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Approach to the investigation and management of patients with *Candida auris*, an emerging multidrug-resistant yeast

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Abstract

Candida auris is an emerging, multidrug-resistant yeast that can spread in healthcare settings. It can cause invasive infections with high mortality and is difficult to identify using traditional yeast identification methods. *C. auris* has been reported in over a dozen countries, and as of July 2017, 99 clinical cases have been reported in the United States;. *C. auris* can colonize skin and persist in the healthcare environment, allowing for transmission between patients. Prompt investigation and aggressive interventions, including notification of public health agencies, implementation of contact precautions, thorough environmental cleaning and disinfection, infection control assessments, contact tracing and screening contacts to assess for colonization, and retrospective review of microbiology records and prospective surveillance for cases at laboratories are all needed to limit the spread of *C. auris*. This review summarizes the current recommended approach to manage cases of *C. auris* and control transmission of *C. auris* in healthcare facilities.

Keywords

Candida Drug Resistance; Multiple; Fungal Communicable Diseases; Emerging Infection Control

Background

Candida auris is an emerging, multidrug-resistant yeast that can cause invasive infections, and has been associated with outbreaks in healthcare settings. *C. auris* was first described in 2009 after isolation from external ear discharge from a patient in Japan [1]. Reports of bloodstream infections followed quickly thereafter from South Korea and India, in which persistent infection despite treatment and drug resistance to fluconazole and amphotericin B were described [2–7]. Subsequently, *C. auris* infections have been reported in over a dozen countries [8–13] (Figure). Although attributable mortality is unknown, 30–60% of patients

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with *C. auris* infection have died [8]. In some places, *C. auris* now accounts for an increasing proportion of candidemia cases; an unknown pathogen before 2009, *C. auris* caused 4–8% of candidemia in Indian intensive care units (ICUs) during 2011–2012 and 38% of candidemia in one Kenyan hospital during 2010–2013 [11, 14]. Whole-genome sequencing of *C. auris* isolates has revealed four distinct clades that cluster geographically (South Asia, East Asia, South Africa, and South America) with a high degree of relatedness within clades, suggesting independent emergence with transmission within a geographic area rather than a single emergence and spread [8].

In April 2015, a specialty hospital in the United Kingdom (U.K.) identified a *C. auris* outbreak among patients in a cardiothoracic intensive care unit. [15]. Testing revealed colonization of additional patients and *C. auris* on hospital surfaces and equipment. Control of the outbreak required implementation of aggressive infection control practices, including use of contact precautions and thrice-daily room disinfection with bleach. Although outbreaks of *Candida parapsilosis* have been reported, *Candida* infections are usually thought to result from autoinfection with host flora rather than transmission from external sources [16, 17]. The U.K. outbreak clearly demonstrated that *C. auris* can be transmitted in healthcare settings [18].

In response to global reports and the U.K. hospital outbreak, the Centers for Disease Control and Prevention (CDC) issued a clinical alert to U.S. healthcare facilities about *C. auris* in June 2016 [19]. As of July 14, 2017, 209 patients (99 from clinical cultures, 110 screened contacts) were reported to have *C. auris* infection or colonization [20]. All but one of these cases occurred in 2015 or later, suggesting that this organism has emerged only recently in the U.S. Nearly all cases have occurred within limited geographic areas. Given the recent emergence and geographic concentration of cases, an opportunity exists to control the spread of this organism before it becomes more widespread.

Experience with other multidrug-resistant organisms (MDROs) suggests that an early, aggressive approach to control the organism when newly emerging is more effective and efficient in controlling transmission than responding when more widespread [21,22]. This review summarizes the current recommended approach to managing cases of *C. auris* and control transmission of *C. auris* in healthcare facilities. This effort requires coordination between all involved stakeholders, including healthcare facilities, clinicians, public health practitioners, and industry. Many of the principles for containment of *C. auris* are similar to those for other MDROs.

