PIONEERING DIAGNOSTICS

EXCLUSIVE

LEARNING LOUNGE EXCLUSIVE : CLINICAL MYCOLOGY & ANTIMICROBIAL RESISTANCE

Viewpoints Series: **Kristen Smith, PhD, D(ABMM)**
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Fungal infections contribute to global Antimicrobial Resistance (AMR), yet they are historically underrepresented compared to viral and bacterial infections. Fungal species have shown the same ability to spread across the world, and recent studies have shown an increase in species (such as Candida auris) that carry natural immunity to well-established antimicrobial treatments. Additionally, there is a significant lack of trained clinical mycologists – individuals who study fungal species – in the laboratory setting, and the manual detection of fungal species can be a time-intensive and lengthy process.

Kristen Smith, PhD, D(ABMM) is a Senior Medical Science Liaison at bioMérieux and recently presented an overview of clinical mycology – the study of fungi – to the American Society for Clinical Laboratory Science in Butte, Montana. We at bioMérieux followed up with Dr. Smith to hear her perspective on the specific challenges that fungal infections pose in the clinical setting, the current threat of antimicrobial resistant fungal species, and to ask her advice on how diagnostics can be a game changer to help slow the spread of AMR in fungal infections.

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bioMérieux: In October 2022, the World Health Organization released the first Fungal Priority Pathogens List (FPPL) that stated, "Despite posing a growing threat to human health, fungal infections receive very little attention and resources globally.[1]" Why do you think fungal infections are not talked about nearly as much as bacterial and viral infections within the context of antimicrobial resistance?

Dr. Smith: Prevalence is likely the explanation for fungal pathogens being left out of the discussion. Most individuals will get at least one respiratory infection a year and have been on an antibiotic at least once in their life. Fungal infections are more opportunistic, meaning that most healthy individuals do not become sick with these organisms. The exceptions to this would be hair, skin, and nail infections (dermatomycoses) and common yeast infections (thrush and vaginal candidiasis). I would also take this question farther and say that there is much to be done in the form of education surrounding antimicrobial resistance overall, and not limited to just fungal infections.

bioMérieux: The WHO FPPL goes on to note that there is a "paucity of quality data on fungal disease distribution and antifungal resistance patterns. Consequently, it is impossible to estimate their exact burden.[1]" One report estimates that fungal infections cause over 1.7 million global deaths per year.[2] How can we get a better understanding of what the true burden actually is?

Dr. Smith: The first step to knowing the burden of disease is to track it, keeping in mind that microbes don't recognize state lines or country borders. There need to be uniform reporting requirements for pathogens of interest at the national level. While this exists currently for some select agents and other pathogens of high public health consideration, such as *Mycobacterium tuberculosis*, I believe we have the technological resources available to do this on a much larger scale. Excellent tools have been developed for epidemiology, or near real-time prevalence of pathogens, as well as for antibiograms. These types of charts allow pharmacists and clinicians to know the typical resistance patterns for common pathogens seen locally.

Data analytics is a fascinating subject matter to me and is something that can be harnessed to better understand what infectious etiologies are present in our communities. Tools like this are being developed in high-income countries and could eventually be deployed across the world. Only then will we have a more accurate depiction of what the burden of fungal infections truly is globally.

bioMérieux: In your recent presentation to the ASCLS-MT, you noted that there is a growing need for trained clinical laboratorians specializing in mycology. Given the rising burden that fungal pathogens cause on a global scale, how concerning is the lack of trained professionals to you?

Dr. Smith: The staffing of microbiology laboratories, and particularly those with responsibilities covering the more esoteric sub-disciplines (mycology, mycobacteriology, parasitology), is of great concern to me. In my previous role as a clinical microbiology technical director, I came to fully appreciate the challenges associated with training and retaining laboratory staff in these areas. Working with these kinds of organisms requires an extra level of care across several factors ranging from how the cultures are handled pre-analytically, set-up for culture in the lab, or worked up by the staff since they can present biosafety risks.

Mycology in the clinical laboratory is still very manual and training a clinical mycologist is not a fast process. The lack of diagnostics to support culture-based mycology means that we rely on the experience of our technical team to identify clinically relevant yeasts and molds. The increase in immune-suppressed individuals in our population as well as the changing environmental conditions will likely result in more fungal infections. The lack of trained professionals should be a concern for us all.

bioMérieux: What are the greatest challenges that healthcare professionals face when diagnosing and treating fungal infections?

Dr. Smith: The biggest challenge for our clinicians is time. Even if they suspect that they have a fungal infection, it could take weeks to months to get a positive culture and identification. The next challenge would be sample collection. We are covered in normal flora – bacteria and fungi that do not make us sick. These organisms can contaminate our cultures and overgrow or outcompete the pathogens that may be causing an infection. This is particularly problematic for skin and respiratory samples. For invasive fungal infections in tissue, the challenge is quantity. A swab is rarely going to provide a sufficient specimen for culture, so surgical tissue is oftentimes necessary. Antibody and antigen detection assays are also available and can provide a shorter time to result, however, these assays can be inaccessible to many labs and they can also suffer from a lack of sensitivity and specificity depending on the assay.

