In search for *Candida auris,* labs all in

Karen Titus

June 2023—A bad-news, good-news, bad-news, good-news bass line thrums through the ongoing story of *Candida auris* as it continues to spread in the United States.

Initially identified in Japan, in 2009, in an ear specimen—hence the *auris*—the yeast was first reported in the United States in 2016.

Like certain other pathogens, *C. auris'* domestic presence appeared to be linked to travel-related cases, then quickly spread, first to the metropolitan regions of Chicago and New York City and now to more than half the states.

That's worrisome. Yet the spread hasn't been unbridled. Early fears that it would sweep indiscriminately through all patient populations have not been realized.

"It's not as virulent as *albicans,*" says Sixto M. Leal Jr., MD, PhD, director of the clinical microbiology laboratory and of the fungal reference laboratory, University of Alabama at Birmingham, and a member of the CAP Microbiology Committee. "It's about as virulent as *Candida glabrata.* It's not too much of a significant threat if you're healthy."

For patients with multiple comorbidities, however, the impact can be severe. This would include those in ICUs or in long-term care facilities, and patients who are connected to IV or urinary catheters, or who are ventilated, says Dr. Leal, who is also director of UAB's regional biocontainment laboratory and associate professor in the Department of Pathology. Those who are getting sick from *Candida auris* often have multiple comorbidities and a high likelihood of prior exposure to antibacterial agents, he says, allowing room for nonbacteria to colonize and expand their population, providing a niche for the growth of *C. auris*.

When *Candida auris* was found to be multidrug resistant, MRSA-tinged fears soon followed. Those concerns remain, but not every *C. auris* clade has turned out to be pan-resistant. And though breakpoints for commonly used antifungals are not available—and are likely to remain elusive—other options have emerged.

Finally, *C. auris* remains difficult to identify using traditional biochemical methods. But in recent years MALDI-TOF has become a reasonable option for many labs, and it's a fast, straightforward way to identify the organism.

Even those who felt prepared for the arrival of *Candida auris* found their first case jarring.

Erin McElvania, PhD, D(ABMM), recalls the first case at the Chicago-area NorthShore University HealthSystem, in 2017. From the literature, "We knew of its existence," says Dr. McElvania, director of clinical microbiology. It was a shock nevertheless. "There it is. Your jaw just drops." It felt even more dire at the time, she says, given the unknowns and unsettling predictions.

Loyola University Medical Center also belonged to that early hotspot, identifying its first isolate in 2017, says Amanda Harrington, PhD, D(ABMM), director of the clinical microbiology laboratory and professor, Department of Pathology and Laboratory Medicine. "I hear people say, *Oh, this is our first isolate*. We're well past that, unfortunately."

Dr. Sixto M. Leal Jr. at the University of Alabama at Birmingham. “There is a lot of interest in generating breakpoints for *Candida auris*,” says Dr. Leal, an advisor to the CLSI antifungal susceptibility testing subcommittee and a member of the CAP Microbiology Committee. [Photo: Brian Pride]

UAB, on the other hand, didn’t encounter its first specimen until the latter half of 2022. Immediately following that, two more cases emerged. “Now we’re up to about seven,” says Dr. Leal, speaking in mid-May. “So we’re seeing a lot more of these cases.” That’s true nationwide, he adds, pointing to the CDC’s website: https://www.cdc.gov/fungal/candida-auris/tracking-c-auris.html. And as an article published this year points out, the recent spread showed a dramatic increase in 2021, particularly among cases that are resistant to echinocandins, a first-line therapy for *Candida* infections (Lyman M, et al. *Ann Intern Med.* 2023;176[4]:489–495).

Dr. Harrington minces no words. “It’s very, very tenacious and that makes it a threat. In the right patient at the right time, especially if it’s in an invasive site, it can be very detrimental clinically.”

Dr. McElvania echoes concerns about the organism’s spread. Studies done in long-term care settings show extremely high rates of colonization, she says. “So when they enter the hospital there’s a good chance they’re going to bring it with them.” Infection control oversight at these facilities may not match that at hospitals, making them a vector for hospital spread.

