Summary of Educational Need & Gap Analysis

Executive Summary

Invasive candidiasis, a bloodstream infection of fungal pathogens of the *Candida* genus, is a significant cause of nosocomial morbidity and mortality (Magill 2014). Almost 20 *Candida* species can infect humans, and among them multidrug resistant *Candida auris* is emerging as a dangerous multidrug-resistant pathogen. First isolated from a Japanese hospital patient in 2009, *C auris* has since been detected on five continents (Satoh et al, 2009; Al-Siyabi et al, 2017; Calvo 2016; Chowdhary et al, 2013; Lee, 2011; Lockhart et al, 2017; Schelenz et al, 2016; Vallabhaneni et al 2017; Schwartz and Hammond, 2017, Emara et al, 2015; Magobo et al 2014; Ruiz et al, 2017). As of March 2018, 257 clinical cases and 475 screening cases have been identified in the US, (CDC, 2018c). *C auris* is transmitted in hospitals and has the largest effect on the sickest individuals, as the majority of known infections have been in critically ill patients (Calvo, 2016). In one case, the pathogen was responsible for 5.2% of candidemia cases in an Indian hospital, a location in which *C auris* it is more prevalent (Chakrabarti, 2015).

In lieu of species-specific data regarding *C auris* transmission mechanisms, authorities have adopted prevention strategies that are used to combat other multidrug resistant organisms like methicillin-resistant Staphylococcus aureus (MRSA) (CDC, 2018b). New research findings constantly motivate updates to these strategies in hopes of decreasing transmission, but clinicians must be made aware of the changes for them to be effective. Current detection methods consist of biochemical, phenotypical, and genetic strategies, each with unique limitations and the potential for misidentification if these limitations are not understood (CDC, 2018a). Resistant isolates and strains with reduced susceptibility have been reported for the commonly used antifungal medications fluconazole, amphotericin B, and echinocandins, including cases within the United States (Jeffery-Smith et al, 2017; Vallabhaneni et al, 2017). In light of this widespread antifungal resistance, controlling and preventing *C auris* outbreaks is a key component to preventing an international health crisis and is required to protect the most vulnerable patients.

Despite recent advances in understanding *C auris* biology and transmission, the pathogen continues to spread. This dispersion combined with the organism's resistance to therapeutics triggered a "Call to Arms" for the "international medical community to attack the *C auris* challenge before it escalates further" (Clancy and Nguyen, 2017). To prevent future infections and the development of new resistant strains, clinicians must be up-to-date with the most recent *C auris* transmission and detection methods. Medical Education Company X will address this need by developing an educational program designed to update clinicians with the latest research findings and best practices for identifying sources of transmission and detecting *C auris* infections, so that the appropriate prevention mechanisms can be implemented.

Title of Initiative	Updates on *Candida auris* modes of transmission and detection methods.
Target Audience	Clinicians

Identified Gaps in Practice

Differences between current and best practices define the educational gaps that will be addressed in this initiative. The planned learning objectives(s) for each gap are what participants should be able to do upon completion of this educational initiative. (For more detailed information, please see the "Literature Review Supporting the Educational Need" in the appendix.)

Gap 1: Clinicians may not be up-to-date with recent progress in understanding *C auris* transmission.	
Current Practice	Clinicians may not be up-to-date with recent progress in understanding *C auris* transmission. *C auris* is a new pathogen that is transmitted in hospitals and is mainly contracted by the most compromised patients (Vallabhaneni 2017). Because research is

