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COMMENTARY

Thinking beyond the Common *Candida* Species: Need for Species-Level Identification of *Candida* Due to the Emergence of Multidrug-Resistant *Candida auris*

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ABSTRACT *Candida* species are one of the leading causes of nosocomial infections. Because much of the treatment for *Candida* infections is empirical, some institutions do not identify *Candida* to species level. With the worldwide emergence of the multidrug-resistant species *Candida auris*, identification of *Candida* to species level has new clinical relevance. Species should be identified for invasive candidiasis isolates, and species-level identification can be considered for selected noninvasive isolates to improve detection of *C. auris*.

KEYWORDS *Candida*, *Candida auris*, identification

The genus *Candida* encompasses an array of more than 400 asexual yeasts, many of which are only distantly related. A small proportion of *Candida* species cause invasive infection in humans. In the United States, *Candida* species are among the most common organisms causing health care-associated bloodstream infections (BSIs), and all-cause mortality is 20 to 40% (1–3). The species *Candida albicans* causes a substantial portion of invasive infections, but non-*albicans* species have become increasingly common. Non-*albicans* species have been associated with higher mortality and greater antifungal drug resistance than those seen with *C. albicans* infections (4, 5). The distant phylogenetic relationship between some species, even among pathogenic species, helps explain some of their various characteristics, including degree of pathogenicity and antifungal resistance. It is important to know the species of *Candida* causing infection because each species has specific antifungal drug susceptibility patterns that can inform treatment decisions. However, many laboratories in the United States do not automatically perform species identification, even for invasive *Candida* infections, unless specifically requested by a clinician. Invasive *Candida* infections are commonly treated without species confirmation. This practice is similar to treating a Gram-negative bacterial infection without knowing whether the causative bacterium is *Escherichia coli*, *Pseudomonas aeruginosa*, or a rare pathogen.

The Infectious Disease Society of America (IDSA) treatment guidelines on management of invasive candidiasis recommend that antifungal susceptibility testing be performed on all *Candida* isolates from sterile body sites (6). Implicit, but not specified, in this guidance is that *Candida* needs to be identified to the species level because interpretation of MICs performed for susceptibility testing depends on the species. For example, an MIC of ≥8 is considered susceptible dose dependent for *Candida glabrata*, but the same MIC is considered resistant for *C. albicans*. Species identification can usually be obtained at least 48 h before susceptibility testing results are available.

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Availability of species-level information earlier can aid in antifungal stewardship efforts and in stepping down therapy appropriately. For instance, ≥98% of all U.S. *C. albicans* isolates have been susceptible to fluconazole for the last few decades (4, 5, 7, 8); patients with invasive *C. albicans* infections can safely be transitioned from echinocandins, the recommended first-line treatment for all invasive *Candida* infections, to fluconazole in most situations once the species is determined. In contrast, ~10 to 12% of isolates of *C. glabrata* are resistant to fluconazole, and resistance can develop with treatment, making echinocandins the treatment of choice for most *C. glabrata* infections until susceptibility testing results are available (4–7). The ability to step down therapy earlier can help prevent unnecessary use of echinocandins, preserve these drugs as options for future treatment, and reduce the cost of therapy.

The recent emergence of *Candida auris* is another compelling reason to identify *Candida* to the species level (9, 10). *C. auris,* first reported in 2009 after being isolated from a patient's external ear canal, is an often multidrug-resistant yeast. *C. auris* can cause invasive infections (e.g., bloodstream and cerebrospinal fluid) and clinical infection or colonization of other sites (e.g., urine or a wound). Unlike most other *Candida* spp., for which the source of infection is thought to be translocation of *Candida* species that live as commensal organisms in the host, *C. auris* appears to be transmitted from infected or colonized individuals in health care settings. Several large outbreaks of *C. auris* in health care settings have been documented (11, 12). To prevent health care-associated transmission, management of *C. auris* requires *C. auris*-specific infection control measures such as a single room, contact precautions, appropriate hand hygiene, and disinfection with an EPA-approved agent with activity against *Clostridium difficile* (https://www.cdc.gov/fungal/diseases/candidiasis/c-auris-infection-control.html). Because contact precautions and other infection control measures are not recommended for most other *Candida* species but are essential for the control of *C. auris,* species identification is becoming increasingly important (9, 11, 13).