“Until we can control it in those settings, we won’t ever be able to eradicate it,” she cautions. “I feel like it’s gone too far already.”

Perhaps the biggest—and most hopeful change in recent years is that even as the spread of *Candida auris* is worsening, it’s also becoming easier for more labs to identify it.

Because *Candida auris* was such a pressing matter, manufacturers (BioMérieux, Bruker) made it a priority to update their databases—which are now FDA-approved—for the organism, says Dr. Leal. Moreover, MALDI-TOF

itself, long a rich lab's game, is now within reach of many labs, he says. "Once it was added to FDA-claimed databases, labs with MALDI-TOF MS started identifying *C. auris* readily," he adds. "It's just as straightforward to identify as *Candida albicans*—not hard at all."

His own lab had been using the updated FDA-claimed MALDI-TOF database for about a year prior to identifying UAB's first case, he says. "So I don't think *C. auris* was hanging out and we were just missing it," he says. The lab did identify one *haemulonii*, which was assessed by sequencing to see if it might be *Candida auris*. It wasn't. "So I do think we caught the first *auris* that came through, and we caught it easily because of the MALDI-TOF system we have."

At UAB, where case numbers are still relatively low, every time a Candida auris case is identified, the lab does susceptibility testing. "And then we sit down with infection prevention and key folks from antimicrobial stewardship, and we talk about the isolate and tentative breakpoints," Dr. Leal says. [Photo: UAB News/Steve Wood]

For labs that don't use MALDI-TOF, the matter is much more complicated, and those who are using biochemical methods to try to identify *Candida auris* have a much higher likelihood of missing infections, Dr. Leal says. "You have to figure out whether you think that isolate is important for patient care and then have the optimal systems in place to be able to identify it." It's possible for *C. auris* to "hide" in the background when another concerning organism—group A *Streptococcus,* for example—is predominant.

Without MALDI-TOF, the lab may identify it as *haemulonii*. "That's what gives you the initial concern that it might be *auris*," he says. "If in-house culture or molecular assays are not available, you'll then need to send it to a state lab or reference lab for definitive identification."

That could cause lengthy delays. State laboratories that see a large number of cases and have a specific, high level of interest in *C. auris* will have faster turnaround times than states with lower volumes, Dr. Leal says. In Alabama, the turnaround time is typically five to seven days for results. "Fortunately, we have the MALDI."

For labs that do need to send out specimens for confirmation, Dr. Harrington suggests a possible intermediate strategy: A potential case identified on chromogenic media could be identified as "presumptive" until the final identification is confirmed. Whatever strategy labs use will require good coordination and communication between the lab and the infection prevention team as to what those results mean, she says.

Institutions are using several types of strategies to address both surveillance and clinical testing needs.

NorthShore University HealthSystem developed a screening protocol for high-risk patients shortly after identifying its first *C. auris* isolate. “It’s not very labor-intensive or difficult,” says Dr. McElvania. Swabs are collected from the skin—nares, axilla, groin—and cultured on basic fungal media. Any yeast that’s grown is identified by MALDI-TOF. (“We validated our instrument before FDA approval was sought, so we still use our research-use-only database,” she notes.)

Currently the CDC does not recommend screening patients for *Candida auris* when they are admitted to the hospital, which makes sense, observers say, given that costs would be high and yield would be low.

“If you did want to establish screening,” says Dr. Leal, “the way to do it is either by culture or PCR.” Though companies are working on rapid commercial *C. auris* PCR tests, for now most institutions that perform this assay use a laboratory-developed test.

Dr. McElvania doesn’t see much need for a point-of-care test. (“Though faster is always more fun,” she concedes.) “We don’t do universal screening, but we know it’s circulating in our area.”

She and her NorthShore colleagues have not found an automated way to use Epic to identify patients who need to be screened, as happens with MRSA. They are mainly concerned about high-risk hospitalized patients—typically from long-term care facilities who are ventilated or have a tracheostomy. She praises the close and flexible relationship between the lab and the infection control group. “Right now we don’t have any what I would call stringent infection control screening protocols, but we have regular meetings with them, and our infection preventionists do look for those patients manually and request they be screened for *Candida auris*.”