C. auris identification

The first step in controlling *C. auris* is identification. *C. auris* can be misidentified when using traditional biochemical methods [23]. Depending on the identification method used (e.g., VITEK-2, API-20C, BD-Phoenix, Microscan), *C. auris* should be suspected when an isolate is identified as certain *Candida* species, such as *Candida haemulonii*, *Candida famata*, *Candida sake*, *Candida catenulata,* or *Rhodotorula glutinis*, or if species identification cannot be obtained [23]. Currently, accurate identification for *C. auris* can be performed by Vitek MS and Bruker Biotyper brand MALDI-TOF using research use only databases. Molecular methods based on sequencing of the D1–D2 region of the 28s rDNA or internal transcribed

spacer (ITS) region can also reliably identify *C. auris* [12, 24–26]. Clinicians should be aware of the diagnostic instruments used in their hospital laboratories and their ability to detect *C. auris* [27]. Clinical laboratories can request testing of suspect *C. auris* isolates from their state or regional public health laboratory or CDC. Laboratories should also consider reviewing historical microbiology records for suspect isolates (e.g., *C. haemulonii)* to identify missed cases of *C. auris.*

Antifungal resistance

Antifungal susceptibility testing (AFST) for all clinically-relevant *Candida* isolates is recommended in the 2016 Infectious Diseases Society of America (IDSA) Clinical Practice Guidelines for Candidiasis [18]. Resistance to ≥1 antifungal drugs in an isolate with ambiguous identification should raise the suspicion of *C. auris* and prompt further testing. In one collection of 54 *C. auris* isolates from five countries, 93% were resistant to fluconazole, 35% to amphotericin B, and 7% to echinocandins. In total, 41% were resistant to ≥2 antifungal classes [8]. In the U.S., 86% of the first 35 cases were resistant to fluconazole, 43% to amphotericin B, and 1 (3%) to echinocandins [20]. Although minimum inhibitory concentration (MIC) breakpoints have not been established for *C. auris*, breakpoints are suggested based on those used for closely-related *Candida* species and expert opinion, especially for amphotericin B, for which no breakpoints exist for any *Candida* species [28]. Tentative MIC breakpoints (in μg/mL) for resistance include ≥32 fluconazole, ≥2 amphotericin B, ≥2 caspofungin, and ≥4 for anidulafungin and micafungin.

Treatment of *C. auris* infection

Consultation with an infectious disease specialist is highly recommended. Despite its multidrug resistant nature, most *C. auris* isolates to date have been susceptible to echinocandins. The recommended initial therapy for clinically relevant infections with *C. auris* in adults is an echinocandin at standard dosing. Patients should be monitored closely for resolution of infection given that resistance to echinocandins has been documented and because resistance has emerged on serial isolates from a single patient after exposure to the drug. Switching to, or adding, liposomal amphotericin B (5 mg/kg daily) could be considered if the patient is clinically unresponsive to echinocandin treatment or has fungemia for >5 days. Other management considerations for *C. auris* are similar to *Candida* infections with other species; practitioners should refer to the 2016 IDSA Clinical Practice Guidelines [18].

Controlling *C. auris* Transmission in Healthcare Settings

The presence of a single case in a healthcare facility should prompt an aggressive response and investigation because *C. auris* can cause healthcare-associated outbreaks. Patients can remain colonized on their skin and other body sites indefinitely after resolution of invasive infections, allowing *C. auris* to be shed into the healthcare environment, where it persists on surfaces and can be transmitted to other patients [15, 29]. Containment efforts should focus on identifying patients who are infected or colonized with *C. auris* and implementing infection control interventions, including hand hygiene, contact precautions, and thorough environmental cleaning and disinfection [28].

Response to a case of *C. auris*

As soon as *C. auris* is suspected, the patient should be placed in a single room under contact precautions until definitive identification is available. When *C. auris* is confirmed at a healthcare facility, the following actions should be taken:

Notify—A case of *C. auris* should be reported as soon as possible to the state or local health department and CDC. CDC has established an email address for reporting: candidaauris@cdc.gov.

Institute infection control measures—Standard and contact precautions with placement of the patient in a single room is recommended. Adherence to proper hand hygiene with alcohol-based hand rub or soap and water should be reinforced [30].