	ongoing to describe the behavior of this pathogen and new data is frequently available, clinicians may not be aware of recent transmission findings. Continued nosocomial spread of *C auris* indicates that healthcare providers may not be aware of the potential for *C auris* spread through common treatment practices (Walker, 2018).
Best Practice	Clinicians should be aware of the most recent information regarding modes of *C auris* transmission. New studies have identified the presence of *C auris* in several locations on the body and have determined hospital surfaces that the pathogen can persist on for extended periods of time (Vallabhaneni, 2017; Schelenz 2016; Piedrahita et al, 2017). With this information, the CDC has updated guidelines on how to prevent transmission from a colonized individual (CDC, 2018b). A critical component of containing *C auris* spread is ensuring that colonized individuals are identified and treated with the proper precautions. Clinicians must be able to both identify colonized individuals and ensure that eradication measures are effective to prevent nosocomial *C auris* dissemination. To combat the spread of *C auris*, clinicians must know how to locate it.
Learning Objective	List non-sterile locations that *C auris* can colonize Identify potential sources of *C auris* transmission

Gap 2: Clinicians may not be familiar with recent advancements in *C auris* detection methods.	
Current Practice	Clinicians may not be familiar with recent advancements in *C auris* detection methods. New research continues to expand what is known about *C auris*, resulting in new strategies for *C auris* identification (CDC, 2018a). Commonly used detection methods have limitations and the potential for misidentification, and clinicians must be aware of these shortcomings to avoid implementing incorrect treatment and containment practices (Clancy and Nguyen, 2017).
Best Practice	To make the best decisions regarding pathogen treatment and containment, clinicians should be able to make informed decisions about the way culture samples are evaluated. Understanding the benefits and limitations of common laboratory identification procedures will facilitate better, more accurate identification of *C auris* and other pathogens. Improved identification practices will translate to more effective treatment and more appropriate containment precautions, resulting in better patient care and decreased pathogen spread.
Learning Objective	Describe methods for identifying *C auris* Identify limitations of common *C auris* detection methods Combine complimentary identification strategies

Appendix: Literature Review Supporting the Educational Need

Since its identification in 2009, multidrug-resistant *C auris* has rapidly spread to hospitals on five continents (Al-Siyabi et al, 2017; Calvo 2016; Chowdhary et al, 2013; Lee, 2011; Lockhart et al, 2017; Schelenz et al, 2016; Vallabhaneni et al 2017; Schwartz and Hammond, 2017, Emara et al, 2015; Magobo et al 2014; Ruiz et al, 2017). To avoid future outbreaks, measures must be taken to prevent the spread of this fungal pathogen. Currently, there is an opportunity to contain *C auris* before it spreads further, which is a more effective means of pathogen control than treating it following an outbreak (Real, 2005; Vandenbroucke-Grauls, 1996). The United States and other countries have established guidelines for transmission prevention that are continually updated as researchers discover new information about the *C auris* biology and approve new methods of detection (CDC, 2018a,b). Despite these advancements, *C auris* continues to colonize new patients, indicating a need for clinician education in this area.

Gap 1: Clinicians may not be up-to-date with recent progress in understanding *C auris* transmission.

Due to the recent and rapid emergence of *C auris*, researchers are actively and continuously revealing new information about transmission modes. *C auris* is often drug resistant and effective treatments are lacking, so to combat this, steps must be taken to prevent exposure. Migration of *C auris* to the United States appears to have been transmitted through healthcare facilities, via patients who acquired *C auris* while receiving treatment abroad in countries that were known to harbor the pathogen. The researchers that performed this study stated that their data "demonstrate the need for attention to infection control measures to control the spread of this pathogen" (Vallabhaneni, 2017). Because of the rapid improvements in this area and the impact these measures have on pathogen control and patient health, clinicians should be informed of the most recent advancements in understanding *C auris* transmission.

Hospital surfaces

Hospital surfaces are emerging as an important reservoir for harboring *C auris*. The pathogen can survive on surfaces for more than 7 days in wet and dry locations, and it can persist in locations that differ from other *Candida* species (Piedrahita et al, 2017). Given the propensity to live in moist areas, locations like sinks are key areas to consider when decontaminating rooms and tracing outbreaks.