They also continue to talk about whether and how testing should be expanded to other patient groups. “There’s no slam dunk,” she says. Oftentimes information about where the patient is coming from is essentially free-texted into the electronic health record so the data cannot be pulled and identified easily.

The other end of the process is also conversation-heavy, Dr. McElvania reports. When a positive case shows up, “there’s a lot of activity around screening patients who may have been in contact with the case patient, isolation, and cleaning procedures.

“So a lot of flurry on the front end and the back end,” Dr. McElvania continues. “But for us, the lab part is straightforward.” Plates are incubated for five days and read for organism growth twice during that period—at 48 hours and five days. Though it would be nice to perform testing at a somewhat faster pace, she acknowledges, the elevated cost would not be worth it, given the hospitals’ low rates of *Candida auris*.

It does show up on routine blood, urine, and respiratory cultures. For the first quarter of 2023, the lab identified eight different clinical cases, Dr. McElvania says. “That’s a little higher than we typically see. Every quarter we get a handful, usually in the one to four range. It’s still rare enough to us that whenever we get one, it’s, *Whoa!*”

Loyola has also maintained its culture-based surveillance strategy, in no small part because of the onslaught of demands placed on the lab during the pandemic, says Dr. Harrington.

The lab uses a chromogenic media, which is helpful, Dr. Harrington says, because *C. auris* is not the same color as *Candida albicans* (which is more common in many of their colonization sites). “So we can weed that out very quickly, and you’re not missing this bug in a mixed population.” It’s not particularly challenging to grow, she adds, though “culture is a little slow for cultivation, so we hold it for a couple days to make sure we’ve grown the organism.”

Loyola uses two types of surveillance. One, which Dr. Harrington describes as a passive strategy, involves more extensive searching beyond typical clinical testing strategies, she says. For sites like urine or respiratory, where yeast may not be clinically significant, “we’re going to go ahead and identify if there’s a *Candida auris* there, as sort of a broader, safety-net strategy. We just don’t want a colonizing strain, even if it’s not clinically invasive. That’s an approach we’ve taken from a very early standpoint.”

The active surveillance strategy calls for patients in the designated risk groups to have samples from axilla/groin swabs sent to the lab for culture. This is done primarily using CHROMagar. If an organism consistent with *Candida auris* is identified, it's sent to MALDI-TOF for a full identification.

Echoing others, she says MALDI-TOF makes identification fairly easy. "The labs that don't use MALDI are the ones that really need to understand where the pitfalls are," says Dr. Harrington. "We still know that our old biochemical methods may or may not be able to accurately identify this organism."

At UAB, patients are screened only when the laboratory identifies a case of *Candida auris* through its standard-of-care culture. The lab will contact infection prevention, which then conducts an investigation. Those on the affected unit—typically 10 to 20 patients—will then be screened, with the lab using CHROMagar to do an initial identification on specimens collected from axilla and groin swabs.

Though transfer of *Candida auris* between patients is reported to be relatively common, "We haven't seen it yet," says Dr. Leal. "Many isolates are identified in urine or lung cultures." These patients are symptomatic, but unlike patients with fungemia, it is not clear if *Candida auris* is the true cause of the illness.

"If it happens to show up, then we start looking for it in the highest yield areas of the hospital," he says. Hospitals with more cases of *C. auris* will find it helpful to be more proactive, Dr. Leal suggests, such as setting up preemptive *C. auris* screening in the ICU. "We haven't reached that level yet," he says. "Hopefully we never will."

Matters seemed grim when Loyola first encountered *Candida auris.* Dr. Harrington and her colleagues perceived the biggest threat to be the multidrug- or pan-resistant nature of the isolates. "That tends to get your attention. You think, *Oh my goodness—this is going to be horrible.*"

But after that initial jolt, "We were surprised in two ways," says Dr. Harrington, who offers her own bad-news, good-news scenario. "If you have to be a hotspot," she says, "not having a pan-resistant clade in your population is at least fortunate." That's the case in the Chicago area—the clade may be resistant to some of the azoles but not to other classes of drugs. "So our organism didn't look quite as nasty as the threat."

