Facing the Challenges of Invasive Fungal Infections: Clinical Updates & Best Practices

Faculty:
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Digital Guidebook

Jointly provided by ProCE, Inc. and the Society of Infectious Diseases Pharmacists (SIDP), and supported by an educational grant from Astellas Scientific and Medical Affairs, Inc.
Invasive fungal infections (IFIs) are life-threatening conditions that require an astute diagnosis and management to mitigate the high associated morbidity and mortality risks. IFIs are also associated with a high economic burden, owing to prolonged hospitalization, the need for intensive supportive care, and the use of costly new antifungal agents. Opportunistic IFIs occur predominantly in immunocompromised patients, and the incidence of these infections is on a steady increase, as more and more patients undergo surgical procedures, transplantation, or cancer treatment and are receiving immunosuppressive therapies. Several classes of antifungal agents can be used to treat these invasive infections, but some fungi have developed resistance and no longer respond to standard antifungals intended to eradicate them.

New therapies offer the potential to improve outcomes for patients with IFIs, but early diagnosis remains a critical component in the effective management of these deadly infections. Clinicians should be aggressive in seeking a diagnosis in patients who are suspected of having an IFI, and the use of available diagnostic tools can improve rates of detection.

As medication experts, pharmacists in health-system settings need to assess antifungal use as part of their antimicrobial stewardship programs. This enduring webcast presents the proceedings from a live satellite symposium held at the 2016 ASHP Midyear meeting in Las Vegas, NV. Faculty will review emerging data and strategies on the diagnosis and pharmacologic management of IFIs, and will use case examples to demonstrate the clinical application of these principles.

**Learning Objectives**

The target audience for this activity includes pharmacists and infectious-disease pharmacists in health-system settings. At the completion of this activity, the participant will be able to:

- Outline the benefits and limitations of available tools for early diagnosis of invasive fungal infections to select appropriate diagnostic methods.
- Design guideline-based management strategies for invasive fungal infections, particularly for immunocompromised and immunosuppressed patients, including appropriate prophylactic and empiric treatments.
- Identify the risk and benefits of new therapies for invasive fungal infections to incorporate them into safe and effective treatment plans.
- Discuss the role of susceptibility testing and therapeutic drug monitoring in ensuring efficacy and safety of antifungal treatments.

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This CE activity is jointly provided by ProCE, Inc. and the Society of Infectious Diseases Pharmacists.
About the Faculty

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Dr. Douglas Slain is a Professor and Infectious Diseases Clinical Specialist at West Virginia University. He received his B.S. Pharmacy degree and his Pharm.D. degree from Duquesne University in Pittsburgh. He completed a residency and fellowship in Infectious Diseases Pharmacotherapy at the Medical College of Virginia (Virginia Commonwealth University) in Richmond. Dr. Slain has the distinction of being a Board Certified Pharmacotherapy Specialist (BCPS) with added qualifications in Infectious Diseases. Additionally, Dr. Slain was selected as “Clinician of the Year” by the Society of Infectious Diseases Pharmacists in 2007. Dr. Slain’s clinical practice sites at WVU include the Infectious Diseases Consult Service and the outpatient Infectious Diseases clinic.

Melissa Johnson, PharmD, MHS, AAHIVP

Melissa Johnson, PharmD, MHS, AAHIVP is a Liaison Clinical Pharmacist for Duke Antimicrobial Stewardship Outreach Network (DASON) and Associate Professor of Medicine in the Division of Infectious Diseases & International Health at Duke University Medical Center in Durham, North Carolina. Dr. Johnson received a B.S. in Biochemistry from University of Georgia, a Doctor of Pharmacy degree from Campbell University, and a Masters in Health Science in the Clinical Research Training Program from Duke University School of Medicine. Following a fellowship in Infectious Diseases Pharmacotherapy at Duke University Medical Center, she joined the faculty in the Division of Infectious Diseases & International Health. Dr. Johnson has served as investigator for numerous clinical trials with antifungal, antiretroviral, and antibacterial agents. Her clinical research interests include invasive fungal infections in immunocompromised hosts with special focus on immunogenetics, pharmacogenetics, and pharmacodynamics. She was the recipient of a 5-year NIH/NIAID Mentored Career Award to pursue patient-oriented research in invasive candidiasis, and was co-investigator on an NIH program grant to investigate microfluidic methods of detection for infectious pathogens including Candida spp. She rounds on the Transplant Infectious Diseases Consult service at Duke University Hospital, and precepts PGY2 residents on this rotation. She has been a member of the Duke Antimicrobial Stewardship Evaluation Team since 1997. In 2015, Dr. Johnson joined DASON to expand involvement in stewardship efforts as a Liaison Clinical Pharmacist in a network of community hospitals in the Southeastern United States. Dr. Johnson serves as a scientific reviewer for numerous journals, and is Associate Editor of Infectious Diseases for “Frontiers In” journals. She has been an invited international and national speaker on topics such as antibiotic resistance, HIV, invasive fungal infections, and management of bacterial infections. She is an active member of the American College of Clinical Pharmacy, American Society of Microbiology, and Society of Infectious Disease Pharmacists.

Ryan Shields, PharmD, MS

Ryan Shields, PharmD is an Assistant Professor in the Departments of Medicine and Clinical and Translation Research at the University of Pittsburgh. He is also a clinical pharmacist in the Division of Infectious Diseases at the University of Pittsburgh Medical Center, where he provides patient care through the Transplant Infectious Diseases service, and the Antibiotic Management Program. Dr. Shields’ NIH-funded research focuses on antimicrobial drug resistance, including antifungal drug resistance among Candida species. His work in this field addresses the use of molecular markers of antifungal resistance to improve patient outcomes.

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We’re going to begin with an audience response question. The first question is: Which Candida species is responsible for significant increases in antifungal resistance within this past decade? You can see there are four species listed there. We have responses all over the place here, which is always good for discussion. That means that we have a lot we can add. So, the correct answer is actually Candida glabrata. And what we’re going to find out is that it’s not just one class of drugs that we’re seeing increased resistance in over this past decade.

One more question: Which antifungal class has the greatest increase in hospital inpatient use during the past decade? Think about the past ten years. Which of these classes has the greatest increase? The correct answer, most of you got: echinocandins. And I’ll show you some data that come from the CDC.

This is a slide that shows you what the most common invasive fungal infections are that we see, largely in hospitalized patients. It shows you some amount of incidence based on these life-threatening infections per year. You can also see mortality rates in the infected population. You can see that the mortality rates have great variance. Some of them get very high. Remember, though, that these are not attributable mortality, but these are all-cause mortality rates that are reported here. So, there is some variance. Obviously, the ones that have the greatest mortality tend to be the molds, like Aspergillus and mucormycosis. But in terms of commonality, Candida is by far the most common, or it’s the most common that we see; but in terms of life-threatening infections, Cryptococcus actually has quite a bit.
Now, depending on the types of services that you offer at your hospital, the types of fungal infections that you’re going to see are going to vary. This is some data collected from the PATH system, the PATH Alliance, which is a network of hospitals. And you can see what the variability is between having invasive candidiasis, invasive aspergillosis, mucormycosis, and Cryptococcus. And it’s quite different depending on the types of services that you’re seeing. Most hospitals obviously have surgery, so you tend to see more Candida than you see of the others. Also, in medicine you see a lot more Candida. It’s really when you get into the more immunocompromised hosts where you start to see some of the mold infections. And if you’re dealing with a significant population of HIV patients, that’s where you’re going to see a greater percentage of cryptococcal infections.

You’ve probably heard the stat before, but Candida is often referred to as the fourth most common bloodstream isolate in a hospitalized patient. These are some data from what was the SCOPE database, and this one is from their report in 2004. But others tend to think that the rate of Candida bloodstream infections is still probably about this, where it falls into about the fourth most common. You can also see they’re reporting the mortality rates, and compared to some of these other organisms that we think of being very virulent, Candida can have a rather high mortality rate. But again, I will tell you that this is not necessarily attributable rates of mortality, but people can have mortality based on their underlying disease states.
In terms of what species we see, this is the breakdown from 2004 to 2008, from a series of hospitals throughout North America. This has not changed that much overall, when you take all comers. Candida albicans is typically about 50% of the pie. It might flux a little bit. The next most common isolate, of course, is typically Candida glabrata. And we can often see things like parapsilosis and tropicalis.

