candidozyma auris* or *Candida tropicalis*, *C. parapsilosis* belongs to the CUG-Ser1 clade in which the CUG codon has been reassigned to code for serine rather than leucine[1]. Notably, *C. parapsilosis* is part of a complex of closely related species (*C. parapsilosis* sensu stricto, *Candida orthopsilosis*, *Candida metapsilosis*, and the two recently described *Candida theae* and *Candida margitis*), some of which emerged through hybridization events[2,3]. However, *C parapsilosis* sensu stricto (from here on indicated as *C. parapsilosis*) is by far the predominant species of the complex in human clinical samples. Behaving as a natural commensal of the skin and digestive tract, *C. parapsilosis* may also act as an opportunistic pathogen and cause bloodstream infections (i.e. candidemia), endocarditis, peritonitis, and other invasive diseases in susceptible hosts[4].

Candida parapsilosis has a global distribution and is particularly prevalent in healthcare environments[4]. It is recognized as the second or third most common cause of invasive candidiasis worldwide, following *C. albicans* and, in some regions, *Nakaseomyces glabratus* (formerly *Candida glabrata*)[5]. The incidence of *C. parapsilosis* infections is notably high in neonatal intensive care units (NICUs) and among immunocompromised patients. Geographically, higher incidence rates have been reported in Southern Europe, South Africa and Latin America, reflecting regional variations in species distribution and possibly infection control practices[6]. Global mortality rates for *C. parapsilosis* bloodstream infections range from 17% to 47%, which—while lower than those associated with *C. albicans* and *N. glabratus*—still represent a substantial clinical burden[7,8]. According to the recent multicentre study Candida III, the attributable mortality rate for *C. parapsilosis* candidemia was ~8%, underscoring the serious nature of these infections[9].

Several risk factors contribute to the susceptibility to invasive *C. parapsilosis* infections, including the use of central venous catheters, total parenteral nutrition, broad-spectrum antibiotics, corticosteroids, neutropenia, and prolonged hospital stays. It was recently demonstrated that prophylactic treatment with broad-spectrum antibiotics induces gut dysbiosis in hematopoietic stem transplant recipients (10). The resulting reduction in bacterial load promotes yeast overgrowth in the gut, thus facilitating the translocation of *C. parapsilosis* into the bloodstream to cause candidemia[10]. In neonates, particularly premature infants, additional risk factors include low birth weight and immature immune systems, making *C. parapsilosis* a leading cause of fungal sepsis in this vulnerable population[11]. Moreover, *C. parapsilosis* ability to form biofilms on medical devices (e.g. intravenous catheters) often results in infections that are persistent and

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difficult-to-treat (though this trait is highly strain-dependent)[12]. It is interesting to note that candidalysin, firstly discovered in *C. albicans* and further unveiled as a major virulence factor of *C. albicans*, *C. dubliniensis* and *C. tropicalis*, does not have an ortholog in the genome of *C. parapsilosis*[13,14].

Until not long ago, the vast majority of *C. parapsilosis* isolates were susceptible to azoles. However, since 2018, the frequency of isolation of azole-resistant *C. parapsilosis* strains has been alarmingly increasing, parallelled by a higher number of reports of fluconazole-resistant *C. parapsilosis* causing clonal outbreaks in the clinics[4,15,16]. Although there are some conflicting data regarding whether or not fluconazole resistance in *C. parapsilosis* results in a higher mortality[17–19], the delay in effective therapy – as sometimes fluconazole is started empirically - together with the ability of these strains to spread across different hospitals, cities, and potentially continents[20,21], make for an explosive mix. It is therefore not surprising that this species has been included in the high-priority group of the recently published WHO Fungal Priority Pathogen List (FPPL)[22].

Candida parapsilosis can adapt to and thrive in various environments

C. parapsilosis has long been known in the medical setting as a skin colonizer, which helps explaining its potential for inter-human transmission via horizontal transfer[23]. Besides humans, it has also been isolated from a large variety of animals, including wild birds[24–26]. Of note, animal isolates of *C. parapsilosis* - and other opportunistic yeasts - displaying acquired azole resistance to medical antifungals have been reported, suggesting that selective pressure may occur outside the human host, raising additional concerns[27,28].

An environmental study conducted in the US identified several *Candida* species (including *C. parapsilosis*) in soil samples, suggesting that they may evolve and possibly thrive outside human hosts, which challenge the dogma of these yeasts being strict commensals[29,30]. *C. parapsilosis* has also been isolated from different environmental niches, such as agricultural fields, compost, fruits and recreational water[31–35]. It is however still unclear whether *C. parapsilosis* is merely leaking into the environment passively from animals, waste or human activities, or if it actively evolves and persists independently from human/animal presence. Notably, *C. parapsilosis* has been frequently isolated from environmental and water samples within hospital settings[36]. As an example, 42% of environmental samplings taken from an intensive care unit in Italy grew *C. parapsilosis*[37]. Like *C. auris*, *C. parapsilosis* has a remarkable ability to survive for several days to weeks under harsh conditions, such as dry surfaces and nutrient limitation[38,39]; this species is even frequently isolated from laundry machines[40]. In addition, quaternary ammonium disinfectants are poorly effective in killing *C. parapsilosis*, as is the case for other *Candida* species[41,42]. Moreover, many strains of *C. parapsilosis* are robust biofilm producers, a trait that enhances their ability to colonize and persist on medical devices[43].