As for the second surprise: "It turns out the real threat is the inability to eradicate this organism," says Dr. Harrington. Once it enters a health care facility, "it really takes hold."

"And it seems to be transient in some of our patients," she adds. "We haven't been able to identify a single source. It just continues to be a problem."

In some ways, *Candida auris* has turned out to be more deceptive than dire, at least for now. But that doesn't rule out the possible future arrival of a more resistant organism. "We're watching closely for the emergence of new kinds of strains or clades," Dr. Harrington says. "Interestingly, it looks like what's in Indiana, right next door, is different than what's in Chicago." But, she adds, that could change. "So that also needs to be put under consideration—that a colonized patient can quickly progress to having a more resistant strain."

Resistance raises the problem of breakpoints. Only one CLSI breakpoint is available for *C. auris* and it applies to rezafungin, a new FDA-approved once-weekly injectable echinocandin. However, there are no CLSI breakpoints for the agents most commonly used to treat *C. auris*, Dr. Leal says, including fluconazole, voriconazole, micafungin, and amphotericin B.

Dr. Mc Elvania

Breakpoints are usually the purview of the FDA and CLSI, but to counter this unique multidrug-resistant emerging threat, the CDC Mycotic Diseases Branch took the unusual and important step of developing tentative breakpoints to interpret susceptibility testing results for *Candida auris.* "That's different from any other pathogen, bacterial or fungal, that I've ever come across," Dr. Leal says. "This is the first time to my knowledge that there have been CDC tentative breakpoints."

For a time, NorthShore performed susceptibility testing in the background for a surveillance screening, says Dr. McElvania. "Just for our infection control group, to make sure we weren't seeing these very high MICs across all the antifungal classes." But they have since discontinued it for surveillance and now report it only for clinical isolates. The lab includes a clinical comment noting it's using the CDC's tentative breakpoints.

The lack of established breakpoints has not been particularly constraining for Dr. Leal and his UAB colleagues. Though cases are rising, the number remains relatively low, allowing for a more personal approach. Every time a *Candida auris* case is identified, the lab does susceptibility testing. "And then we sit down with infection prevention and key folks from antimicrobial stewardship, and we talk about the specific isolate and tentative breakpoints," he says. "And I explain from a lab perspective what the data mean."

If the case numbers were higher, "we probably couldn't use that approach," he acknowledges.

But for now the case-by-case, nuanced discussions are invaluable. There's urgency to doing the susceptibility testing, and it's tricky to interpret results, he says. "You have to make sure your providers understand that the MIC values are going to be interpreted with the CDC tentative breakpoints. They should know that. And for the most part they should be treated as if they are CLSI breakpoints."

Dr. Leal is an advisor to the CLSI antifungal susceptibility testing subcommittee. "There is a lot of interest in generating breakpoints for *Candida auris*," he says.

It's an arduous process, requiring enormous amounts of time and data. With *Candida auris*, the process is even more complicated because the initial clinical trials that provided patient outcome data to establish breakpoints for the most common medically important yeasts and antifungal agents (fluconazole, etc.) were completed decades before its emergence as a medical threat. "It probably existed, but it wasn't causing issues," Dr. Leal says. Investment in and execution of new clinical trials are needed to help generate this patient outcome data.

Given the vast number and diversity of infection-causing yeasts and molds, paired with the fact that they don't cause as many infections as bacteria, it may simply not be possible to generate sufficient clinical outcome data to establish breakpoints for many fungal drug combinations. "The chances of being able to generate that data is actually very, very low," says Dr. Leal, "and it would take a very, very long time."

Absent that data, the CLSI fungal group has been focusing on epidemiological cutoff values (ECVs) as a possible alternative. CLSI has developed ECVs for a number of uncommon yeasts as well as molds, though there are currently none for *C. auris*.

"This is on the horizon," says Dr. Leal, noting that the CAP has distributed a survey asking about the use of ECVs and barriers to adoption, etc. His own lab uses ECVs for molds and includes ECV interpretations in the EHR. Along with other academic institutions, he says, "We're kind of pioneering this approach. We think there's significant value to the use of ECVs for organisms in which there are no established or tentative breakpoints. ECVs provide significantly more informed guidance than the alternative approach of reporting lone MIC values into the EHR abyss."