The next two slides really emphasize the point about the importance of having appropriate antifungal therapy administered as early as possible in patients that have invasive fungal infections.

This is a study that was done that looks at association between hospital mortality in patients that ultimately are diagnosed with candidemia, showing when you diagnose it and start therapy. You can see that the quicker you start, you can actually have lower mortality. There have been several studies that have shown this.

This slide is by one of our colleagues, Kevin Garey, and his colleagues. You can see in this study, specifically with starting fluconazole in patients that had candidemia, when it was initiated on culture day versus day one, day two, day three, how the mortality difference is significant, based on when you started. Ryan will talk to us a little bit about some of the diagnostic tests that we have. And we really struggle now, because a lot of times it’s hard to find these isolates to get the drug therapy in there as quickly as possible.
This is a slide about some resistance issues that we’ve seen in recent years. The blue bar represents fluconazole resistance, the pink or red bar is echinocandins and the green bar is multidrug resistance. That mainly is talking about resistance to both these classes. For years, we always had some rate of fluconazole resistance in particular, and you can see that it’s remained pretty steady. You can also see that over recent years we’re seeing a little bit of an increase in echinocandins. Obviously, that’s going to increase our multi-drug resistance. There can be some differences within the azole class, and we’ll have some discussion about that.

This is a slide that comes from another network, and this is actually put together by the CDC. Now, I want to show that the “X” axis here is not time. It looks almost like it’s over time and something is increasing. This is from a network of hospitals that generated a certain number of positive bloodstream isolates for Candida, and it’s just showing you the rate of Candida glabrata that they see, and the rate of drug resistance or nonsusceptibility, specifically to echinocandins. You can see, in a network of hospitals that submitted their data and had to have 20 good isolates of Candida glabrata, the rates are a little bit all over the board. That reflects the mix of the hospital. But you can see where it has gotten even as high as 25% and 28%.
You’re probably familiar with some of the data here. This is just a nice pie chart published in an article in the *New England Journal of Medicine*. You can see that the impact of antifungal prophylaxis can actually explain why you ultimately might see different species of *Candida*. Because we know that the use of antifungals, based on duration and also sometimes on dose, could even select certain *Candida* species that we might see. And here you can see that, if there’s no antifungal prophylaxis, you can use that to compare if prophylaxis was short-term, less than seven days or greater than seven days, and it can cause differences.

Specifically, some people will use fluconazole and maybe some other azoles, for antifungal prophylaxis or preemptive therapy; or they can even use echinocandins. And this is just a display to show you how the impact of the different preemptive agent might change the species that you might ultimately see. We know that a lot of use of fluconazole, for example, will increase things like your percentage of *Candida krusei*, *glabrata*, and even *tropicalis* in some reports. Now, caspofungin, which typically you’ll see higher MICs to parapsilosis – you can see where the parapsilosis distribution is a little higher in the patients that would have received caspofungin.

Very briefly, these are the species of *Aspergillus* that we see in our hospitals. Obviously, *A. fumigatus* is the most common.
And there hasn’t been a lot on drug resistance here, but this was a nice report. This actually comes from England—the UK. Also, some of the isolates that were submitted to this came from the Netherlands. In this study, over the years, they looked at the rate of resistance to azoles in aspergillosis. So, this was a reference lab. And you can see there was an increase over time. They specifically looked at itraconazole, voriconazole and posaconazole, because those were the agents that were available. So, there seems to be some increase that has been reported, and this was just one of many studies that are indicating that. Of course, the rates are still not very high, but the concern is that they’re increasing.

The last thing I want to point out is that now we do have some drugs that are available for some mucormycosis indications. It turns out that actually Mucor is one of the nastiest fungal diseases that we see, and there has been some increase reported in the literature with mucormycosis. Some of this may also reflect diagnostics and factors like the increased use of steroids.

The last slide I’m going to show before we get to our next speaker is from the CDC, in which they collected some data looking at antifungal use in US hospitals over the past several years. You can see this is the answer to our one question. The class that has consistently shown an increase over that time has been the echinocandins. There was a time we were using a lot more azoles. We were using more azoles in our critical care units, and I think we’ve trimmed some of that back. Especially, moving forward with the new guidelines from the IDSA, we may even continue to see certain azoles decrease in that Candida setting.
So, that’s all I have. And at this point I’d like to welcome our next speaker, Dr. Ryan Shields, so please join me in welcoming him.

We’re going to get started and the topic of this presentation is “Diagnostic Testing - The Need for Speed.” We’re going to start this session with another audience response question. This questions asks: In what percentage of blood cultures do they remain negative despite patients actually having invasive candidiasis? So, blood cultures remain negative in approximately what percent of invasive candidiasis cases?

The correct answer is actually 50%, which may surprise some people. So, up to 50% of patients with invasive candidiasis actually have blood culture-negative disease, and we’ll talk about some of the reasons why that is.

I want to kick off where Dr. Slain left off. And really, what I’m going to talk about, and what we’re going to focus on for the rest of the presentation today, is three of the more common causes of invasive fungal infections. Those are Candida, Aspergillus and Mucor.
Aspergillosis and mucormycosis, of course, are mold infections and have different clinical manifestations. These are typically opportunistic fungal pathogens that affect immunosuppressed patients, specifically patients with hematologic malignancies or those undergoing bone marrow transplantation or other types of solid-organ transplant. For aspergillosis, we predominantly see pulmonary disease, so pulmonary aspergillosis.

Aspergillosis and mucormycosis, of course, are mold infections and have different clinical manifestations. These are typically opportunistic fungal pathogens that affect immunosuppressed patients, specifically patients with hematologic malignancies or those undergoing bone marrow transplantation or other types of solid-organ transplant. For aspergillosis, we predominantly see pulmonary disease, so pulmonary aspergillosis.

We can also see tracheobronchitis and, more rarely, rhinosinusitis, and the symptoms are consistent with diseases we see. Typically, patients have fevers, pleuritic chest pain, hemoptysis, shortness of breath and cough, and the first three symptoms there are kind of the classic triad for identifying invasive candidiasis, particularly among neutropenic patients. The difference with Mucor is that this causes more rhino-orbital disease, particularly in the sinuses, although it can cause pulmonary disease as well; and the symptoms are, again, consistent with that. We see nasal ulcersations, periorbital swelling, decreased vision and headaches.

Despite the differences in these three diseases, in diagnosing them there are three really important points that bridge these diseases together. Point number one is that routine cultures are fairly insensitive for diagnosing all of these diseases. You see the percentages listed across there, but in general, our routine cultures that we’re sending for our patients to the microbiology lab only pick up about 50% of these invasive fungal infections. So, number one: routine cultures are insensitive.

Number two: routine cultures take time. This time results in a delay in treatment. The typical time to culture positivity is a number of days—two to three days for candidiasis, and longer for the mold infections. And we know that if cultures do turn positive, they typically turn positive late in the disease course, and that has a direct correlation then for delayed treatment.
The other thing that we see, and point number three, is that we know for all of these invasive fungal infections, delayed treatment is associated with worse patient outcomes. Are there, then, opportunities that we as pharmacists have to help improve this delayed treatment and start antifungals sooner, and thereby improve patient outcomes? I think this is really an important avenue for pharmacists to be involved with.

We’ll start with invasive candidiasis. With this disease, it’s important to know what exactly we’re trying to diagnose. Invasive candidiasis really encompasses three entities. One is candidemia, which is a low-incidence disease among wide populations. This includes all hospitalized populations and predominantly our medical patients, and we see that the sensitivity of blood cultures for candidemia is about 60 to 80%. So, in patients that have true bloodstream infections the sensitivity for blood cultures is pretty good.

On the other end of the spectrum is deep-seated candidiasis, i.e., intra-abdominal candidiasis and other deep-seated diseases, which is typically a high-incidence disease among very narrow patient populations. So, these are your abdominal surgery patients that the surgeon goes in and tells you they find this nice abscess. And of course, they didn’t send it for culture, but we know a lot of these abscesses are consistent with Candida infections. In this case, blood cultures are much less sensitive, because we know that Candida from deep-seated sites only enters the bloodstream in a minority of cases, and that’s in the middle of the Venn diagram here, and that’s deep-seated candidiasis with candidemia. If you look cumulatively then, and this is the answer to our initial audience response question, we’re missing about 50% of the disease across the spectrum of invasive candidiasis.
Preemptive therapy is again using antifungals before the onset of signs and symptoms. That’s an important part that we’re going to talk about today—the idea of using non-culture-based diagnostic tests to find the right patient populations in which we can give them preemptive antifungals before the onset of signs and symptoms of the disease.