C. parapsilosis response to stressful stimuli has been investigated in several studies: this species has demonstrated tolerance to high concentrations of potassium chloride (KCl), sodium chloride (NaCl), and lithium chloride (LiCl), as well as the ability to grow across a wide range of pH levels[39,44,45]. Compared to the other common opportunistic yeast species, it shows greater tolerance to oxidative stress induced by hydrogen peroxide and cell wall stress induced by calcofluor white[45]. However, it is less thermotolerant than other species, although some isolates may grow at temperatures as high as 47 °C[45]. A large gene disruption library recently revealed a unique regulation of sulphur metabolism in this species, which may be involved in scavenging essential sulphur from its environment[46].

Overall, *C. parapsilosis* ability to persist in harsh environments suggests that contaminated surfaces/devices may act as reservoirs in healthcare settings, thus contributing to its propensity to spread and cause outbreaks.

In the last years, acquired antifungal resistance has been emerging dramatically

C. parapsilosis intrinsically shows diminished susceptibility to echinocandins as a consequence of the naturally occurring P660A amino acid substitution in the hot spot region 1 (HS1) of the *FKS1* gene[47]. Nonetheless, this species has historically been reported as mostly susceptible to azoles[48,49]. Unfortunately, the landscape is evolving as *C. parapsilosis* isolates showing echinocandin resistance, azole resistance, or both, are looming in many parts of the globe since the turn of the XXI century. To date, true echinocandin resistance is still anecdotic, but has been reported in Greece, Iran, and China[50–52]. Some isolates may show echinocandin tolerance rather than true resistance, but the clinical impact of this observation is still unknown[53].

On the contrary, the sharp increase in the number of azole-resistant isolates has been a matter of concern in hospitals located in a growing number of countries during the last 10 years[15]. A study by Pfaller et al. based on data collected under the radar of the SENTRY Program in 2019 reported an overall fluconazole resistance rate of up to 4.6% in Europe — the region where the highest rates were observed[54]. However, rates of azole resistance are quite variable from one centre to another; whereas many hospitals remain unaffected, other ones report extremely high rates of azole resistance, as reported in Spain, South Africa, Greece, and Italy[49,55–59]. Of note, high resistance rates should be interpreted with caution, as they may reflect extensive horizontal transfer of resistant strains between patients rather than increased selection of resistant strains. Notably, whereas a study on candidemia conducted in 29 Spanish hospitals in 2010 and 2011 reported fluconazole resistance in up to 3% of *C. parapsilosis* isolates[48], two recent studies conducted in Madrid between 2019 and 2022 revealed that some hospitals experienced a rising number of fluconazole-resistant *C. parapsilosis* isolates throughout the study period, while other hospitals in the same city did not report the presence of such isolates[49,58]. If the centre-to-centre variation requires performing antifungal susceptibility testing in clinical isolates to obtain a close monitoring of the local epidemiology, national data are also needed to establish a framework of the situation on a wider level. A prospective study on antifungal resistance in isolates causing fungemia among patients admitted to 85 hospitals located across Spain is currently ongoing in 2025. Data from this study will be useful to monitor epidemiological changes in the country in the last 15 years. Recently, a US reference laboratory reported an increase in fluconazole resistance in *C. parapsilosis*, rising from 8.2% in 2015 to 20.3% in 2024[60]. Altogether, fluconazole-resistant *C. parapsilosis* is an increasing problem that can affect hospitals in a disparate manner, even in hospitals settled in the same city, highlighting the need for prospective surveillance programs. It is worth noting that a recent multicentre retrospective study from Italy identified fluconazole resistance as a risk factor for recurrent candidemia within one year[18].

Molecular mechanisms of antifungal resistance in *C. parapsilosis* are highly diverse

The publication of the draft genome of the *C. parapsilosis* CDC 317 strain in 2009 was a significant milestone in the study of this major human fungal pathogen, which among other impacts, facilitated research into the molecular mechanisms underlying antifungal resistance[61]. This genome assembly is regularly updated and accessible via the *Candida* Genome Database[62]. Last year, the first chromosome-level genome assembly of *C. parapsilosis* was published[63]. *C. parapsilosis* has a diploid genome of 13 Mbp, containing ~5800 genes, spread across eight chromosomes. Compared to other *Candida* species, its genome exhibits an exceptionally low level of heterozygosity, with only one heterozygous single nucleotide polymorphism (SNP) per 15,553 bases[44,61].