C. auris can persist on surfaces in the healthcare settings [31]. Thorough daily and terminal cleaning of the patient's room and any mobile equipment used should be performed with an Environmental Protection Agency (EPA)-registered hospital-grade disinfectant effective against *Clostridium difficile* spores [32]. Preliminary laboratory testing suggests that certain commonly-used hospital disinfectants, notably quaternary ammonia compounds, are not sufficiently effective against *C. auris*.

Perform detailed case review—Basic information about the case-patient, including demographic characteristics and clinical history should be obtained. In the United States, patients with *C. auris* were found to have had on average three healthcare facility encounters in the 90 days preceding their diagnosis; the majority had been admitted to a high acuity LTCF. It is important to obtain records of recent healthcare encounters, including stays at other acute care hospitals and LTCFs in order to assess for possible transmission at the other facilities.

Taking a detailed travel history, especially receipt of healthcare in countries where *C. auris* cases have been reported, is important. Several U.S. case-patients have had a recent history of hospitalization in countries with a large burden of *C. auris,* including India, Pakistan, South Africa, and Venezuela. Based on whole-genome sequencing at CDC, most isolates from U.S. patients are closely related to isolates from South Asia and South America.

Identify colonized patients through contact investigation—Contact investigation should be conducted to identify persons who were exposed to an incident case to detect transmission. As part of a detailed *C. auris* case review, it is important to identify epidemiologically-linked patients for possible screening, as colonized patients pose a risk for transmission. Current or past roommates are considered at high risk for becoming colonized and should be screened even if they are no longer admitted to the facility. Other potential contacts might include patients who overlapped on a ward with a patient with *C. auris* and patients who moved into a room recently vacated by a patient with *C. auris*, especially if cleaning practices were suboptimal.

To identify colonized people, one or more high-yield body sites should be sampled with a swab. For example, studies evaluating screening for methicillin-resistant *Staphylococcus*

aureus (MRSA) have shown nares to be the highest yield site, ranging from 71–84% [33–35]. Yield can be increased further if additional body sites are included; for example, MRSA detection is >90% if nares, throat, and perineum are all sampled [35]. Because no studies on sampling sites exist for *C. auris*, early cases were sampled from multiple body sites (including nares, ears, oropharynx, axilla, groin, and rectum) to determine those with highest yield. Approximately 90% of cases were positive by axilla or groin swab. Nares was the second most commonly positive body site. Screening of epidemiologically-linked patients with a composite swab of the bilateral axillae and groin is recommended; additional body sites, including nares, may be sampled if feasible. Unlike screening for MRSA or CRE, laboratory processing of swabs taken to identify *C. auris* colonization is not currently commercially available and should be coordinated through local or state health departments and CDC. All patients identified as colonized with *C. auris* should be managed in the same manner as the index patient and placed in single room on contact precautions. It is also important to ensure that the patient's status and required infection control measures are communicated at the time of transfer to another healthcare facility.

No known decolonization methods have been established. *C. auris* is susceptible to chlorhexidine *in vitro* and has been used in certain settings for source control; however, despite daily chlorhexidine bathing, patients described in the U.K. continued to be colonized with *C. auris* [15]. Further study is needed on efficacy of chlorhexidine and other products for decolonization before recommendations for their use can be made.

Review of microbiology records—Because *C. auris* is commonly misidentified as other *Candida* species, clinical laboratories serving the affected facility should review microbiology records to identify other suspected cases, as should clinical laboratories serving other facilities where the patient recently received care. These reviews should include specimens from all body sites and include ≥1 year of microbiology records, preferably as far back as 2015. Laboratories that have identified a case of *C. auris* should be on heightened alert for additional cases of *C. auris*.

Response to more than one case of *C. auris*

Although a case of *C. auris* is enough to prompt an investigation, >1 case raises the concern for transmission. When >1 patient with *C. auris* is identified at a healthcare facility, including patients identified through screening, additional actions are recommended.