Empiric therapy is at the onset of signs and symptoms of disease. So, this would be your patient that has had fevers in the ICU for four days despite being on broad-spectrum antibiotics. Initiating early empiric antifungal therapy may help us get early antifungal therapy on board.

And then finally, targeted therapy is at the point where we have a positive culture and we’re initiating antifungal therapy in response to that positive culture. So, this is the highest amount of microbiologic evidence, but also you’re initiating antifungal therapy at a delayed point, after the organism’s already been identified.

This is a busy slide, but I want to give you a couple of takeaways for invasive candidiasis here. Because we know that the incidence of invasive candidiasis ranges very widely across patient populations, this is important for how we’re going to initiate early antifungal therapy. So, we know at the high end of the incidence, we have high-risk patients. These are liver transplant patients with bile leaks, for instance, or other abdominal surgery patients that have ongoing surgeries. Their incidence of invasive candidiasis at the beginning is somewhere between 20 to 40%.

And if you look across the literature, we know that when you have a patient population with an incidence of disease that exceeds 15%, prophylaxing them with antifungal therapy shows benefit. We use this benchmark as 15% of really where we want to initiate antifungal therapy, when we have an incidence of at least 15%. We know our high-risk patients meet that, and these are patients we’re typically going to use prophylactic strategies for.
On the other end of the spectrum, we have patients that are at risk for invasive candidiasis, but the incidence is so low. These are hospitalized patients with any blood culture that’s sent, or maybe your low-risk ICU patient, such as those in the cardiothoracic ICU, where the incidence of invasive candidiasis is so low that using early antifungal strategies and trying to identify those patients is tough, because you have to screen so many patients to find those one or two that might be at risk for the disease. But in the middle, there’s this sweet spot where the incidence of invasive candidiasis ranges from anywhere from 3 to 15%, and this is the place where empiric and preemptive antifungal strategies really might be important for our patients moving forward.

Let me show you how we’re going to incorporate some of these things. First, let’s talk about some of the tests that are available. These are the non-culture-based diagnostic options for Candida, the first of which is an antigen antibody detection method. This detects mannan antigens and anti-mannan antibodies. This is a test that’s been around for a long time, and meta-analyses data have shown us that the pooled sensitivity and specificity is about 85% for these tests, meaning that they are fairly good tests.

But there are some problems with antigen and antibody-mediated tests, first of which is, antigens are rapidly cleared from the blood. Mannan antigens—mannan is a part of the fungal Candida cell wall—is rapidly cleared from the blood, so it’s hard to detect early.

The other problem is that there are concerns with immunosuppression. If you have patients that are on immunosuppressive agents, they may not mount the same sort of antibody responses as an otherwise immune-competent host would. Because of that, there are very few prospective studies that have looked at mannan and anti-mannan detection methods, and those have shown a relatively lower specificity, so in general these tests aren’t used clinically all that commonly.

The second test we’ll talk about is detection of beta-D-glucan. Again, beta-D-glucan is a major constituent of the Candida cell wall, and this is an FDA-approved test as an adjunct to culture. Here, your pooled sensitivity is about 75%, but you see the specificity ranges widely. The reason there is the potential for false positive tests here. We know that certain gram-negative pathogens like Pseudomonas can elicit a false positive glucan assay, as well as human blood products like albumin or IVIG. And then, we know that glucans can be found in cellulose filters so, filters that are used in hemodialysis or other types of membranes also contain glucans. We know that these things can cause false positives. The other thing that is important about beta-D-glucan is it’s less sensitive for deep-seated candidiasis, which we know is a very important entity for invasive candidiasis overall.

The third test we’ll talk about for early diagnosis of Candida is a nucleic acid detection, or a PCR-based assay. This detects Candida DNA using PCR probes, and this can be used to initiate early...
antifungal therapy. It’s typically positive before blood cultures are, and it has persistently positive prognostic value, which we’ll talk about. The major problem with PCR assays is, despite having a very high sensitivity and specificity, there’s no standardization across these assays. There are a lot of mom-and-pop shops out there that have their PCR-based assays for Candida, but between them there’s no standardization. They all use different primers and different probes to detect Candida, and there are no FDA-approved PCR-based tests at this point. There are companies working on this, and hopefully in the future we can have some standard PCR-based assays, because you can see the sensitivity and specificity for these assays is really good.

Most recently, however, there’s a new technology that has entered this space for non-culture-based-type diagnostics, and that’s a magnetic resonance technology. T2Candida is the first company to incorporate this technology into their platform. This is also an FDA-approved assay that uses these nanoparticles coated with Candida-binding components that, in whole blood samples, bind Candida, and uses the same technology as MRIs to detect Candida at a very high sensitivity and specificity. Here, with this assay, we can get results from whole blood samples in four hours.

So, let’s compare that to what we’re doing with routine blood cultures for diagnosing candidemia, which typically turn positive about three or four days after we collect the blood culture; then it may take another day or two to identify the organism, and then potentially another day to do susceptibility testing. Here, you’re identifying the bug in four hours. So, it’s a huge opportunity to initiate antifungal therapy sooner. It also uses a multiplex PCR-based platform to identify the five major Candida species that Dr. Slain pointed out.

But there are limitations to this new technology. There are not a lot of clinical data yet, and we’re certainly not sure how to best incorporate this into clinical practice. Also, it hasn’t been studied for deep-seated candidiasis. The final limitation is that we wonder if some of these assays may become too sensitive. What do you do when your non-culture-based diagnostic test is positive but your blood culture is negative? Does that mean the patient really has a blood culture or a bloodstream infection? We don’t know the answers to some of these questions yet.

Let me pause there for a second and ask the audience a question. How many of you in your hospitals are using some of these non-culture-based diagnostic methods to detect Candida in your patients? By a show of hands, anybody out there? It looks like in the vast minority of patients.
So What’s the Problem?

- Improved technology
- Non-culture-based diagnostics are highly sensitive and specific
- Able to identify major Candida species
- FDA approved

So, what’s the problem? We certainly have an improved technology and a number of non-culture-based diagnostic assays that are now FDA-approved and that can even identify Candida to the species level. We have the technology and we have the test available. Why aren’t we all using them?

For your patients. We’ll talk next about what patients are likely to benefit.

So What’s the Problem?

- Tests are expensive
- Compared with suboptimal “gold standard”
- Takes time to redefine treatment approaches
- Which patients will benefit?

Well, one reason why is that these tests are expensive. It costs money to order tests—several hundreds of dollars in some cases—and we’re comparing them to a suboptimal gold standard. Remember, blood cultures are only sensitive for about picking up 50% of the disease. So, we don’t know the true burden of disease, because we’re comparing to a suboptimal gold standard. And we know with new technology it takes time to refine some of these approaches. I want to help you try to refine some of these approaches for your patients. We’ll talk next about what patients are likely to benefit.

Invasive Candidiasis Across Populations

I hope everyone’s had their coffee this morning, because we’re going to get nerdy here for just a minute; but bear with me, because I think these are really important data. So, if we take the same slide as before and we look at the incidence of invasive candidiasis in the same patient populations, look at the positive and negative predictive values of some of these non-culture-based diagnostics.

By positive predictive value, we mean if you have a positive non-culture-based diagnostic, a positive PCR assay, what’s the likelihood that that patient has true invasive candidiasis? And on the other hand, negative predictive value is, if your test is negative, what are the odds that the patient does not have invasive candidiasis?

So, we know in our highest-risk patients that already have a high incidence of disease, your positive test only helps you a little bit. It pushes your percentages up to give you some more
certainty, but it also doesn’t have a great negative predictive value. Meaning, if your test is negative, there’s still a high chance, maybe of 10 to 15%, that the patient truly has disease. So, for high-risk patients, these non-culture-based diagnostics may not be that beneficial. And if we use our cutoff that we talked about before as 15%, when we draw the positive predictive values here, we know that for our lowest-risk patients – again, they’re not hitting that threshold to initiate antifungal therapies of at least having a baseline incidence of 15%. So, we know that our lowest-risk patients may not benefit as well. But for these patients in the middle, where you see the positive predictive values now go from a baseline incidence of 3 to 15%, if you have a positive test, now these patients have a 21 to 60% chance of having disease, so that certainly helps you diagnostically.