Molecular studies of clinical isolates exhibiting acquired antifungal resistance, particularly to azoles, have uncovered a broad array of mechanisms that enable *C. parapsilosis* to evade antifungal treatments[15]. Specifically, mutations leading to amino acid substitutions in the *ERG11* gene, which encodes lanosterol demethylase—the target enzyme for azole drugs—have been documented in several studies[55,56,64–82]. To date, about 20 distinct Erg11 amino acid substitutions have been identified in clinical isolates. Importantly, the advent of genome manipulation, and more recently the introduction of CRISPR-Cas9, have streamlined dissecting the potential contribution of these variants to azole resistance[67,83,84]. A map of the

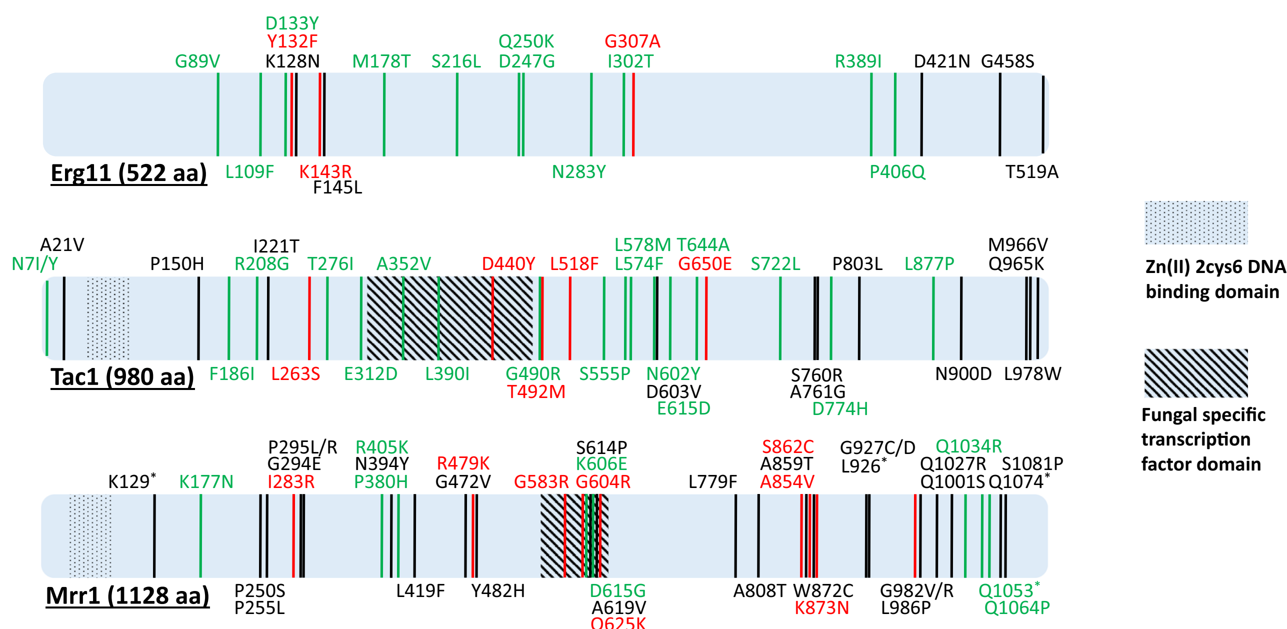

Fig. 1 | Mapping of amino acid substitutions reported in Erg11 (top panel), Tac1 (middle panel) and Mrr1 (bottom panel), respectively, and their possible contribution to fluconazole resistance. Amino acid changes associated with fluconazole resistance by functional validation are highlighted in red. Substitutions only reported in fluconazole resistant/susceptible dose-dependent isolates are depicted in black; note that these do not necessarily confer fluconazole resistance, as the resistant phenotype may be due to their combination with other mutations/other mechanisms completely. Substitutions either identified in fluconazole-susceptible strains or not associated with resistance according to functional validation are depicted in green. *Mutation leading to a frameshift/stop codon. Note: although Erg11^{G458S} direct impact on resistance was not experimentally validated, this amino acid change has already been associated with fluconazole resistance in *C. orthopsilosis*[140] and is related to G464S in *C. albicans*, which is also known to confer fluconazole resistance[141].

ERG11 variants described so far, along with their documented impact on fluconazole susceptibility is provided in Fig. 1. The effect of an amino acid substitution on susceptibility to fluconazole depends on its location within the enzyme 3D structure, allelic dosage (heterozygous or homozygous), and the genetic background of the clinical isolates[84]. For example, while the R398I mutation is a neutral polymorphism (i.e. no impact on azole resistance), the Y132F mutation—the most commonly reported worldwide and also present in the type strain CDC317—primarily affects short-tailed azoles (fluconazole and voriconazole), long-tailed azoles (posaconazole) being mostly unaffected[84]. Other mechanisms include the upregulation of *ERG11* and active efflux resulting from the overexpression of membrane transporters belonging to the ATP-binding cassette (Cdr1) or Major Facilitator (Mdr1) super families. Both are driven by gain-of-function mutations which produce hyperactive alleles in genes encoding transcription factors, namely *UPC2*, *MRR1*, and *TAC1*[83,85,86]. The presence of both *ERG11* mutations and hyperactive transcription factors is likely to contribute synergistically to resistance. Although Tac1, Mrr1 and Upc2 orchestrate the regulation of *CDR1*, *MDR1* and *ERG11*, respectively, in *C. albicans*, Mrr1 has been shown to regulate *MDR1*, *MDR1B* (*CPAR2_603010*) but also *CDR1B* (*CPAR2_304370*) in *C. parapsilosis*[87]. Doorley et al., further demonstrated that Tac1 in *C. parapsilosis* directly modulates fluconazole susceptibility by interacting with multiple *CDR* transporter genes, namely *CDR1* (*CPAR2_405290*), *CDR1B* (*CPAR2_307370*) and *CDR1C* (*CPAR2_300010*)[83]. Multiple amino acid variants have been reported from clinical isolates in Tac1[20,53,65,68,71,77,83,88,89] and Mrr1[20,56,64,65,68,74,76,79,86–91] (Fig. 1). Yet, only a few of them have been demonstrated to result in hyperactive alleles, thereby contributing to azole resistance. One of these is G583R in Mrr1, which also reduces the susceptibility of *C. parapsilosis* to flucytosine[84]. A similar cross-resistance pattern has been reported in *C. lusitaniae*, and related to *MDR1* upregulation[92,93]. Compared to Tac1 and Mrr1, fewer than 20 variants have been reported in Upc2, and none have been shown to alter fluconazole susceptibility[68,71,88,94]. However, the current picture of amino acid variants occurring in these transcription factors is possibly incomplete as most studies focus only on Erg11 amino acid polymorphism.