But similar to his discussions with providers about using the tentative CDC breakpoints, he says using the ECVs requires detailed conversations with colleagues to explain what they mean.

Amid the serious concerns *Candida auris* has created, the organism has also generated real curiosity. It forms biofilms, enabling it to survive in catheters, rooms, and the like, even though it's more typical for yeasts to prefer wet areas. "But this one seems to survive in the environment just like *C. diff* survives, which is a little weird," says

Dr. Leal.

Dr. Harrington

He continues: “It can handle high salt, so it can live on your skin, and it likes high temperatures, so fevers don’t significantly impair its growth.” In vitro studies suggest that *Candida auris* can evade being killed by neutrophils. And some wonder if global warming has helped *Candida auris* expand its ecological niche, similar to the way *Coccidioides* has spread north and east from the American Southwest. “That’s one hypothesis,” says Dr. Leal. “But we really don’t know.”

What question would Dr. Harrington like to see answered? She’s concerned that there’s no clear understanding of how the organism spreads; one of the challenges is that it’s highly clonal. With the clades apparently localized to particular areas, and with the various strains in those communities seemingly closely related, it’s hard to track the movement of *Candida auris*.

“That’s a piece we need to understand so we can figure out how to stop it,” she says. “The epidemiology is challenging.”

The geographic spread also puzzles Dr. McElvania. The most vulnerable patients are less likely to travel widely, given their poor health, which may have meant a slower spread than first feared. But she still anticipates a steady encroachment, especially as infected patients from one long-term care facility are discharged from the hospital to another LTC residence.

Dr. Harrington has seen one bright piece from the pandemic transferring over to *Candida auris:* a public-academic lab partnership between the Chicago Department of Public Health and Rush University Medical Center, called the Regional Innovative Public Health Laboratory. It was launched to do typing for COVID-19, but it since has expanded its capabilities. “They have been a great partner with us to work with some of our strains here at Loyola, to help us get a better idea of what’s going on in our facility. It’s unfortunate it takes a pandemic to create that kind of opportunity.” She also recognizes that such efforts are an outgrowth of political will as well as medical need. In funding public health, “Every climate is unique.”

On the other hand, COVID-19 also delayed a fully attentive response to *Candida auris*, including at her institution. “It was impossible to focus on everything that was important. Hopefully *Candida auris* didn’t take advantage of us in that time.”

Labs that haven’t encountered their first case might also want to reconsider their current surveillance strategy, Dr. Harrington suggests. She suspects some may be underestimating the prevalence of *Candida auris.* Those with high-risk populations in particular might want to sharpen their scrutiny if they haven’t already.

“From time to time we rethink our strategy,” Dr. Harrington says, to ask if *Candida auris* might now be in a wider population. “Do we need to expand our efforts?” For now, prevalence in the high-risk groups has remained relatively low. “I don’t think we need that same type of strategy that we used to talk about when MRSA first came on the scene. *Candida auris* doesn’t seem to be there yet.

“But for places that think they don’t have it, I’m sometimes a little bit skeptical,” she continues. “Places that aren’t looking for it may have it and not know it until that clinical case pops up.”

She notes the difference between looking at samples from both a clinical and a surveillance point of view. When

her lab first began looking at urine and respiratory samples, *Candida* was not considered a primary pathogen. “We would just say ‘yeast isolate’ and leave that as part of the clinical report.

“But when we started asking, *Is this Candida auris—yes or no?*, we did start to find it,” she continues. “So for hospitals trying to put in an infection prevention strategy, that information is helpful. You need to know if it’s lurking in the background for when your respiratory therapists are contacting patients with equipment or other clinical procedures.”

“I would encourage any facility that thinks this isn’t a threat to be proactive,” Dr. Harrington says. “It’s not just a New York City or Chicago thing. Unfortunately, *Candida auris* is probably going to turn out to be an ‘everybody’ thing at some point,” she says.

Karen Titus is CAP TODAY *contributing editor and co-managing editor.*