But perhaps the best utility of these agents is to look at these negative predictive values here in this sweet spot that we talked about. Now you have a 98% to 99% certainty that your patient does not have the disease. This could be used to incorporate strategies to stop antifungal therapy, or at least to withhold antifungal therapy, in patients that you have a high degree of certainty do not have the disease. So, the negative predictive value here is extremely important.

Keeping with our nerdy theme for a second here, I want to point to an article that was published by Terry Fagan in the *New England Journal of Medicine*, where he used some Bayesian reasoning or Bayes’ Theorem to essentially establish this nomogram that says, if you know the pre-test likelihood of your patient having disease, you can use this formula using a likelihood ratio, and that and your non-culture-based diagnostic will give you some post-probability test of disease.

If we use an example of a patient that has a baseline incidence of 10% for invasive candidiasis, and we use a sensitivity and specificity of 90%, which we know is true for PCR if you have a positive test, we know that the likelihood ratio is 9, and that they have a 50% chance of having invasive candidiasis. And similarly, if you have a negative PCR assay, they have a very low incidence of having invasive candidiasis. So, if you can model some of this, you can see how these tests help you across patient populations.
Again, going with our example patient that has a baseline incidence of invasive candidiasis of 10%, in the absence of any of these culture diagnostics, they continue on this linear scale, where their pre-test and post-test likelihood of disease is the same. You know the baseline incidence, and that’s all you know. But if you have a positive assay, like a positive PCR that has a 90% sensitivity and specificity, what that assay tells you, then, if it’s positive, is that your patient now has a 50% probability of having disease; and if your assay is negative, they only have about a 1% chance of disease.

So, what these non-culture-based diagnostic tests really can do, then, is shift the paradigm, where if we use our threshold of 15% as our cutoff to initiate antifungal therapy in the absence of non-culture-based diagnostics, we’re really only initiating antifungal therapy in our highest-risk patients. But with non-culture-based diagnostics, what you can do is initiate early antifungal therapy in a much wider variety of patient populations, including patients with low to moderate risk of invasive candidiasis. So,

I want to transition into talking a little bit about diagnosing invasive aspergillosis. This is a moving target, right? Because we know for diagnosing invasive aspergillosis, some of the definitions are based on our degree of certainty that the patient has the disease—either possible, proven, or probable disease. Where I see non-culture-based diagnostics useful for Aspergillus is that it helps in our degree of certainty that the patient really has disease; but they have to be used in combination with all the other things we use to diagnose invasive aspergillosis. First of which is, you have to identify the right patients that have signs and symptoms of the disease. We use cultures, histopathology and radiographic imaging to help us as well.
Perhaps the most commonly-used culture aid, or non-culture-based diagnostic, is galactomannan, specifically, the galactomannan antigen detection. Galactomannan is another major constituent of the Aspergillus cell wall, and this is an FDA-approved test for both serum and BAL samples, and it’s measured on an optical density-based report, where a value greater than 0.5 is positive. Meta-analyses show galactomannan is fairly sensitive and specific, and this test really performs best in your hematologic malignancy and stem cell transplant patients. It’s less useful for non-neutropenic patients, specifically solid-organ transplant patients, and it’s unclear if that’s because the disease is different in these patients, or they just haven’t been studied to the same degree. It also has decreased sensitivity with the initiation of antifungals.

Now, galactomannan can also give you false positive results, which is very important. One of the things for years and years that has been talked about is the false positive results with piperacillin/tazobactam, and the formulation of that drug. That’s become less of an issue most recently. The manufacturer really hasn’t released why, but the formulation now does not appear to have cross-reactivity with galactomannan, so I see that as less problematic moving forward. Because of that, there are fewer false positive galactomannan results.

Your other option for diagnosing Aspergillus early is beta-glucan. Just like Candida, beta-glucan is also FDA-approved and has a positive value greater than 80, but it cannot distinguish between fungal species. So, if you have somebody with both Candida and aspergillosis, this assay will turn positive, but it’s not going to tell you which fungal pathogen you’re trying to diagnose.

There are also PCR-based assays for Aspergillus, which also are fairly sensitive and specific. We know that, with all these assays, if you have at least two positive results, that increases your specificity, and that’s certainly true for PCR as well. PCR, keep in mind, identifies DNA of the fungal pathogen, so it’s not going to tell you the difference between colonization versus infection. You’ll need some clinical insight to do that.

Finally, lateral flow devices are a relatively new player in this field. This is an inexpensive, rapid diagnostic test with no equipment required that detects a mannoprotein with monoclonal antibodies, and really can be used as a point-of-care test. These lateral flow devices can give you results in as quickly as ten minutes, and that’s particularly useful for even doing at the patient’s bedside from a BAL sample.
There’s been one study that’s looked at all these assays together and given us some indication of what’s the best assay for identifying aspergillosis in your patient. And what you can see from the slide here is that we know cultures are relatively poor—again, keeping consistent with our theme, 50% sensitivity—and you see that, individually, galactomannan, beta-D-glucan, PCR and lateral flow devices do okay. But you can have some benefit if you combine tests, and if you look specifically at the idea of having either a positive galactomannan or positive PCR, you now have 100% sensitivity and 98% specificity. So, perhaps using these tests in combination is a way forward for the field.

Here’s my take on the role of diagnostics for invasive aspergillosis—using the tests in combination improves sensitivity, particularly repeating the test. If you have a negative PCR, and you repeat that, having two negatives gives you almost 100% certainty that you do not have the disease.

There have been screening strategies proposed for both galactomannan and PCR, particularly among hematologic malignancy and stem cell transplant patients. I’m less in favor of this. I think the more you look for positive tests, the more you can find them. There’s a high probability that you find positive tests that you don’t know how to incorporate. To me, the usefulness of these tests is in the right patient populations where you have a high clinical suspicion of disease. This is where you should be using these tests. And the negative predictive value, just like Candida, is extremely useful. The negative predictive value here is so high it essentially excludes the possibility of disease, at least at that time point.
Briefly, then, my last slide on mucormycosis. Beta-D-glucan and galactomannan are not useful. These are not major parts of the Mucor cell wall. There have been PCR assays investigated that have shown promising results so far, but these things are a long way away from being primetime to this point.

In summary, what we can say is that we know delayed antifungal therapy is associated with worse patient outcomes, and routine cultures take time and are poorly sensitive. Because of that, non-culture-based diagnostic tests may help to improve approaches to early initiation of therapy. These are less commonly employed for invasive candidiasis but used fairly commonly for aspergillosis. But the key for all these things is that you have to identify the right patient populations for these tests to be useful.

With that, I thank you for your attention, and we’ll be happy to turn it over to my co-speaker today, Dr. Johnson. Thank you.

Now we’re going to turn our attention to talking about our approach to therapy, and choosing between the available antifungal agents for patients at risk of, or who are experiencing, an invasive fungal infection.
First, an audience response question: Which of these antifungals is NOT recommended as monotherapy for invasive pulmonary aspergillosis? And the correct answer is “C,” caspofungin. As we’ll discuss in a few moments, caspofungin has data in salvage therapy but not initial therapy, or at least not an FDA indication for initial therapy; and the other drugs listed here do have FDA indications as initial therapy for treatment of invasive pulmonary aspergillosis.

So, when thinking about our approach to these patients and how we manage them, we really do need to think about those risks. Both the prior speakers did cover a little bit of this, and we’ll talk about it a little bit later again in terms of how you approach empirical and prophylactic therapy for these patients. It largely depends on their risk. Are they more at risk for yeast? Are they more at risk for mold? Or, are they at risk for both? And we know that the transmission mechanisms for these are a little bit different. Yeasts are a commensal organism. They live in the gut and on the skin for Candida. And so things like vascular catheters that allow a portal entry, or mucositis, which disrupt the GI tract, allow yeast to get into the bloodstream and set up shop and cause infection. But, for molds, we know that they’re transmitted primarily by spores in the environment. So, environmental exposures are very important for these, as well as things like respiratory viral diseases, which affect the immune system locally in the lungs and allow then an environment in which the fungi can overgrow, and lead to infection.
Looking at the available systemic antifungal agents, we now have at least 13 different antifungal agents that are available for systemic administration in the United States. We’ve had sort of an explosion of antifungal development over the last 20 years. And the newest kids on the block here are isavuconazole as well as additional formulations of posaconazole. What I depicted here in green are also several new antifungal agents that are under development.