A few isolates harbouring mutations (D14Y, G111R and R135I) that impair C-5 sterol desaturase activity - encoded by the *ERG3* gene - have also been reported[85,95,96]. Although exposure to azoles in wild-type Erg3 yeasts results in the accumulation of toxic sterol intermediates, when Erg3 is non-functional due to missense mutations, these intermediates are no longer converted into the toxic products, thereby reducing cellular toxicity and allowing yeast cells to persist even in the presence of azole drugs. In addition, as a consequence of Erg3 impairment, these mutants also display an altered membrane sterol profile characterized by a marked decrease in ergosterol and the accumulation of intermediate sterols (mainly ergosta-7,22-dienol), leading to a reduced susceptibility to amphotericin B. Surprisingly, this uncommon phenotype is also associated with increased tolerance to echinocandins in *C. parapsilosis*[84,95].

Few clinical isolates showing evidence for acquired echinocandin resistance have been reported so far, and all had *FKS1* mutations[50–52]. Although still uncommon, the simultaneous emergence of echinocandin and fluconazole resistance poses the risk of multidrug resistance, as already observed in Turkey[50]. Interestingly, in vitro evolution experiments exposing *C. parapsilosis* isolates to micafungin have unveiled additional substitutions in HS1 (amino acid 652–660) and HS2 (1369–1376)[97,98]. Substitutions located outside these hotspots were also reported in clinical isolates, although they do not seem to confer resistance[53,99,100]. Instead, they have been associated with echinocandin tolerance (which can facilitate the acquisition of resistance) and enhanced growth, while reducing fitness costs in response to oxidative stress[99]. Table 1 lists all Fks1 amino acid substitutions described to date.

Table 1 | Amino acid substitutions described in *Candida parapsilosis* Fks1 and their possible contribution to echinocandin resistance

AA variant	References	In vitro susceptibility profile	Note
V595I	99,100	S	Clinical isolates. Higher tolerance to micafungin, and propensity to develop echinocandin resistance
F652S	52	R	Clinical isolate
S656P	51,98	R	Clinical isolate and in vitro evolution experiments. Confirmed to be involved in echinocandin resistance by CRISPR genome editing.
R658G	50,142	SDD/R	Clinical isolates. Confirmed to be involved in echinocandin resistance by CRISPR genome editing.
R658S	97	R	In vitro evolution experiments
L703F	98	R	In vitro evolution experiments
S745L	99,100	S	Clinical isolates. Higher tolerance to micafungin, and propensity to develop echinocandin resistance
M1328I	99,100	S	Clinical isolates. Higher tolerance to micafungin, and propensity to develop echinocandin resistance
W1370R	98	R	In vitro evolution experiments
L1376F	97	R	In vitro evolution experiments
F1386S	99,100	S	Clinical isolates. Higher tolerance to micafungin, and propensity to develop echinocandin resistance
E1393G	53	S	Clinical isolates. Higher tolerance to micafungin
A1422G	99,100	S	Clinical isolates. Higher tolerance to micafungin, and propensity to develop echinocandin resistance

Substitutions observed in HS1 (aa 652–660) and in HS2 (aa 1369–1376) are highlighted in bold.
S susceptible, *R* Resistant, *SDD* susceptible dose-dependent.

In light of the increase of azole resistance, new antifungal drugs with original modes of action are now more than even required. Among them, fosmanogepix (formerly APX001)—the prodrug of manogepix—is currently in phase III clinical trials[101]. This new antifungal targets Gwt1, a fungal glycosylphosphatidylinositol acyltransferase. With the exception of *Pichia kudriavzevii*, manogepix displays strong activity against various yeasts, including *C. parapsilosis*[102]. Although resistance to this new drug is still underexplored, in vitro evolution experiments of *C. albicans*, *N. glabratus* and *C. parapsilosis* isolates have led to the selection of resistant isolates showing a 4–32 fold increase in manogepix MIC[103]. Sequencing of the resistant isolates identified point mutations in the *GWT1* gene (leading to amino acid substitutions V162A and V163A in *C. albicans* and *N. glabratus*, respectively), although not in *C. parapsilosis*, suggesting the existence of both *GWT1*-dependent and -independent mechanisms of manogepix resistance. In 2020, Arendrup et al., demonstrated a correlation between manogepix and fluconazole MICs and suggested a possible role for efflux pumps[104]. Recently, it was demonstrated that G650E, a gain-of-function mutation in Tac1 conferring fluconazole resistance, also reduces the susceptibility of *C. parapsilosis* to manogepix through both CDR-dependent and independent mechanisms[105].