Improper or ineffective surface disinfection puts patients at a higher risk for acquiring *C auris*. Researchers from Oxford University Hospital (OUH) in England, in a presentation at the annual meeting of the European Society of Clinical Microbiology and Infectious Diseases, described a *C auris* outbreak that occurred in the OUH neonatal intensive care unit (NICU). The incident, noted as one of the largest *C auris* outbreaks yet, was traced to colonies on the surfaces of multi-use patient equipment. Researchers found that use of multi-patient axial thermometers was a significant predictor of *C auris* infection (OR 6.80, 95% CI 2.96 to 15.64, P<0.001), and the outbreak was only controlled after the thermometers were removed. Notably, 100%, 89%, and 90% of the isolated strains were resistant to fluconazole, voriconazole, and posaconazole, respectively (using *C. albicans* breakpoints) (Walker, 2018).

Research is ongoing to determine the effect that different disinfectants have on *C auris*, but currently the CDC recommends cleaning surfaces with agents approved for the removal of *C. difficile* spores. Both daily and terminal cleaning are recommended for patient rooms (CDC, 2018b).

Patient colonization sites

While the majority (56%) of *C auris* cases are identified from blood, 46% of colonization cases are identified from other, non-sterile locations on the patient's body (CDC, 2018a). *C auris* can colonize multiple bodily locations including the groin and axilla, which are the most common, but the pathogen has also been found on the rectum, nares, urine, wounds, and sputum. *C auris* can persist on a patient's skin even after an invasive infection has been eradicated (Vallabhaneni, 2017; Schelenz 2016). If colonization goes unrecognized, patients may re-infect themselves and have the potential to expose others, particularly compromised patients, to the pathogen. It is critical to screen both sterile and non-sterile sites to ensure proper control procedures are implemented. The CDC recommends screening infected patients for at least four weeks following treatment to ensure eradication (CDC, 2018a).

The CDC also recommends screening healthcare workers (HCW) and caretakers that spend time with colonized patients. One study in a United Kingdom hospital screened 258 HCWs

across multiple body sites and detected one positive nose swab. The HCW carrying the pathogen had been caring for a heavily colonized patient. This colonization posed a potential threat to other patients, although no further transmission was determined (Schelenz et al, 2016). Because *C auris* can colonize these sites, they must be checked to ensure the spread of the pathogen is contained.

It is critical for clinicians to be updated on potential *C auris* colonization sites, so patients and caregivers can be thoroughly screened for colonization. Accurately tracking colonized individuals will facilitate more effective pathogen control and improved protection of colonized patients.

Gap 2: Clinicians may not be familiar with recent advancements in C auris detection methods.

It is important to identify pathogenic organisms to the species level, because *C auris* exhibits colonization and transmission features that are distinct from those understood for other *Candidia* species. Misidentification can lead to implementation of the wrong containment precautions, putting immunocompromised patients and others at risk. Clinicians should become familiar with the methods used in their facilities to detect *C auris* and the limitations inherent in the processes (CDC, 2018a).

Biochemical and Genetic Techniques

In April 2018, the FDA approved the first test for *C auris* identification. For this test, cultured patient samples are subjected to matrix-assisted laser desorption/ionization (MALDI-TOF) spectroscopy. This method ionizes the sample and determines the “protein fingerprint” present in the culture (Overview, 2018). The fingerprint data is checked against a reference library to identify what organisms are present in the sample. This technology has been used in the past to identify over 300 other types of microorganisms, but only recently has data for *C auris* been determined and added to the database (Overview, 2018). Research laboratory use of MALDI-TOF has been effective for accurate *Candida* species identification (Kathuria et al, 2015), but clinical systems have only recently become available. Other molecular techniques have been shown to confuse related species leading to misdiagnosis, but this information is still being determined for this method (Overview, 2018).

Automated commercial platforms perform biochemical organism identification using a single machine. These systems are simple to operate, are feasible to maintain in a clinical laboratory, and often perform an additional level of screening that provides information about the drug resistance profile of each sample. Different instruments are available from a variety of companies that have their own FDA-approved organism libraries. This is an attractive option for clinical identification of *C auris*, as few groups have experience working with this new pathogen and automation has the potential to decrease misidentification.

