Is *Candida auris* here to stay? An interview with Dimitrios Kontoyiannis

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“This is the first time a fungus has been implicated in nosocomial inter/intrahospital transmission”

In this exclusive interview, Dimitrios P Kontoyiannis discusses current mycology hot topic, *Candida auris*. With a focus on the current knowns and unknowns for the pathogenesis, resistance and transmission of this emerging fungal pathogen, in addition to a look at therapeutics and future perspectives. This interview was conducted by Ellen Colvin, Commissioning Editor of *Future Microbiology*.

Dimitrios P Kontoyiannis is the Texas 4000 distinguished endowed professor and deputy head in the Division of Internal Medicine at MD Anderson Cancer Center in Houston (TX, USA). Dr Kontoyiannis has authored over 550 peer-reviewed manuscripts and has given over 330 lectures in national and international conferences and academic institutions in the USA and abroad. He is considered a leading mycology expert world-wide with an H index of 101 and over 43,000 citations. His research group is credited for many and sustained contributions to clinical, translational and experimental mycology. He is the recipient of many national and international awards and is the past president elect of Immunocompromised Host Society (2016–2018).

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Your research is focused on *Candida auris*: a killer yeast that may be here to stay. Can you tell me about this & your research in this area?

This is one of the hottest topics in medical mycology over the last 5 years, as the *Candida auris* epidemic presents with many unique features. It is a multidrug-resistant *Candida* that rose spontaneously from several corners of the globe without any warning. Its resistance nature and resilience in the hospital environment is not unlike that of carbapenemase-resistant bacteria such as *Clostridium difficile*, in how they create infection control nightmares. This is the first time a fungus has been implicated in nosocomial inter/intrahospital transmission. My career has focused on fungal pathogenesis and resistance as I have been fascinated with the emergence of this epidemic. Some of my recent experimental research involved developing a *Drosophila* model of infection for *C. auris* and testing different treatments on these. I have been also involved in work trying to find innovative solutions to impede or prevent biofilm formation by *C. auris*.

Why are there so many unknowns about colonization, origins & pathogenesis of *C. auris*?

At present, *C. auris* infection transmission and epidemiology is not fully understood, as there are no identified animal reservoirs. Currently, the observation is that arising infections have appeared simultaneously but with no link to environmental transmission; international travel has also been implicated in transmission. In hospitals, patients can be colonized with *C. auris* for months or even years and with no spontaneous decolonization, the pathogen persists in the environment and is extremely difficult to eliminate. The recommended decolonization procedures are similar to those for *C. difficile*. It is unheard of to have a bacteria-like hardiness in a *Candida* species. Usually, patients get *Candida* infections from translocation of *Candida* through the gut, the mouth or from catheters, but it

has never been described that a *Candida* species can be transmitted from patient to patient or from a thermometer to a patient, this is a bacterial-like feature. As a multidrug-resistant *Candida* with limited patient therapeutics or environmental decontamination options, in addition to many unknowns about its pathogenesis and resistance, *C. auris* creates the perfect storm for epidemic challenges and that is the worry.

What needs to be done to improve diagnosis & clinical identification? Why is this important?

Accurate and rapid diagnosis for *C. auris* is one of the major unmet needs for curbing this epidemic. The species is very rare and thus, routine clinical microbiology labs are not well equipped to recognize this as a causative agent. The morphological and biochemical identification is complex and can often lead to the *Candida* species being misidentified. The most promising way to identify is through MALDI-TOF mass spectrometry-based recognition. There has been a lot of work with molecular PCR-based techniques in the blood or T2 nanoparticles type identification but at this point, the major issue is the lack of infrastructure and enough resources for identification in a routine clinical microbiology laboratory. Furthermore, it is unclear when, who, or how persons should be screened for this pathogen. The recommendation, in general, is to look for this if there is known invasive *C. auris* infection cases in the hospital, or if there is a patient with candidiasis from a country of endemicity like India, Pakistan or Kenya, for example, where they may have been exposed to the local healthcare environment, previously. Routine screening for all is not recommended, but it is not known yet whether you can have community transmission, for example, someone who came from a foreign endemic country and was not themselves hospitalized locally. Whether this identification can be introduced with point-of-care testing identification in a local lab or in specialized labs, with rapid turnover, remains to be seen. For now, we can fill the gap with MALDI-TOF.