So, the pipeline is not yet dry, and this is still an area that is ripe for more research.

Looking at the available agents, they really do differ in terms of spectrum of activity and the clinical trials data that is used to support them. This is a summary slide where I show how these agents differ for each of the indications. And as you can see in green, that indicates where we have clinical trials as well as an FDA indication for use. And black just depicts where we have clinical trials data but no specific FDA indication. And we’ll use this as a roadmap as we talk about these individual uses throughout the talk. But clearly, there’s no one-size-fits-all approach to fungal infections in these patients.

Looking at the pharmacokinetics of the drugs, they do differ dramatically. In terms of oral bioavailability, we have limited oral bioavailability for both polyenes and echinocandins. However, I would mention that there are formulations of amphotericin B cochleates as well as an oral glucan synthase inhibitor that are under development and may change this landscape in the future.

So, what we are left with, in terms of orally-available agents right now, are the azoles. These generally have at least 90% bioavailability and are well-tolerated when given that way.

In terms of CSF penetration, we see dramatic differences as well. Fluconazole has the highest CSF penetration, while polyenes and echinocandins have very little. Despite this, polyenes seem...
to be effective in treating things like cryptococcal meningitis and CSF infections because they have other immunomodulatory effects that make them effective in those settings.

Urine continues to be a big challenge for these drugs as well. Fluconazole has the highest urinary excretion of all the antifungals here. We have much less urinary excretion for polyenes as well as echinocandins, and this creates a lot of challenges when dealing with it, because the urine can often be a source for many patients’ yeast infections.

Focusing in more on the azoles specifically, we can see that several of these agents, such as posaconazole and itraconazole, require acid for absorption. This has been an Achilles heel for some of these azoles, and the newer formulations of posaconazole are sort of designed to address this issue. We also have the issue of non-linear pharmacokinetics that really stands out for voriconazole, and this can wreak all kinds of havoc for you when you’re trying to dose and do therapeutic drug monitoring for voriconazole, because just a simple, small dose change can result in dramatic changes in concentration with this agent. And we’ll talk about that a little bit more after this section.

In addition, you can see that for isavuconazole, it differs a little bit in that it is both available IV and orally, has good absorption, and has linear pharmacokinetics. So, there are a few properties there that make it stand out, and may have more reliable PK and therapeutic drug type of levels.

Thinking more about the posaconazole and these new formulations, the delayed-release tablets really have changed how we can administer posaconazole in the clinical setting. This oral suspension had a saturable absorption process, which really made it difficult to get therapeutic drug concentrations in patients receiving this agent. The suspension is depicted here in green. As you can see, when administered to patients, only less than half could receive target concentrations with this oral suspension.

However, when switched to the delayed-release tablets, we can see that at least 70% of patients would achieve target concentrations for treatment of an invasive infection. The trough levels of the delayed release tablets, here in blue, are about twice that of the suspension formulation. And so, most centers have really switched over to using the delayed-release tablets, because you get much more reliable absorption.
In terms of food interactions, there are some with the azoles, and I’ve just listed this summary slide here for you as a guide when dosing these in the clinical setting. Some do require to be given with food and others without food, and some require fat for absorption. So, this is important to remember when optimizing PK and doses for your patients.

These drugs differ in terms of drug-drug interactions as well. Polyenes, because they don’t go through the P450 system for metabolism, really have limited drug interactions, primarily in the areas of overlapping toxicity, such as nephrotoxicity or electrolyte imbalances, and compatibility issues with other IV products. Echinocandins – with caspofungin, you may see that it’s reduced by P450 inducers such as rifampin. This is really a minor issue and can be managed often in the clinical setting. And then micafungin is a weak inhibitor of P450 3A4, and this can lead to some interactions with sirolimus and nifedipine, and those agents need to be monitored more closely when given with micafungin. Anidulafungin doesn’t really go through the P450 system, and isn’t limited by a chemical degradation problem, so anidulafungin does not have these interactions.
Interactions really come into play with theazole class. And as you can see here, I’ve delineated which P450 isoenzyme sites are the major problems for these different agents. Voriconazole is notorious for 3A4 as well as 2C9 and 2C19 interactions, because it is both a substrate and inhibitor at this isoenzyme site. Most of the azoles do have P450 3A4 interactions, whereas 2C19 and 2C9 are predominantly with voriconazole.

We’re also getting more information on these agents and how they interact with transporters such as P-glycoprotein (PgP). As you can see here, posaconazole as well as itraconazole have PgP interactions, and they are both substrates and inhibitors of PgP. We’re getting more information on this, and I think that we’ll see more data in the future about these types of transporter interactions. But isavuconazole does not appear to have significant interactions other than the P450 3A4 issues.

Looking at that a little bit more closely, if we’re comparing the newer azoles, voriconazole still has probably the most significant interactions with other immunosuppressants. Looking at sirolimus, it will increase it by 11-fold, and posaconazole also increases sirolimus levels to a similar degree. Isavuconazole has much less of an interaction here, increasing sirolimus by twofold, and tacrolimus or cyclosporine one to two times. So, these interactions are thought to be more manageable, and may be a differentiating feature for patients that require these agents to be given concomitantly.
Common Side Effects of Antifungals

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Other differentiating features:
- Long term toxicity, skin cancer, HCC
- QTc prolongation

In addition, the side effects really separate these drugs. Polyenes are notorious for their nephrotoxicity, electrolyte imbalances, and other renal or infusion-related reactions that you can have. With echinocandins, you can see some infusion-related reactions when they are administered rapidly, but echinocandins are generally very well-tolerated. Azoles, on the other hand generally, are generally well-tolerated. You may see some LFT elevations, particularly in patients with hepatic comorbidities like hepatitis C, for example, or other hepatotoxic agents on board. And voriconazole really stands out, because we see side effects such as skin effects, ocular effects, and central nervous system effects with this agent that are different than the other azoles and can sometimes make it challenging to manage.

Other differentiating features are some concerns about long-term toxicity with these agents. For those of you that are in transplant centers, or centers treating oncology patients, these patients might end up receiving an agent like voriconazole for two or three years, and there have been emerging concerns about genotoxicity of these agents that can lead to skin cancers as well as hepatocellular carcinomas. And so, there are some concerns about that, and we don’t know probably enough about some of the newer agents in regards to that long-term toxicity, but we will be monitoring that in the future.

QTc prolongation is another issue that often comes up. Voriconazole has been associated with that, as well as posaconazole. You can also see it with itraconazole. And interestingly, isavuconazole in the clinical trials was not shown to increase QTc interval in patients, and that may be another differentiating feature of that newer agent and might give particular advantage for some patients.

Comparative Clinical Trials: FDA Indications

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Looking closer, specifically at invasive candidiasis and how we treat these infections, and looking at the available agents, you can see that we have a lot of clinical trials data for several different antifungal agents. It may surprise you that fluconazole does not actually have an FDA indication for treatment of candidemia or invasive candidiasis. That was shocking to me when I started preparing for this talk, because we use it so frequently. I think that it’s just that the company never applied for it. They do have indications for esophageal candidiasis and other oropharyngeal diseases. And it is very effective in clinical trials if you have a susceptible strain. We’ll talk about that a little bit more in the future – how it’s positioned.
The IDSA guidelines, based on recent trials data comparing these different agents that all have data, have put echinocandins as the first-line recommended agents for treatment of invasive candidiasis and candidemia, primarily because there’s one study showing potentially a survival advantage; others showing general good efficacy, as well as excellent tolerability. And echinocandins do have activity against most of these potentially resistant strains that are sort of a problem with some of the azoles.

Alternatively, they state, if a patient is clinically stable or is not likely to have an azole-resistant strain, then they may receive fluconazole as an alternative. Fluconazole is also possible as a stepdown therapy, once you know that the patient has a susceptible isolate. Another alternative would be lipid formulations of amphotericin B, and these agents are certainly going to be effective, and they may be even good choices if you believe a patient has an azole-resistant strain of infection. It’s just the tolerability issues that lead them to be further down the list.

For neutropenic patients, the guidelines switch it up just slightly and put lipid formulations of amphotericin B above fluconazole on this list. And the reason for that is that most of these patients with neutropenia have received azoles in the past or they were receiving azole prophylaxis at the time they had a breakthrough candidemia, and therefore they don’t want to use fluconazole first-line until they’re sure that a patient has a susceptible strain.