Perform infection control assessments—Infection control assessments should be conducted to look for opportunities for improvement. These assessments offer an opportunity to collaborate with staff and provide comprehensive education that benefits the facility beyond the control of *C. auris*. Particular areas to target during these assessments include hand hygiene, contact precautions, and environmental cleaning and disinfection.

Hand hygiene assessment should include evaluating the availability of appropriate resources, like alcohol-based hand rub and ready access to sinks with soap and water. Use monitoring programs to ensure staff adherence and to target ongoing education and encouragement. When evaluating the implementation of contact precautions, assess the availability of personal protective equipment (PPE), clear signage outside patient rooms, and staff

adherence. In resource-limited settings, facilities may have to consider cohorting patients with *C. auris* together; however, if patients have multiple MDROs, care should be taken not to cohort patients with different MDROs together.

In the U.K. outbreak, *t* horough cleaning and disinfection with sodium hypochlorite-based products and hydrogen peroxide vapor was reported to be a key factor in eventual control of the outbreak [15]. Environmental cleaning and disinfection in healthcare facilities should be a collaborative effort between environmental services, patient support staff, and healthcare workers. Training on use of the proper agent, mixed to the proper concentration (if required), and appropriate contact time are essential to ensuring surfaces are adequately disinfected. Samples from *C. auris* patient rooms in the after terminal cleaning with sodium hypochlorite-based products have not yielded growth of *C. auris*. If these measures fail to stop transmission, closure of an affected ward for a certain period may be needed to interrupt transmission [15].

Perform additional case finding—Broader patient screening should be strongly considered in facilities with >1 patient with *C. auris*, especially in high-acuity nursing homes, where substantial transmission of *C. auris* has occurred. Point-prevalence surveys (PPS) for *C. auris* colonization of affected units or an entire facility can rapidly assess the extent of transmission and identify patients who may be sources of ongoing transmission.

Results from the initial PPS can help determine need for further screening. For example, if multiple patients on a particular ward are colonized, the next step might be to screen the entire floor or facility. In general, if further transmission is detected on PPS, additional PPS are warranted after interventions are undertaken to assess the impact of these interventions on transmission.

Consider environmental or healthcare worker sampling in limited settings—Early U.S. investigations of *C. auris* included environmental sampling of surfaces in case-patients' hospital rooms during active infection, and many different types of surfaces yielded positive cultures for *C. auris*. Based on these results, contamination of affected patients' rooms is expected, and environmental sampling is generally not recommended. However, environmental sampling could be considered if epidemiologic evidence links specific environmental sources to *C. auris* transmission or in situations where ongoing transmission is identified despite adherence to recommended interventions.

Whereas transient contamination of hands of healthcare personnel (HCP) is likely to play a role in *C. auris* transmission, the role of chronic HCP colonization is unclear. Systematic sampling of the hands, nose, axilla, groin, and throat of 258 HCP was conducted as part of the U.K. investigation and identified a single HCP with a positive nares swab who later tested negative from the same site, suggesting transient carriage [15]. Screening of HCP should be considered only if an epidemiologic investigation suggests HCPs as a likely source or in situations where ongoing transmission is identified despite adherence to recommended interventions.

Consider regional notification to laboratories and other healthcare facilities— When ≥1 *C. auris* case is identified, local or state health departments may consider notifying laboratories and healthcare facilities in the region to raise awareness and aid in additional case-finding. Laboratory messaging from public health agencies should include information about when to suspect and how to identify *C. auris* and highlight the importance of determining *Candida* species and AFST [18]. Microbiology record reviews can also be requested on a wider scale at other facilities in the region to identify other suspect cases. These laboratories should also be encouraged to conduct prospective surveillance for new cases. Because other *Candida* species do not typically cause outbreaks, heightened infection control practices are not typically recommended in the control of *Candida* infections. Therefore, it is particularly important to educate HCPs in the region about the distinct ability of *C. auris* to spread in healthcare settings and about current control recommendations to improve identification, notification, and implementation of infection control measures.