One study used sequencing and MALDI-TOF to evaluate the number of *C auris* strains present within a group of 102 isolates that were initially identified to be *C. haemulonii* or *C. famata* by commercial systems. 88.2% of these isolates were determined to be *C auris* by ITS sequencing (Kathuria 2015). This is a significant discrepancy that could lead to the mismanagement of pathogen containment.

Many of the shortcomings for commercial identification platforms are attributed to the need to add additional information to the sequence databases, which are likely to see improvements

and expand coverage over time (Mizusawa et al, 2017). This approach, while convenient and useful as a starting point for infection diagnosis, should be approached with caution and used in conjunction with other identification methods.

Before the advent of MALDI-TOF techniques, the only method that could differentiate *C auris* from other closely related species (specifically *C. haemulonii*) was genetic sequencing. The sequences of specific genetic loci, particularly D1/D2 domain of the large ribosomal subunit of the 26s rRNA gene, RPB1, RPB2, and the internal transcribed spacer (ITS) domain of the nuclear rRNA gene, can correctly identify *C auris* from patient samples (Satoh et al, 2009; Kim et al, 2009; Kumar et al, 2017; Mizusawa et al, 2017). While sequencing is accurate, it is not frequently used in hospitals as it requires specialized laboratory equipment and sequence databases. Additionally, while sequencing has provided useful information for tracking the spread of *C auris* on the global scale, it is less powerful for identifying specific strains (Sharma et al, 2015).

PCR assays have recently been developed as rapid genetic tools for *Candida* species identification. These systems amplify the ITS region of the rRNA gene from a cultured patient sample and preliminary analysis indicates that this method is fast and accurate. (Kordalewska et al, 2017). Recent developments suggest levels of accuracy that are similar to ITS sequencing (Theill et al, 2018). Further testing, however, is warranted to characterize the accuracy of this new identification technique.

Phenotypic identification Methods

C auris can be identified through phenotypic characteristics using either commercial tests or standard laboratory equipment (Kumar et al, 2017). These detection methods have the potential to be inexpensive and fast but have important shortcomings that usually require further examination steps to correctly identify a pathogen (CDC, 2018a).

Chromogenic agar and liquid assays are popular phenotypic methods of *C auris* identification. In these methods, chromogenic compounds are either added to agar plates or liquid culture media, and the compounds change color in response to the presence of *Candida* species. Agar plates are simple to use and are inexpensive, and commercial assays are advertised to work in 4 hours, but both do not have the ability to identify *Candida* to the species level (CDC, 2018a). Recent work has shown that certain additives can alter the growth of different yeast species, leading to measureable differences in growth between *C auris* and *C. haemulonii* (Kumar et al, 2017). Further development of these methods could lead to more specific organism identification.

When cultured on cornmeal agar, some *Candida* species, including *C. guilliermondii*, *C. lusitaniae*, and *C. parapsilosis,* will form pseudohyphae. Typically, *C auris* does not form hyphae or pseudohyphae under these conditions, although some isolates can. This low-cost method can be used in conjunction with other methods as verification, but should not be used as sole identification, as *C auris* can easily be confused with other non-hyphae forming yeasts like *C. famata* (Mizusawa et al, 2017).

Need for Education

Knowledge regarding the spread of *C auris* and other *Candida* species is rapidly expanding, and new detection methods with increased sensitivity are constantly being developed. With this quickly changing landscape comes updates to clinical practices to control the spread of pathogens. In order to provide the best care and prevent further pathogen spread, it is critical

that clinicians are up-to-date on the newest information regarding these procedures so they can immediately be put into practice. This educational program will ensure that clinicians are armed with this information and ready to apply it, thus leading to a decrease in pathogen spread and better quality of care for the most vulnerable patients.

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