Treatment is also a major challenge for several reasons. The literature is lacking on the management of fungal infections. Antifungals can cause toxicity, and until recently, the pipeline for new antifungal therapeutics was dry. Difficult growth requirements were mentioned earlier, which can also impact susceptibility testing. Many laboratories do not have the expertise to perform this kind of testing in-house. There are also limited organism/antifungal breakpoints established, so there are not clear directives on what will be an effective therapy. And to add the proverbial cherry on top, many fungi can exhibit intrinsic resistance, including some multidrug-resistant organisms (MDRO) as is the case with *Candida glabrata, Candida auris*, and *Aspergillus fumigatus*.

bioMérieux: What are the unique challenges associated with the detection and diagnosis of fungal species, compared to bacteria or viruses, for example?

Dr. Smith: Viral and bacterial detection have both benefitted from progress in diagnostic testing. The introduction of polymerase chain reaction (PCR) into the clinical virology space was rapidly adopted for testing direct from specimen and is now a complete replacement to viral culture in many laboratories. There are also many assays that can rapidly detect bacteria from specimen or from an isolated colony utilizing matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS). In contrast, fungi were later additions to MALDI databases and are still not as well represented as bacteria. In contrast, there are very few tests that detect fungi direct from specimen and they are mainly geared towards candidemia. The time is now to grow our fungal diagnostic portfolios!

bioMérieux: *Candida auris* is one particular fungus that was first reported in Japan in 2009, but has seen a dramatic rise in cases across the globe and that the CDC states "presents a serious global health threat." What is particularly concerning about this fungal species and its cases? What other trends among fungal species are particularly concerning to antimicrobial resistance?

Dr. Smith: The Annals of Internal Medicine just released an article by Meghan Lyman, MD and her colleagues at the CDC (*Worsening spread of Candida auris in the United States*, 2019 to 2021) that highlights the most concerning aspects regarding *C. auris*. The first is that it is spreading in the United States, with a significant uptick that started in the early months of the COVID-19 pandemic. The other is that the rate of antimicrobial resistance to azoles, a first line therapy to many fungal infections, is approaching 90%. Additional drug resistance can be seen against Amphotericin B (~25%) and the Echinocandins (1.2%).[3] The low percent of resistance to Echinocandins should still illicit concern. The rate tripled in a 3-year period and there is evidence to show that this increase in resistance was acquired by patients during treatment with this therapy. The reality is that we are seeing pan-resistant isolates in increasing numbers.

Increasing azole resistance is not limited to *C. auris*, it is also observed in other clinically relevant Candida species such as *C. albicans* and *C. glabrata*. *C. glabrata* is showing the ability to gain resistance to Echinocandins, making multidrug resistance in this organism a concerning trend. Molds can also develop resistance during antimicrobial treatment. The example of this would be *A. fumigatus*. This organism is highly prevalent in the environment, and it is therefore understandable that it is a well-known cause of respiratory infections in immunocompromised populations.

bioMérieux: The WHO FPPL also states, "diagnostic capacity underpins antibiotic and antifungal stewardship. Accurate diagnoses promote the rational use of antifungal agents and reduce unnecessary empiric antimicrobial use."[1] What diagnostic tools can assist laboratory and healthcare teams in combating drug-resistant fungal pathogens?

Dr. Smith: The first step in combating fungal pathogens would be knowing what organism(s) you are up against. I believe the inclusion of yeasts and molds in MALDI databases was a great first step. Additional focus should be placed on growing the reference databases with a broader range of isolates. Syndromic testing could be expanded to include more fungal pathogens or for standalone fungal panels, helping decrease the time to diagnosis. New tools are also needed so that the clinical mycology labs of the future have less reliance on manual methods for fungal identification. More research is needed to characterize the genes important in antifungal resistance so that these too could be included on nucleic acid based panels, similar to what has been done for mecA and the carbapenemases. This could open the door for whole genome sequencing to be utilized for faster insight into treatment options, similar to what was accomplished for *M. tuberculosis*.

bioMérieux: How can healthcare professionals and laboratorians work to support antimicrobial stewardship initiatives, including combating the growing threat of drug-resistant fungal species?

Dr. Smith: Together, laboratorians, pharmacists, and clinicians are an integrated team to support not only antimicrobial stewardship initiatives, but also diagnostic stewardship goals. In order to assess the fungal burden of disease in our hospitals and communities more studies focused on fungal infections and heightened awareness of drug-resistant fungal species are needed, including increased financial support to create diagnostics that can more rapidly identify fungal pathogens.

Education is a key to success. We need to ensure that all clinicians are familiar with the most common fungal infections for their patient population and what specimens are needed to test for those organisms. Laboratorians should keep their teams knowledgeable on any new and emerging pathogens, as well as new technologies available for fungal diagnoses. Finally, healthcare leadership teams should financially support these efforts and advocate at regional and national levels for more fungal awareness.