What current treatments are available? What are the most promising drugs being developed?

This pathogen can often be multidrug-resistant to several commonly used antifungals. Luckily, resistance to all classes of antifungals only applies to a small minority of *C. auris* isolates – no more than 5%. Importantly, resistance to azole drugs is common – the most frequently used drugs to treat candidiasis – and resistance to Amphotericin B is not uncommon. Of the modern antifungals, the most reliable seem to be the echinocandins. The Centers for Disease Control and Prevention, and many other authorities, recommend an echinocandin-based approach to therapy with subsequent use of *in vitro* suitability data to decide if a switch therapy or step-down therapy, e.g. to an oral azole, is necessary.

Novel drug development and testing is ongoing with promising activity seen for APX001, SCY078, and the long-acting echinocandin called Rezafungin. Other innovative combinations have also been tested such as Amphotericin B combined with flucytosine (5FC) or voriconazole with TMP/SMX. Currently, these are only at *in vitro* stages or have experimental animal model data but are yet to undergo clinical trials. In the future, much more activity is anticipated for *C. auris* antifungal testing as there is already promising data at these early stages.

Why is *C. auris* resistance on the rise? Is there any way to combat this resistance?

One theory is that *C. auris* has been exploding due to indiscriminate use of antifungals. Epidemiological studies from India found that people with *C. auris* infection had previous heavy exposure to antifungals but the broad applicability of this observation for *C. auris* remains to be seen. In general, removing the antifungal selection pressure is a major determinant in our effort to combat fungal resistance. This is not only iatrogenic antifungal usage but is also for antifungal use in agriculture. However, there have not been any specific studies linking the curbing of antifungal use with *C. auris* abundance. If anything, the most important thing to do, in my opinion, to combat the rise of *C. auris* is to have impeccable infection control practices with high adherence to highly effective therapeutics, contact isolation, and effective decontamination measures.

What research are you hoping to do next? What do you hope to see?

We do not know with this epidemic, like with other fungal epidemics, whether it will take its peak and die away or persist, like *C. difficile* in modern hospitals, or whether this infection will be a widespread threat or if it will set its foothold in niche environments. At this point, there are many unknowns, but I remain relatively optimistic as the threat has been recognized by the medical community and there is a lot of public awareness. The Centers for Disease Control and Prevention is extremely involved, and has been a big protagonist for trying to curb the epidemic, which is great, as it increases available resources not only just to the USA but, with guided strategies, throughout the world. People are working very hard to develop new disinfection strategies and formulations in

hopes of decontamination from hospitals. Furthermore, novel drugs in clinical development appear promising. All these factors make me cautiously optimistic that although the epidemic will still be present, it may not turn into a pandemic and will hopefully be controlled. There have been some other near-global epidemics from fungi that have recently become geographically confined such as the Australian *Cryptococcus gattii*. I do not foresee a vaccine or any unconventional therapies such as immunotherapies for *C. auris*. The most fascinating and important part of this epidemic for me is the question of how this fungus seemingly came from out of the blue. Many theories exist such as global warming 'waking up' a dormant fungus, increased virulence from fungicidal use, or spread from migratory birds/international travel, in addition to the inherent complexity of the medical system. This is an epiphenomenon of the world in which we live, from climate to interconnectedness to healthcare systems. This is what makes this interesting for everybody.

Overall, I think that mycology is often an afterthought in the infectious diseases field and, if anything, this is a prominent reminder that fungi are here to stay and that they are evolutionarily agile with amazing genetic plasticity. They are not to be forgotten.

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