When addressing antifungal resistance, genomic plasticity—an important trait in fungal pathogens—should be considered, as it enables fungal cells to adapt rapidly and withstand stressful conditions. As in other yeast species, aneuploidy has also been reported in *C. parapsilosis*[106]. As an example, chromosome 5 trisomy has recently been shown to facilitate in vitro adaptation to caspofungin—likely due to *CHS7* gene amplification —and cross tolerance to flucytosine[107]. Genomic plasticity can also translate into segmental aneuploidy or shorter-range amplifications, triggering copy number variations (CNV). CNVs have recently been reported for both *ERG11* and *CDR1B*, and may explain azole resistance in some clinical isolates[79,108].

Finally, heteroresistance, which has been elegantly demonstrated in *C. parapsilosis*, could explain breakthrough infections in haematology patients receiving echinocandin prophylaxis[109]. Heteroresistance refers to a phenomenon in which a small subpopulation of cells—typically around 1 in 10,000—displays resistance to a given antifungal agent, while the majority of the population remains susceptible. Notably, these resistant cells can proliferate under antifungal pressure, but the phenotype is reversible upon removal of the selective agent. Yet, although documented in other opportunistic yeasts, heteroresistance to azoles has not been observed in *C. parapsilosis*[110,111]. Importantly, heteroresistance detection poses a significant challenge for clinical laboratories, as standard antifungal susceptibility tests often fail to identify it. Instead, it requires a dedicated approach such as population analysis profiling[112].

Overall, the emergence and selection of allelic variants in *C. parapsilosis*, combined with its genome plasticity, allow this species to cope with antifungal drugs.

Azole-resistant *C. parapsilosis* can cause clonal outbreaks in clinical settings

Resistant isolates have been detected as part of the colonising microbiota of patients and in the surrounding environment where the patients are hosted[55]. In the presence of the specific risk factors described above, the isolates can then cause endogenous infections or spread to other patients via patient-to-patient transmission or environment-to-patient transmission. Genotyping of isolates is therefore crucial for understanding the molecular epidemiology of circulating clones. This approach provides better insight into the dynamics of their spread between patients, which may explain the unexpectedly high rates of fluconazole resistance observed at some centres. This route of infection acquisition is now well supported by reports of clonal outbreaks involving *C. parapsilosis* isolates harbouring the Y132F substitution, which is by far the most common Erg11 substitution in fluconazole-resistant isolates[15]. For yet unknown reasons, isolates harbouring this substitution seems more prone to cause clonal local outbreaks and potentially become widespread among many hospitals worldwide[20,21,68,69,71,75,113]. The presence of Y132F isolates was first reported in 2004 in a Turkish hospital[74]. Since then, they have been detected in a growing number of countries. Table 2 summarizes studies reporting outbreaks of invasive candidiasis caused by *C. parapsilosis* isolates harbouring the Y132F substitution over the last 20 years. Most outbreaks have revealed the presence of one dominating genotype, often accompanied by additional, less frequent genotypes that are genetically closely related. Some studies reported the presence of identical genotypes in different hospitals[114], sometimes located at different cities[115], which outlines the capacity of isolates harbouring the Y132F substitution to spread. The fact that the vast majority of patients infected by fluconazole-resistant isolates had not received any azole by the time they became infected strongly points towards the patient-to-patient transmission as the main driver of these outbreaks[116]. There are yet only a few studies comparing the genetic relationship between azole-resistant isolates collected from different countries. A recent

Table 2 | Infections outbreaks caused by *Candida parapsilosis* harbouring the Y132F substitution reported over the last 20 years