Very importantly, the minimum duration of therapy for anybody with candidal bloodstream infections is at least two weeks after they clear the bloodstream. I cannot emphasize this point enough, that patients must receive follow-up blood cultures before you discharge them, ensuring that they’ve cleared this infection; that they don’t have some other ongoing source of infection. So, I really point that out, because that’s an area where I think pharmacists can really help and ensure that patients have documented clearance before they head out the door.
So, the IDSA has come up with a checklist of sorts that I’ve given you here, and other people have examined this sort of list as a bundle that you can look at to improve process measures for outcomes in patients with candidemia. So, on this list are the follow-up cultures that I mentioned; as well as the IDSA now recommends susceptibility testing for all patients with fungal infections of the yeast variety with Candida. This can be challenging, I think, in the community hospital setting. I spend a lot of time in community hospitals, and there is a delay often. You have to do a send-out; it comes back a week or two later; and by that time the patient’s already getting better and out the door. I think it’s important to get a sense of the species that are common in your institution, and perhaps on a batch basis look at this, or carefully monitor this in your setting to see if that’s appropriate. But due to the rates of resistance that we’ve seen, susceptibility testing can be important.

Other things that are important for these patients are a dilated ophthalmologic exam, removal of central venous catheters whenever possible, as well as evaluation, as I mentioned, of other sites of infection. Hepatosplenic candidiasis can linger and lurk in patients, and you might need to do imaging to evaluate that once neutrophils have recovered. And consider stepdown and overall duration of therapy based on the progress of the patient, and whether or not they clear this infection. But certainly, stewardship programs can have a huge role here in ensuring that patients meet these criteria and these procedures are performed appropriately before they leave the hospital.

This is some of the data that supports echinocandins as first-line options for IDSA. This was a meta-analysis performed by David Andes, and he looked at seven randomized controlled clinical trials for candidemia in almost 1,000 subjects and found that echinocandins were associated with a twofold increase in success. This was also correlated with a decrease in mortality and was significant for both albicans and non-albicans species. So, there seems to be something maybe with the cidal nature of echinocandins that allow them to be better than azoles as upfront therapy for these candidemic patients.
Looking at aspergillosis, we have much less data here. As I said, for caspofungin we really only have salvage data; but we have clinical trials data for voriconazole, isavuconazole and lipid formulations of amphotericin B.

Looking at the IDSA guidelines, they really recommend voriconazole as first-line therapy. This is based on the Herbrecht trial, which shows a documented mortality benefit of voriconazole over lipid formulations of amphotericin B for patients with invasive pulmonary aspergillosis. So, the alternatives would be the lipid formulations of amphotericin B, which had about a 13% worse outcome than voriconazole in those trials; or isavuconazole, which we’re going to talk about in a moment, which had similar efficacy as voriconazole in a comparative study; or a combination of voriconazole plus an echinocandin. Overall treatment duration should be at least six to twelve weeks, and these patients may require secondary prophylaxis if they have ongoing immunosuppression.

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* No randomized, comparative clinical trials

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/


### IDSA Guidelines: Aspergillosis

**Invasive Pulmonary Aspergillosis**

**First Line**
- Voriconazole
  - Treatment duration: 6-12 weeks
  - May consider secondary prophylaxis

**Alternative**
- L-AmB or LFAB
- Isavuconazole

**Combination: Voriconazole + Echinocandin**

Looking at the data behind this, with the voriconazole versus voriconazole plus anidulafungin therapy, you can see that clinical outcomes were similar whether patients were given monotherapy or combination therapy at six weeks and twelve weeks. There was certainly a trend towards success in the combination therapy arm in terms of mortality—a lower mortality. However, this did not reach statistical significance. Clinical success was based on a combination of complete and partial response. There were more patients in the combination therapy arm that were stable, and therefore didn’t meet as much clinical success as the voriconazole that had more patients with a complete or partial response. But essentially, this was a negative trial. It did not find any differences that were statistically significant, and that’s why you’ll see combination therapy be positioned lowest in the guideline, behind voriconazole and those other formulations.

Looking at isavuconazole versus voriconazole in the SECURE study for invasive pulmonary aspergillosis, it had similar clinical outcomes in terms of mortality as well as success for both isavuconazole, in blue, and voriconazole, in green; and there were no statistically significant differences in terms of efficacy for these drugs in this trial.

However, there were some differences in terms of adverse events (AEs). Overall, the patients had a similar rate of adverse events. However, if you hone in on three key adverse events, which were skin effects, ocular effects, and hepatobiliary adverse events, there was a statistically significant difference for all three of these, favoring isavuconazole. Isavuconazole had lower rates of AEs for each of these three, and in total that sums up about a 20% lower rate of adverse events with isavuconazole in this trial than voriconazole.
Moving on to mucormycosis, we have even less data here. We have no randomized controlled trials. These are difficult-to-treat patients, and we are unlikely to have a big trial of this any time soon. So, what we’re left with are some sort of series – case series of patients that have received isavuconazole or lipid formulations of amphotericin B or conventional amphotericin B.

What’s important here is what we mentioned earlier: identify these to a species level, because sometimes labs can get it wrong. Make sure that you do susceptibility testing, because the drugs can differ in terms of activity. Proceed with imaging and histopathology to really get a good diagnosis.

There are no United States guidelines from IDSA to help us manage these. However, the Europeans do have guidelines, and I saw a few Europeans in the room getting breakfast this morning, so I’m glad you’re here with us. What’s recommended really is surgery. Generally, these patients do better if you can cut this fungal infection out of the tissue, and then use adjunctive antifungal therapy, perhaps with liposomal amphotericin B; salvage might be an option for posaconazole or combination therapy upfront; and isavuconazole does have an FDA indication for this and was released after these guidelines were published. So, we’ll be looking forward to new versions of these guidelines and seeing how they incorporate that new option. Of note, it’s important just to remember that voriconazole lacks activity here.
Now we’re just going to focus a little bit on prophylaxis and neutropenic fever.

And for both of these, what you’re going to use in terms of fungal therapy depends on the risk of your patient. Are they more at risk of yeast? Are they more at risk of molds? And I’ve organized the agents here in terms of that spectrum, knowing that echinocandins lack the cryptococcal activity that fluconazole has, that covers both Candida and Crypto, so it has the broadest yeast activity, and the agents with more broad mold activity are here to the right.

We do have emerging data in the prophylaxis area. And again, depending on which organism you’re targeting, would guide your approach. So, Candida prophylaxis is now only recommended in patients who are in the ICUs, where there is at least a 5% incidence of candidemia or invasive candidiasis. We do have those diagnostic issues, but if you do believe that your ICU has a high rate, then fluconazole prophylaxis may be of benefit there.

In stem cell transplant patients and those with hematologic malignancies, the prophylaxis strategy depends on the risk. Again, if they’re higher-risk, with myeloablative agents, or lower-risk, where you can use posaconazole first-line or perhaps fluconazole in lower-risk patients. And then for lung transplant patients, not to forget the solid organs, azoles plus inhaled lipid formulations of amphotericin B are commonly used in a lot of centers.
Finally, for neutropenic fever, this is an area of a lot of study. We’ve had several randomized controlled trials with these agents, as well as several with FDA indications.

This is a busy slide, but I just want to point out a few key points. Without antifungal empirical therapy in the old trials, we saw an incidence of invasive fungal infections up to 30% in patients with neutropenic fever. We were able to decrease that anywhere between 1 to 6% incidence with antifungal therapy. So, this is a key area where antifungals can be administered to neutropenic patients. Choosing between the agents is a little bit difficult because these randomized trials all show them to be pretty equivalent. What was not equivalent was voriconazole, which was not non-inferior in some of these clinical trials. So, lipid formulations of amphotericin B may be acceptable here, as well as echinocandins; and some shops may also use an azole.

The IDSA does have some guidelines here, and for neutropenic fever they list all of these choices, and UpToDate has a nice guide that helps you, depending on whether a patient has been receiving prophylaxis or not, what to choose. Because obviously if a person has been receiving fluconazole prophylaxis, you don’t want to start out with that as your agent of choice when they get a fever. So, this helps guide you. If they’ve been on azole prophylaxis with fluconazole, you would then use a mold-active agent to treat them when they break through with fever. Likewise, if they’ve been on mold prophylaxis, then you would use an alternative class of a mold-active agent.
For ICU patients or non-neutropenic patients, we have these choices. And again, your selection may be based on whether or not they had received a recent azole, in which case, if they have not, then you could proceed with fluconazole; and if they had, you might use an alternative agent.