Identification of *C. auris* is important not only for infection control but also for treatment. Most isolates are resistant to fluconazole, and amphotericin B resistance is present in ~50% of isolates (14, 15; CDC, unpublished observation). Of particular concern given the use of echinocandins as first-line therapy, echinocandin resistance has been documented in multiple world regions and has developed in patients treated with these drugs. Three *C. auris* isolates from around the world tested at CDC to date were resistant to all three classes of antifungals, making infections with them especially challenging to treat (15). In the case of *C. auris*, identification to the species level does not predict antifungal susceptibility; antifungal susceptibility testing and close follow-up of the patient with repeated cultures are required to determine the effectiveness of treatment and monitor for the occurrence of new resistance. Clinicians should suspect *C. auris* when a patient with an unidentified *Candida* infection fails treatment with antifungals and *Candida* spp. are repeatedly isolated.

The emergence of *C. auris* presents a further diagnostic challenge. While ~70% of the clinical cases identified in the United States have been bloodstream infections, the remaining cases have been identified in other body sites, including wounds, urine, respiratory specimens, bile fluid, and ear canal (13). Furthermore, *C. auris* has been detected in wound and urine cultures from four U.S. patients who had recent hospitalizations in India, Pakistan, South Africa, and Venezuela, all locations with reports of extensive *C. auris* transmission (12, 15–17). *Candida* isolated from these nonsterile body sites may not be routinely identified to the species level in many clinical settings since treatment may not be required. However, because the presence of *C. auris* at any site presents risk for transmission, it is important to know the species of *Candida* in order to implement infection control measures when necessary. Additionally, other *Candida* species with concerning features may emerge, and identifying species is essential to their early detection.

Species-level identification for all *Candida* isolates, including those from noninvasive sites, can be challenging because the volume of isolates from these sites is often severalfold higher than the number of *Candida* organisms isolated from the blood-

stream or other invasive sites. This could overburden laboratories and may lead to treatment of *Candida* in sites where it is not causing infection. However, given the emergence of *C. auris,* species-level identification should be considered even for noninvasive isolates in the following situations:

1. When clinically indicated in the care of a patient.
2. When a case of *C. auris* infection or colonization has been detected in a facility or unit, in order to enhance surveillance for the organism and detect additional patients colonized with *C. auris*. Species-level identification from nonsterile sites can be implemented for a limited time until there is evidence that there is no further *C. auris* transmission.
3. When a patient has had an overnight stay in a health care facility in the previous 6 months in a country with *C. auris* transmission. Over a dozen countries have reported outbreaks of *C. auris* (https://www.cdc.gov/fungal/diseases/candidiasis/candida-auris.html). In the four patients with previous international hospitalizations in whom *C. auris* was detected in a nonbloodstream body site, the organism was identified quickly because of the species-level identification practices at those specific laboratories. Based on early species determination, infection control measures were immediately implemented and there was no evidence of transmission to other patients.

Laboratories should know when to suspect *C. auris*. Because laboratories do not always have the complete clinical picture for the patient, this should be a joint effort between the care team, the laboratory, and often the infection control officer. Laboratories should have the ability to accurately identify *C. auris,* or they should send the isolate to a reference laboratory for further identification if they are not able to identify it in their own laboratory. As described by Mizusawa et al. (18), many commercial yeast identification systems (such as Vitek-2, BD Phoenix, API-20, and MicroScan) used in U.S. hospitals are not capable of identifying *C. auris*. Instead of giving a result of "no identification," these systems misidentify *C. auris* as a different *Candida* species (18). Currently, the only way to accurately identify *C. auris* is through matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) using the "research use-only" databases and DNA sequencing. Laboratories should review CDC guidance (https://www.cdc.gov/fungal/diseases/candidiasis/recommendations.html) on how to identify *C. auris* accurately. Laboratories should also note that CDC has initiated the Antimicrobial Resistance Laboratory Network (ARLN) to assist with the identification and antifungal susceptibility of *Candida* species (https://www.cdc.gov/drugresistance/solutions-initiative/ar-lab-networks.html). The ARLN consists of seven regional laboratories that serve as sentinel surveillance sites for emerging antimicrobial resistance, as seen with *C. auris*. Clinical laboratories should determine how the ARLN or their state public health laboratory might assist them in identifying *C. auris* from suspected isolates.

Identifying *Candida* to the species level is important for multiple reasons. Species-level identification can detect *C. auris* and trigger necessary infection control measures needed to prevent its spread in health care settings. It can also aid in antifungal stewardship efforts by allowing for earlier stepdown of therapy by using species-specific susceptibility patterns when appropriate. Renewed focus on *Candida* species-level identification is needed, and consideration should be given to automatically identifying *Candida* species in specific situations without a clinician order.

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