References	Outbreak description	Other comments
74	No genotyping analysis	First report of the Y132F substitution in Turkey (isolates from 2004)
68	Isolates belonging to two genotypes, each one affecting a different hospital	First report of the Y132F substitution in South Korea (isolates from 2006)
64	Clonal outbreaks in different hospitals Isolates mostly from Atlanta hospitals	First report of the Y132F substitution in the United States of America (isolates from 2008) Patients in a given hospital affected by different clones; conversely, a given clone found in different hospitals
143	Isolates collected in hospitals from Atlanta's area in 2021 Increasing number of resistant isolates One clade (whole genome sequencing) included resistant isolates and spread across hospitals	Genotypes identical to those previously found in 2019 and 2020
56	Four clonally related genotypes involving fluconazole-susceptible isolates, and fluconazole-resistant isolates harbouring either the Y132F substitution or other substitutions	First report of the Y132F substitution in South Africa (isolates from 2009)
80	No genotyping analysis	First report of the Y132F substitution in Kuwait (isolates from 2012)
66	Clonal spread across an intensive care unit of a hospital in Brazil	First report of the Y132F substitution in Brazil (isolates from 2013)
72	Clonal spread across an intensive care unit of a hospital in Brazil	The first clonal fluconazole-resistant isolate appeared in June 2013. Additional eight patients at the same unit harboured fluconazole-resistant isolates afterwards
55	Oncology ICU in a Brazilian hospital Four genotypes involving resistant isolates	One large cluster involving isolates harbouring the Y132F substitution which consisted of both clinical isolates, and for the first time reported, environmental isolates
144	Clonal spread of Brazilian genotypes across a cardiology referral centre; genotypes previously reported in the hospital	Genotypes transferred during the COVID-19 pandemic to an oncology adjacent hospital which had been unaffected
70	Increasing number of non-susceptible isolates Several clones in a single hospital, but one clone was dominating Multiple wards affected	First report of the Y132F substitution in Italy (isolates from 2014)
75	Increasing number of non-susceptible isolates All but one isolate were included into two clonally related genotypes; some wards affected, mostly the ICU	First report of the Y132F substitution in Mexico (isolates from 2014)
20	Isolates sent to a referral centre in Germany Clonal outbreaks detected at some hospitals and patients transfers may explain the presence of identical clones at different hospitals in Berlin	First report of the Y132F substitution in Germany (isolates from 2014) Isolates from Canada were genetically related to the ones from Germany
67	Two large clusters, clonally related, and found at 11 hospitals scattered all over India	First report of the Y132F substitution in India (isolates from 2015) Five additional clusters involving only 2–3 isolates each and randomly distributed in seven hospitals
71	20 hospitals with isolates harbouring the Y132F substitution, some clones were endemic clusters and were even present in different hospitals	First report of the Y132F substitution in China (isolates from 2012–2017)
69	Isolates from the SENTRY program (2016–2017) and no genotyping analysis	First report of the Y132F substitution in France (isolates from 2017), before the description of the first clonal outbreak in this country[113] First report of a fluconazole-susceptible isolate harbouring the Y132F substitution Isolates harbouring the Y132F were particularly frequent in Italy
145	No genotyping analysis	First report of the Y132F substitution in Colombia (isolates from 2016–2020)
146	No genotyping analysis	First report of the Y132F substitution in Pakistan (isolates from 2018–2020)
136	Clonal outbreak	First report of the Y132F substitution in Lebanon (isolates from 2016–2018)
116	Clonal outbreak, many wards affected One dominating genotype and some others clonally related	First report of the Y132F substitution in Spain (isolates from 2019)
127	No genotyping analysis	First report of the Y132F substitution in Greece (isolates from 2019) and Israel (isolates from 2020)
147	Clonal outbreak in the neonatology unit affecting three neonates	First report of the Y132F substitution in the UK (isolates from 2024)

Studies were chosen based on reporting the Y132F substitution in a country for the first time or reporting relevant epidemiological data concerning the outbreak.

regional study conducted in Spain showed that the genotypes found were city-specific, except for some genotypes found simultaneously at relatively close cities, which may suggest transmission across hospitals after patient transfers[115]. Another study recently demonstrated that a 2018–22 outbreak that occurred at multiple hospitals in Berlin, Germany, was caused by isolates that were closely related to those responsible for outbreaks in Turkey, Kuwait and South Korea[20]. The fact that unrelated genotypes (or lineages) harbouring the Y132F substitution have been emerging at different geographic areas for the last 20 years is an enigma[20,115].

Fast detection of fluconazole-resistant *C. parapsilosis* isolates

The emergence of fluconazole-resistant strains represents both a therapeutic and epidemiological challenge. Empirical treatment may be ineffective in such cases, potentially delaying appropriate antifungal therapy and thereby increasing patient mortality. Traditional antifungal susceptibility testing methods, such as broth microdilution (CLSI or EUCAST), although accurate, require 24–48 h after fungal growth is achieved. This slow turnaround time compromises early antifungal decision-making. Therefore, the availability of rapid detection tools would be a game-changer allowing antifungal

treatment to be adjusted in hours rather than days, improving clinical outcomes and facilitating the control of nosocomial outbreaks.

Among phenotypic approaches, direct gradient strips directly performed on positive blood cultures may speed antifungal susceptibility results[117]. While this method has proven useful for fast detection of antifungal resistance in *N. glabratus* and *C. albicans*[118,119], it has not yet been validated for fluconazole-resistant *C. parapsilosis*. Fluconazole-supplemented agar plates are a low-cost alternative used as screening tool for identifying colonizing or invasive resistant strains, including *C. auris*[120,121]. This approach has been shown to be effective in detecting fluconazole-resistant *C. parapsilosis* strains during hospital outbreaks[122]. The MALDI-TOF MS platform, now commonly used for yeast identification in clinical labs, has expanded toward antifungal susceptibility testing. New methods such as Composite Correlation Index (CCI) and MBT ASTRA (Antifungal Susceptibility Test Rapid Assay) combine mass spectrometry with fungal growth assessment in the presence of antifungals[123–125]. These systems provide results in 3–8 h, with high concordance compared to reference standard methods (CLSI/EUCAST), enabling phenotypic classification of susceptible or resistant isolates without extended incubation. One study showed that MALDI-TOF MS could detect echinocandin resistance in the *C. parapsilosis* complex after just 3 h of incubation, with 95% concordance with CLSI results (for anidulafungin and other drugs), supporting its potential use for fluconazole resistance detection as long as drug concentrations are optimized[126]. Although most studies have focused on *C. albicans* and *N. glabratus*, their principles are applicable to *C. parapsilosis*.