<table>
<thead>
<tr>
<th>Summary of Treatment/Prophylaxis</th>
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<tbody>
<tr>
<td>• Risk and treatment strategies vary depending on clinical factors</td>
</tr>
<tr>
<td>– Organism- and infection site-specific approach</td>
</tr>
<tr>
<td>• Evidence-based guidelines can help</td>
</tr>
<tr>
<td>• Stewardship/monitoring to optimize outcomes</td>
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Finally, we know that the risk and treatment strategies will vary depending on clinical factors, and we need to take organism and site-specific approaches. These evidence-based guidelines can help us, and we can use our stewardship and monitoring through our pharmacy friends here to optimize patient outcomes. Thank you. And I’m going to turn it back over to Ryan.
I want to start by asking another question of you, and this is about therapeutic drug monitoring.

What is the goal voriconazole trough concentration in a patient being treated for invasive aspergillosis? A wide variety of answers here. And I think you’ll see in some of the subsequent slides, we’ve now become pretty comfortable in recommending a trough concentration of at least 1 for voriconazole for the treatment of invasive fungal infections, which we’ll talk about.

We talked a lot today about the epidemiology of invasive fungal infections; the diagnostic tests we can use; and then Dr. Johnson did a nice summary of the antifungal agents. I want to talk to you finally today about two really important avenues for pharmacists to be involved in the management of these invasive fungal infections, and that’s, first, the role of antifungal susceptibility testing in the clinic; and then second, therapeutic drug monitoring of these drugs.
### Antifungal Drug Susceptibility Testing (AFST)

- **Antifungal drug resistance is increasing**
  - Changing epidemiology of *Candida* species
  - Expanded use of empiric and pre-emptive antifungals
  - Growing at-risk populations

- **In vitro AFST is becoming an important part of patient management and surveillance**
  - New agents are being introduced into the clinic
  - Detection of resistance helps prioritize use of antifungals

### IDSA Recommendations

- **Invasive candidiasis**
  - Testing for azole susceptibility for all bloodstream and other clinically relevant *Candida* isolates
  - Testing for echinocandin susceptibility should be considered in patients who have had prior echinocandin treatment
    - Also for those who have infection with *C. glabrata* or *C. parapsilosis*

- **Aspergillosis**
  - Routine susceptibility testing of isolates recovered during initial infection is **not recommended**

### Nuts and Bolts of AFST

- **Standardized methods developed by the Clinical and Laboratory Standards Institute (CLSI) for both Aspergillus and Candida species**
  - Provide antifungal drug minimum inhibitory concentration
  - Broth microdilution and disc diffusion methods

- **MICs are interpreted by clinical breakpoints that have been developed based on antifungal PK-PD, MIC distributions, resistance mechanisms, and outcome data**
  - Goal is to predict the likely outcome of therapy

Antifungal susceptibility testing really has become very important because of the changing epidemiology in *Candida* species. Dr. Slain showed you that we’re seeing increasing rates of resistance to *Candida* species specifically, and we know we have growing at-risk populations. So, because of this, antifungal susceptibility testing is really important in getting patients the right drug as soon as we can.

So, the guideline recommendations are to test azole susceptibility for all bloodstream *Candida* isolates, and echinocandin susceptibility should be considered, particularly among patients with prior echinocandin exposure, and we’ll talk about some of the roles for echinocandin susceptibility testing momentarily. The aspergillosis guidelines, however, do not recommend routine susceptibility testing, and we’ll talk about reasons why.

So, the nuts and bolts of susceptibility testing are that it’s important to understand that the CLSI, or Clinical and Laboratory Standards Institute, has really gone through a very laborious process to standardize the testing methodology for both *Candida* and aspergillosis. And what these standardized tests provide us is some measure of drug susceptibility, which we typically measure in drug minimum inhibitory concentration, or MIC; and then we can interpret these MICs based on clinical breakpoints, which have been developed based on extensive antifungal PK-PD data, MIC distributions, resistance mechanisms, and some outcome data. And the goal of these susceptibility testing methods is to be able to predict the outcome of your patient.
Clinical Breakpoints

### Fluconazole

<table>
<thead>
<tr>
<th>Species</th>
<th>S</th>
<th>S-DD</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. albicans</td>
<td>≤ 2</td>
<td>4</td>
<td>≥ 8</td>
</tr>
<tr>
<td>C. krusei</td>
<td></td>
<td>4</td>
<td>≥ 8</td>
</tr>
<tr>
<td>C. parapsilosis</td>
<td>≤ 2</td>
<td>4</td>
<td>≥ 8</td>
</tr>
<tr>
<td>C. tropicalis</td>
<td>≤ 2</td>
<td>4</td>
<td>≥ 8</td>
</tr>
<tr>
<td>C. glabrata</td>
<td>≤ 32</td>
<td></td>
<td>≥ 64</td>
</tr>
</tbody>
</table>

* C. krusei considered to be intrinsically resistant

### Echinocandins

<table>
<thead>
<tr>
<th>Species</th>
<th>S</th>
<th>I</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. albicans</td>
<td>≤ 0.25</td>
<td>0.5</td>
<td>≥ 1</td>
</tr>
<tr>
<td>C. krusei</td>
<td>≤ 0.25</td>
<td>0.5</td>
<td>≥ 1</td>
</tr>
<tr>
<td>C. parapsilosis</td>
<td>≤ 2</td>
<td>4</td>
<td>≥ 8</td>
</tr>
<tr>
<td>C. tropicalis</td>
<td>≤ 0.25</td>
<td>0.5</td>
<td>≥ 1</td>
</tr>
<tr>
<td>C. glabrata</td>
<td></td>
<td>4</td>
<td>≥ 8</td>
</tr>
</tbody>
</table>

Starting with fluconazole, we now have some pretty reliable susceptibility breakpoints for Candida albicans, tropicalis and parapsilosis, but bear in mind Candida krusei is intrinsically resistant, so you will not see susceptibility breakpoints for fluconazole there. Candida glabrata stands out as the exception here, because there is not a susceptibility breakpoint for Candida glabrata, only a susceptible dose-dependent interpretation, which will be important as we move forward. Similarly, for the echinocandins, we have a number of breakpoints that have been refined since their first adoption, and particularly refined with Candida glabrata, which we know is the problematic pathogen for echinocandin resistance, and we’ll talk about that momentarily.

### Rates of Fluconazole Resistance

- 7% of Candida bloodstream isolates are resistant to fluconazole

<table>
<thead>
<tr>
<th>Species</th>
<th>MIC N %</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. albicans (n=877)</td>
<td>2.3% 550 92</td>
</tr>
<tr>
<td>C. glabrata (n=470)</td>
<td>11.9%</td>
</tr>
<tr>
<td>C. parapsilosis (n=389)</td>
<td>4.1% 52 83</td>
</tr>
<tr>
<td>C. tropicalis (n=241)</td>
<td>6.2% 212 37</td>
</tr>
</tbody>
</table>

* 32 C. krusei isolates considered intrinsically resistant

Let’s start with fluconazole. Again, as Dr. Slain pointed out, the big problem with both antifungal resistance is Candida glabrata, and this is where we see the highest rates of fluconazole resistance. So, I want to talk to you about, what’s the role for fluconazole susceptibility testing? How can you use this test in your hospitals to help your patients?

### What Are the Roles for Fluconazole AFST?

- Some assumptions can be made based upon identification of the Candida species:
  - C. albicans – Usually susceptible
  - C. krusei – Intrinsically resistant

- **Role #1: MICs are associated with patient outcomes**
  - C. albicans candidemia treated with fluconazole (n=217), rates of infection related mortality were:
    - 20.6% if fluconazole MIC ≥ 2 µg/mL
    - 4.9% if fluconazole MIC ≤ 0.25 µg/mL (P<0.001)

Well, I think the first thing to understand is that you can make some assumptions based on what we know from large epidemiology databases, which is that Candida albicans is usually susceptible to fluconazole and Candida krusei is almost always intrinsically resistant.

