Candida auris

An emerging drug-resistant pathogen of global concern

By Dr Jacqueline Gosink

Candida auris (*C. auris*) is a globally emerging multidrug-resistant fungal pathogen, which spreads easily in health-care facilities and causes high mortality in vulnerable patients. Of the laboratory methods that can be used for *C. auris* identification, real-time PCR offers the fastest turnaround time as well as high sensitivity and specificity. In a multiplex procedure, mutations associated with echinocandin resistance can be detected at the same time.

Emerging pathogen

Yeasts of the genus *Candida* are a major cause of morbidity and mortality in critically ill patients. *Candida auris* (*C. auris*) is an emerging species which was first reported in Japan in 2009 and now presents a serious global health threat due to its rapid spread and increasing drug resistance [1,2]. Isolates have been identified across six continents as agents of hospital-acquired infections. In Europe, rising numbers of cases and outbreaks have been reported in at least 15 countries up to 2021 [3,4]. In the USA, the total number of clinical cases and the number of states affected have increased every year [5]. *C. auris* is now classified as an urgent threat by the US Centers for Disease Control and Prevention and is ranked in the highest prioritization category by the World Health Organization (WHO) [3,6].

High mortality

C. auris can cause invasive infections of the bloodstream, heart, central nervous system, eyes, bones and internal organs which can be life-threatening in critically ill patients, such as cancer patients and bone marrow or organ transplant recipients. Further risk factors for severe *C. auris* infection include renal impairment, mechanical ventilation, central venous catheterization, total parenteral nutrition and sepsis. Previous use of antifungal medicines is also associated with an increased risk for *C. auris.* Notably, candidemia caused by *C. auris* leads to longer lengths of stay in hospitals or intensive care units than candidemia caused by other *Candida* species. The overall mortality of invasive candidiasis with *C. auris* ranges from 29 to 53% according to the WHO [6]. There is no vaccine available for *C. auris.*

Rapid spread

C. auris can be spread by both colonized and infected patients. Colonized persons are those who carry the fungus on their skin or other body sites such as respiratory tract, urinary tract or genital apparatus, but do not exhibit symptoms. Further, *C. auris* spreads easily in health-care facilities via contamination of objects or equipment. It is resistant to heat and disinfectants commonly used in hospitals and can survive on surfaces for weeks.

As invasive infections can be difficult to prevent, prevention of colonization and heightened surveillance are of key importance. Early recognition of *C. auris* cases followed by rapid implementation of control measures can help to prevent interfacility and interregional spread and thus reduce future health-care-associated outbreaks [1,4,6].

Drug resistance

Many strains of *C. auris* are now resistant to one or more antifungal drugs. *C. auris* isolates show high resistance rates to fluconazole (87 to 100%), moderate resistance rates to amphotericin B (8 to 35%), and a lower resistance to echinocandins (ECH; 0 to 8%) [6].

ECH are a class of antifungal drugs that work by inhibiting the fungal 1,3-beta-glucan synthase, *FKS1*, which synthesizes 1,3-beta-glucan – a major structural component of the fungal cell wall. As ECH can treat most infections, these drugs are recommended as the first-line treatment for invasive *C. auris* infection. Notably, in 2021 ECH were included in the WHO Essential Medicines List as a requirement for every health-care system (6). Some *C. auris* strains are nevertheless resistant to ECH. Resistance is conferred by certain mutations in the hot spot 1 (HS1) regions of the *FKS1* gene which result in critical amino acid changes, the most common of which are S639F, S639Y and S639P [2].

C. auris identification

Accurate laboratory identification of *C. auris* is important for identifying reservoirs and implementing appropriate control measures. When using traditional phenotypic methods for yeast identification, *C. auris* may be misidentified as various other microorganisms. Therefore, if certain species such as *C. haemulonii* are initially identified, further work-up is needed to establish if the isolate is *C. auris* [7]. The most commonly used tools for *C. auris* identification are polymerase chain reaction (PCR) and matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS), although whole genome sequencing has also been used. PCR offers the advantage of being a culture-independent technique with a much shorter turnround time than the other mentioned methods, yielding results within a few hours [8].

***Candida auris*, emerging multiple-drug-resistant** (Adobe stock)

Real-time PCR is the fastest method and less labour-intensive and easier to perform at higher throughput than conventional PCR. Multiplex procedures additionally enable detection of mutations associated with drug resistance at the same time.

Real-time PCR assays

A suitable target for PCR-based *C. auris* identification is the internal transcribed spacer (ITS) gene. This provides high specificity and, due to the presence of multiple copies in many strains, also high sensitivity. The multicopy ITS 1 & 2 target is used in two new assays developed for the identification of *C. auris*. The Candida auris Real-Time PCR Reagents* (Revvity, research use only) provides qualitative *C. auris* screening. The EURORealTime C. auris ECH-R* (EUROIMMUN, research use only) provides identification of *C. auris* based on the ITS 1 & 2 genes and additionally detects *FKS1* HS1 mutations coding for S639F/Y/P. These serve as ECH-resistance markers and additionally identify *C. auris*.

The identification can be performed using DNA extracted, for example, from human skin swabs or laboratory cultures, and – for the Candida auris Real-Time PCR Reagents – also from environmental surface swabs. Results are generated in less than 2 hours. A semi-automated extraction procedure provides simple DNA isolation, and the assays are applicable on various real-time PCR thermocyclers.

Analytical evaluation

The analytical performance of the two assays was confirmed by *in silico* analyses and *in vitro* analyses using synthetic DNA plasmid constructs or genomic DNA purified from laboratory culture strains. The oligonucleotides used are highly specific, and no cross reactivity was observed with other *Candida* species or microorganisms that are frequently found in skin infections. The limit of detection for both assays and both ITS and *FKS1* HS1 targets amounted to 30 copies per PCR reaction. Using gDNA extracted from *C. auris* suspensions, detection rates of 100% were obtained at concentrations as low as 600 cfu/ml for ITS and 1800 cfu/ml for *FKS1* HS1. In analyses using the EURORealTime C. auris ECH-R, mutations conferring ECH resistance were reliably identified without any cross reactivity to wild-type strains [9,10].

Summary

Real-time PCR assays enable highly specific and sensitive *C. auris* screening as well as detection of ECH-resistance mutations. Results are obtained in a fraction of the time required for other methods such as culturing or MALDI-TOF MS. The new real-time PCR assays could aid surveillance of incidence, distribution and antifungal resistance of this rapidly emerging pathogen.

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