An alternative approach is molecular testing: point mutations in the *ERG11* gene—particularly leading to the Y132F and G458S substitutions—have enabled the development of PCR-based protocols for rapid detection of resistant strains, either directly from fungal DNA or from cultured isolates[80,127–129]. A recent study developed conventional and real-time PCR assays to detect the Y132F substitution in pure cultures, skipping DNA extraction[130]. Both approaches showed 100% sensitivity and specificity; the conventional PCR delivered results in ~3 h, while real-time PCR required only 1.5 h[130]. A rapid method based on real-time PCR and high-resolution melting curve analysis (HRM) was developed to simultaneously detect SNPs in *ERG11* leading to both Y132F and G458S substitutions[131]. This approach differentiated between homozygous and heterozygous strains, showing high specificity, and optimal sensitivity at a threshold of $\sim 5 \times 10^5$ cells per reaction. However, strict PCR conditions are required to avoid false positives.

The fast and accurate detection of resistant clones is key for outbreak control. Combining mutation-targeted PCRs with genotyping methods will enable early detection of transmissible resistant clones, particularly in healthcare settings. Since 2019, nosocomial outbreaks of fluconazole-resistant *C. parapsilosis* have been increasingly reported[15]. These outbreaks were tagged by using molecular typing techniques such as microsatellite markers[130], multilocus sequence typing (MLST), or whole genome sequencing (WGS)[20]. As an alternative to PCR-based genotyping methods, MALDI-TOF combined with deep learning[132] and Fourier-transform infrared spectroscopy (FTIR) using systems like IR Biotyper® has shown promising results for outbreak tracking. While it does not directly detect resistance, FTIR can generate biochemical fingerprints that distinguish clonally related resistant strains. For example, two recent studies demonstrated that FTIR correctly clustered fluconazole-resistant *C. parapsilosis* strains harbouring the Y132F substitution, with 74% concordance compared to microsatellite genotyping[133,134]. Both genotyping and FTIR allow the detection of clonal patterns of transmission and guide infection control measurement; these can be useful tools in epidemiological surveillance and hospital outbreak control. Rapid detection and molecular surveillance should be integral elements of outbreak handling in hospital settings. This multidimensional approach not only improves early therapeutic decisions but also strengthens infection prevention and control strategies in healthcare institutions.

While targeted PCR and accurate detection of *ERG11* gene mutations provide mutation-based prediction of fluconazole resistance in a matter of hours, they do not replace phenotypic antifungal susceptibility testing. However, they are highly valuable in epidemiological surveillance and in settings where prevalent mutations are known. Notably, current PCR methods are still limited to the detection of a few mutations leading to amino acid changes (e.g., Y132F, G458S). In the future, commercial multiplex PCR panels (e.g., FilmArray BCID, T2Candida) should incorporate resistance markers detection, although current platforms primarily focus on species identification rather than antifungal resistance. Since all these methods have limitations (Table 3), future research should focus on specific validations on the fluconazole resistance detection in *C. parapsilosis*, improving standardisation, expanding the mutations detectable by PCR, and demonstrating their direct impact on drug susceptibility and clinical outcomes.

Unanswered questions

Despite significant advances, several critical questions about *C. parapsilosis* remain unanswered, limiting our understanding of its epidemiology, transmission dynamics, and resistance mechanisms. As discussed above, *C. parapsilosis* is commonly associated with nosocomial (hospital-acquired) infections, but the exact transmission dynamics remain unclear although efficient tools are now available (whole-genome sequencing, microsatellite genotyping) for detailed molecular epidemiological investigations, enabling the identification of clonal clusters, distinguishing epidemiologically related strains, and tracing possible routes of transmission such as patient-to-patient spread mediated by healthcare workers' hands or contaminated hospital environments. What are the underlying factors driving the rapid and aggressive emergence of antifungal resistance in this species? Why are there such differences in the prevalence of fluconazole resistance between hospitals? Is person-to-person transmission more common than initially believed, and what role do environmental reservoirs and hospital equipment play in sustaining outbreaks? Although one explanation for the rapid increase and spread of fluconazole-resistant strains may be related to high fluconazole exposure and poor hand hygiene, the absence (or low) fitness costs of *ERG11* substitutions, also supported by recent findings in *C. albicans*, may play a role[84,135]. Interestingly, biofilm production, which might account for the persistence of these strains, could facilitate their persistence in the environment and potentially their spread. However, there are some contradictory results on whether azole-resistant isolates produce less or more biofilm[76,136]. More research is needed to determine whether azole-resistant strains involved in clinical outbreaks may exhibit increased resistance to disinfection protocols.