Stewardship can begin when infectious etiologies are identified in the course of an illness. Without laboratory tests, the clinicians are just guessing. To improve patient care, diagnostics need to be timely and accurate so that targeted antibiotic therapy can be administered as soon as possible. Most empiric therapies do not include antifungal agents, which is why 'better' diagnostics should allow clinicians to determine if they are treating a virus, bacteria, or fungi. Targeted therapy minimizes the likelihood of AMR to the strongest drugs in our antimicrobial toolkit and slows the spread of AMR.

bioMérieux: Three key priorities for action are highlighted in the WHO FPPL, the first of which is surveillance.[1] What role can surveillance play in helping to properly diagnose fungal conditions and control AMR among fungal species?

Dr. Smith: Surveillance is key to understanding what organisms are prevalent in any given area. With this information, informed clinicians can more readily narrow the list of pathogens on their differential and initiate targeted therapy faster. Just like bacteria, antimicrobial therapy that is too broad can lead to resistance. It is also helpful to have an antibiogram or resistance profile for common organism and therapy combinations. With that knowledge, clinicians can more confidently start empiric therapy. This can help ensure that the patient is on the most appropriate therapy for the shortest amount of time, since fungal cultures and susceptibility testing can take weeks or months.

bioMérieux: How great is the need for larger amounts of data on fungal species and collaborative surveillance efforts to combat infections and growing resistance? How could having greater access to this data on resistance patterns benefit healthcare teams at both a patient and population level?

Dr. Smith: Data needs to be a driving force of stewardship efforts globally. As life expectancies increase, and there are more individuals living in an immunocompromised state, fungal infections will become more common. It remains to be seen what impact global climate changes may have, but it seems likely that this will also contribute to an increase in fungal infection cases.

Medical records are a treasure trove of useable population data with significant public health implications. De-identified (HIPAA-compliant) data can be pulled from electronic medical records into a surveillance software tool capable of generating local or regional maps of circulating pathogens, including their susceptibility profiles (antibiograms). The time for data generation and analysis is now so that we can be well prepared to combat fungal infections in the future.

bioMérieux: How do you believe increased use of diagnostics, monitoring of antimicrobial susceptibility trend data, and departmental collaboration on antimicrobial stewardship efforts can help combat the growing public health crisis that fungal pathogens present?

Dr. Smith: Diagnostics and data analytics are critical to understanding what fungal pathogens are present in a given location and monitoring how they change over time. By knowing what is typical, we are better able to detect emerging pathogens such as *C. auris*. Awareness of susceptibility patterns is also very important so that we can detect trends like increasing Echinocandin resistance and institute appropriate infection prevention methods to limit the spread of these organisms locally. Laboratorians, pharmacists, and clinicians must work together to develop successful antimicrobial stewardship programs to help ensure that we have effective antimicrobial therapy for years to come.

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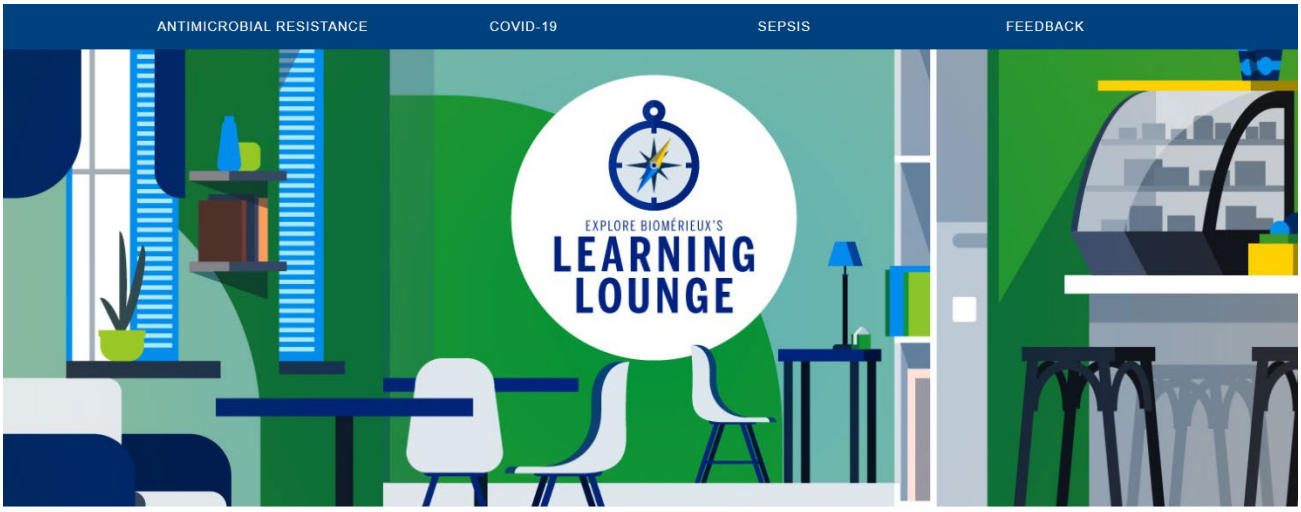

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