Unanswered Questions and Ongoing Work

Even as more becomes known about *C. auris*, many unanswered questions remain that directly affect the implications of testing and identifying cases. These questions include:

1. Where did *C. auris* come from and why is it emerging now?
2. What should salvage treatment consist of in cases where the organism is resistant to the three main classes of antifungals?
3. How can *C. auris* colonization be rapidly detected?
4. How long can a person remain colonized with *C. auris*?
5. What methods are effective for reducing the burden of *C. auris* colonization?
6. What are risk factors for infection in a patient colonized with *C. auris*?
7. How effective are the recommended infection control strategies at containing *C. auris*?
8. What is the prevalence is *C. auris* in the community and does transmission occur there?
9. How rapidly and under what circumstances does *C. auris* become resistant to antifungal drugs?

Future studies will aim to answer these questions in addition to others in order to better understand *C. auris* and how best to contain its spread.

Conclusion

Candida auris is a newly emerging, often multidrug-resistant fungal pathogen, similar in many ways to bacterial MDROs with which hospital epidemiologists and clinicians are already familiar. The ability of *Candida auris* to colonize the skin, persist in the healthcare environment, and cause healthcare-associated outbreaks has changed the way we think about *Candida* infections. Prevention and containment of *C. auris* requires many of the same

interventions that are used to contain other MDROs that spread in healthcare settings, and it critical that these interventions are implemented early and thoroughly.

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Summary

Candida auris is an emerging multidrug-resistant yeast that can spread in healthcare settings. This review summarizes the current recommended approach to manage cases of *C. auris* and control transmission of *C. auris* in healthcare facilities.

Box 1

***CANDIDA AURIS* IS CONCERNING BECAUSE OF THE FOLLOWING REASONS**

- It can cause invasive infections with high mortality
  - 59% all-cause mortality in early studies
  - Majority of cases in the United States to date have been bloodstream infections (candidemia)
- It is difficult to identify.
  - Most often misidentified as Candida haemulonii by conventional biochemical methods
  - MALDI-TOF or DNA sequencing are required to identify *C. auris*
- It is often multidrug resistant.
  - Most isolates are resistant to fluconazole
  - Some are resistant to amphotericin B
  - Small proportion are resistant to echinocandins
  - Resistance to all 3 classes of antifungals has been observed in other world regions
- It can spread in healthcare settings.
  - Persists on patients' skin and the healthcare environment, allowing for transmission to occur between patients in healthcare facilities
  - Outbreaks of *C. auris* have been reported in several countries

Box 2

INTERVENTIONS NEEDED FOR A CASE OF *CANDIDA AURIS*

- Notify public health agency of confirmed or suspected *C. auris* cases
  - Report to the Centers for Disease Control and Prevention at candidaauris@cdc.gov
- Place patient in a single room if possible and institute standard and contact precautions
  - Reinforce and enhance hand hygiene practices
- Institute thorough environmental cleaning and disinfection of the patient care area
  - Use an Environmental Protection Agency-registered disinfectant active against *Clostridium difficile* for routine and terminal disinfection
- Implement contact tracing and testing to identify other patients colonized with *C. auris*
  - Composite swab of axilla and groin to assess for skin colonization
  - Swab roommates and those with longest overlapping contact with the case patient
- Conduct microbiology records review
  - Review past microbiology records (at least for the preceding 1 year) for suspect or confirmed cases of *C. auris* at the institution.
  - Set up enhanced surveillance for *C. auris* in the laboratory serving the healthcare facility to detect any future cases of *C. auris* immediately

Figure 1.

Countries from which *Candida auris* has been reported, as of July 2017. Canada, Germany, Japan, Norway, and Kuwait have each reported a single case of *C. auris.* Larger numbers of cases have been reported in Colombia, India, Israel, Kenya, Oman, Pakistan, Panama, South Korea, Spain, South Africa, the United Kingdom, and Venezuela. Current case counts of *C. auris* for all countries are not available. United States case counts are available on the Centers for Disease Control and Prevention website. Most US cases are concentrated in the New York City and New Jersey area, though at least 7 other states have reported cases as of August 2017.