What should we do now? Roadmap for the future

The emergence of azole-resistant *C. parapsilosis* capable of spreading and causing hospital outbreaks is a major concern that requires action to prevent this phenomenon from following the same trajectory as *C. auris*[137]. When isolation in pure culture confirms *C. parapsilosis* as cause of invasive infections, antifungal susceptibility testing should be prioritized (along with molecular genotyping when an outbreak is suspected). In fact, the results can not only inform clinical decisions regarding treatment options, but also facilitate the early detection of resistant isolates with the potential to cause uncontrolled outbreaks, thereby helping to prevent patients from acquiring new infections. Nipping a potential outbreak in the bud also translates to better outcomes for patients and less need to use more expensive drugs alternative to fluconazole. In this scenario, detecting antifungal resistance through phenotypic testing and simultaneously scan the mechanism of resistance would be the most helpful.

An ideal diagnostic workflow would combine multiple methods including rapid identification of *C. parapsilosis* by MALDI-TOF, simultaneous PCR targeting mutations known to be associated with resistance, rapid antifungal susceptibility testing (AFST) using MALDI-TOF with MBT ASTRA or CCI-performed alongside regular AFST to phenotypically assess antifungal resistance- and DNA-based molecular genotyping—or FTIR—to assess the relatedness between isolates and rule out potential nosocomial outbreaks. This integrated approach would optimize turnaround time and provide valuable epidemiological insights, thereby reducing therapeutic errors, limiting hospital transmission, and strengthening prevention strategies. Further research should include validation of existing

Table 3 | Main characteristics of previously published techniques for the rapid detection of fluconazole resistance in *Candida parapsilosis*

Reference	Method	Principle	Strengths	Limitations	Turnaround
131	Real-time PCR + HRM	Detection of the Y132F and G458S ERG11p substitutions by HRM analysis	It does not require DNA extraction; simultaneous detection of two substitutions; cheap	Other substitutions (such as K143R) are not detected Strict PCR conditions	Not stated
133	FTIR + STR	Fourier transform infrared Spectroscopy – and short tandem repeat	Fast, it allows clonal fingerprinting, useful for epidemiological surveillance	FTIR requires validation Some STR markers may show low genotypical discrimination	<24 h
130	Conventional and real-time PCR	Y132F substitution detection by means of targeted PCR	High sensitivity and specificity, fast, useful for epidemiological surveillance Note: this publication also included a genotyping scheme relying on four markers	Other substitutions (such as K143R) are not detected Strains having Y132F in a single allele (i.e. heterozygous) cannot be detected	1.5–3 h
127	Conventional PCR	Y132F substitution detection by means of two targeted PCR (mutant vs wild-type)	Fast and specific for Y132F Useful for epidemiological surveillance	Other substitutions (such as K143R) are not detected Requires DNA extraction	Not stated
129	T-ARMS-PCR	Y132F substitution detection by means of targeted PCR	Fast and specific for Y132F	Other substitutions (such as K143R) are not detected Probably requires DNA extraction	Not available
128	Conventional PCR	Y132F substitution detection by means of targeted PCR	Fast and specific for Y132F	Other substitutions (such as K143R) are not detected Requires DNA extraction	3 h
99	Conventional PCR	Y132F substitution detection by means of a multiplex PCR	Fast detection of Y132F	Risk of false-positive reactions	Not available

methods specifically for fluconazole resistance detection in *C. parapsilosis*, expansion of the mutation coverage of PCR-based tools, the standardization of protocols across laboratories, and the demonstration of the impact of rapid resistance detection on patient outcomes. Lastly, the wider adoption of WGS in clinical laboratories—enabled by decreasing costs and the availability of robust, standardized pipelines—will enhance our understanding of its resistome, facilitate the detection of acquired resistance, and strengthen epidemiological surveillance of resistant *C. parapsilosis* clones.

Overall, establishing consensual guidelines for the management of *C. parapsilosis* in hospital settings—including environmental cleaning and disinfection procedures—would be highly valuable. Existing guidelines for *C. auris* infection control, such as those issued by the CDC[138] and the UK[139], provide a useful reference, as both opportunistic yeasts share important features, notably their ability to spread between humans and persist in the environment[137].

Finally, the concerning spread of *C. parapsilosis* resistant clones poses a difficult challenge that only a holistic approach combining phenotypic, molecular, and epidemiological tools can win, by improving early therapeutic decisions and strengthening hospital infection control strategies.

Data availability

No datasets were generated or analysed during the current study.

Received: 4 September 2025; Accepted: 23 November 2025;
Published online: 16 December 2025

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Acknowledgements
J.G. has received funds for participating in educational activities organized on behalf of Gilead, Pfizer, and Mundipharma; he has also received research funds from FIS, Gilead, F2G, Shionogi, Scynexis, Mundipharma, outside the submitted work. F.M. has received funds for participating in educational activities organized on behalf of Gilead, and Mundipharma; he has also received research funds from Pfizer, Gilead, Mundipharma, Agence Nationale de la Recherche and CAPES-COFECUB, outside the submitted work. F.M. acknowledges funding from Mundipharma to investigate antifungal resistance in yeasts.

Author contributions
J.G., P.E., and F.M. conceived and designed the manuscript. All authors (J.G., P.E., M.C., L.L. and F.M.) participated in writing, critically reviewed the content, have read and approved the final version of the manuscript.

Competing interests
The authors declare no competing interests.

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