How do you use these things? Well, I think role number one is, we know that MICs for fluconazole are associated with patient outcomes. And in fact, this has been shown in very nice outcome data that’s been put together comprehensively by Dr. Mike Pfaller. But you can look at the table here. As your fluconazole MIC increases, representing lower drug susceptibility, your percent of clinical success goes down. And these are fairly large numbers. So, we know having a low fluconazole MIC and treating that patient with fluconazole is associated with a better outcome than having a higher MIC. So, we know MIC is important for picking the right drug.
What Are the Roles for Fluconazole AFST?

**Role #2: MIC-based fluconazole dosing matters!**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Acceptable target</th>
<th>Optimal target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy in mouse model</td>
<td>AUC/MIC ≥ 25</td>
<td>AUC/MIC ≥ 75</td>
</tr>
<tr>
<td>Clinical success in patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>with candidemia</td>
<td>Estimated AUC/MIC ≥ 32</td>
<td>Estimated AUC/MIC ≥ 75</td>
</tr>
<tr>
<td>Probability of PK-PD target</td>
<td></td>
<td></td>
</tr>
<tr>
<td>attainment in humans</td>
<td>Daily dose/MIC ≥ 50 to achieve AUC/MIC ≥ 25</td>
<td>Daily dose/MIC ≥ 100 to achieve AUC/MIC ≥ 50</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Candida species</th>
<th>Fluconazole MIC (Interpretation)</th>
<th>Daily dose needed to achieve AUC/MIC ≥ 50</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. albicans</td>
<td>≤ 2 (S)</td>
<td>≥ 3mg/kg/day (200mg)</td>
</tr>
<tr>
<td></td>
<td>≥ 4 (M-DO)</td>
<td>≥ 6mg/kg/day (4000mg)</td>
</tr>
<tr>
<td></td>
<td>≥ 8 (R)</td>
<td>≥ 12mg/kg/day (8000mg)</td>
</tr>
<tr>
<td>C. glabrata</td>
<td>16 (S-DD)</td>
<td>≥ 24mg/kg/day (1600mg)</td>
</tr>
<tr>
<td></td>
<td>32 (S-DD)</td>
<td>Not achievable</td>
</tr>
<tr>
<td></td>
<td>≥64 (R)</td>
<td>Not achievable</td>
</tr>
</tbody>
</table>

Role #3: Useful for patients with prior fluconazole exposure and those with recurrent infections

- Rates of prior fluconazole exposure across all Candida:
  - Fluconazole susceptible (n=107) = 8%
  - Fluconazole non-susceptible (n=26) = 35% (P = 0.002)
- Suboptimal dosing also contributes to resistance
- Rates of fluconazole resistance increase significantly among persistent or recurrent candidemia

MIC is also important for dosing fluconazole. There is a wealth of literature out there which I’m going to summarize here for you briefly. This has been shown in both mouse models, clinical success in patients, and then some modeling with PK-PD target attainment that have consistently shown us for fluconazole the best target is an AUC to MIC ratio of at least 50. You can see some of the estimates that have range here, and all the references are at the bottom of the slide if you want to do your own investigation. But the reason why that’s important is because, when we start to look at the MICs of fluconazole, we know that we can clinically achieve some of these AUC to MIC targets if the MIC is low.

For instance, with Candida albicans, if you have a MIC less than 2, you know at least 200 milligrams a day will typically give you an AUC to MIC ratio greater than 50. But as these MICs start to increase, 4 to 8 to even 16, you quickly see that we’re giving very high doses of fluconazole. And in fact, as you get into the higher end of the susceptible dose-dependent range for Candida glabrata, these really aren’t clinically-achievable fluconazole doses. So, fluconazole susceptibility testing is important because that MIC helps you decide what dose of fluconazole you need to give your patients; again, trying to target an AUC to MIC ratio of at least 50.

Role number three for fluconazole – this is particularly useful for patients who have had prior exposure to antifungals. We know that patients that develop antifungal resistance are typically patients that have been previously exposed to these agents. So, fluconazole testing is absolutely necessary for patients that have been previously exposed to these antifungal agents, and these are some data that are showing you just that—that the rate of fluconazole non-susceptibility is 35% among patients with prior exposure, and only 8% among patients without prior exposure.
Let’s transition then to echinocandin resistance. Again, the major problem with echinocandin resistance is Candida glabrata.

And we know that for Candida glabrata, the overall rate ranges from 4 to 18% for echinocandin resistance, is much lower for C. albicans, and rarely reported for the other species. The rate or incidence of resistance typically goes up with prior drug exposure, particularly patients who are on the drug and develop disease. Now, echinocandin resistance is mediated by FKS mutations. FKS is a gene that encodes some of these beta-glucans in the Candida cell wall, and we know that for Candida glabrata that the vast majority of resistant strains have FKS mutations, and both the duration and timing of prior drug exposure is important.

So, why are we talking about FKS mutations? Well, role number one for echinocandin susceptibility testing is to be able to detect these echinocandin-resistant Candida glabrata, because we know echinocandin resistance is associated with worse patient outcomes, as is true for FKS gene mutations. This has been shown in studies that we’ve done in the University of Pittsburgh, as well as Dr. Johnson at Duke University, and Nick Beyda at the University of Houston consistently shows us that if you have an echinocandin-resistant Candida glabrata, that patient is associated with a worse outcome. So, we have to be able to detect these in the microbiology lab.
Role number two for echinocandin susceptibility testing is, as Dr. Johnson just showed you, that the echinocandins are now recommended as front-line therapy for invasive candidiasis. But it doesn’t necessarily mean that you have to treat that patient for 14 days with an echinocandin. These agents are more expensive than azoles. They also require intravenous access. So, there is potentially a role for de-escalation of antifungal therapy, and in order to de-escalate from an echinocandin to an azole agent you need to be able to assure your clinicians that that isolate is susceptible to fluconazole. And there have been very nice data collected by Jose Vazquez, showing that de-escalation strategies are associated with just as good clinical outcomes as using an echinocandin for the duration of therapy.

But there is some hesitation with echinocandin susceptibility testing, which is important for you to be aware of. The reason why this isn’t uniformly recommended and the first issue with echinocandin susceptibility testing is that there’s unclear relevance outside of Candida glabrata. We really only see resistance for Candida glabrata, so why test all the other species? That’s something that remains to be worked out.

Echinocandin MICs also vary between the agents. So, depending on the testing platform you’re using at your hospital, it may or may not even include the formulary echinocandin that you use. Typically, MICs are higher for caspofungin and lower for micafungin. And particularly for caspofungin, there’s significant inter-laboratory variability with testing this agent.

Issue number three is that the clinical laboratories don’t actually use the reference methods. The reference methods are laborious and labor-intensive, they’re expensive, and take time. So, they typically use automated systems like the Sensititre YeastOne panels, maybe Etest or Vitek, which are not the CLSI-recommended methods, and it’s important because some of these methods do overcall resistance for Candida glabrata and Candida krusei specifically.
is, and we’ll classify it as resistance, and this has to be classified as resistance based on the local testing method that you’re using. So, what method are you using? What’s your MIC distribution at your hospital? Because there are some issues with breakpoints in the echinocandins still. So, if the isolate is classified as resistant by your local methods and epidemiology, we know the probability of treatment failure is highest in that patient; and on the other end of the spectrum, if they have no prior exposure and the MICs are low, they have the lowest probability of failures.

Here’s an idea of how you can use some of these tests in your hospital.

Briefly, on Aspergillus antifungal susceptibility testing (AFST), there are not clinical breakpoints by the CLSI. Dr. Slain pointed out that resistance is increasing in Europe. It’s been less so in the US, but I think it’s something that’s coming and we need to be aware of. Until we see more resistance, there really won’t be any clear indications that MICs influence outcomes, because we typically see mostly susceptible strains.
Review the expanding roles for antifungal susceptibility testing in patient management
- Fluconazole and echinocandin testing against *Candida*
- Azole testing for *Aspergillus*

Discuss challenges and opportunities in therapeutic drug monitoring (TDM) of antifungals
- Who, what, when, and how of antifungal TMD

Recommended for patients who receive:
- Azole-based therapy for *Aspergillus*
- Antifungal prophylaxis with azoles
- Concomitant agents that may interact with antifungals

Particularly important for patients with:
- Pharmacokinetic variability (ICU, obese, etc.)
- Severe fungal infections
- Suspected toxicity or breakthrough infections

As we finish up, I want to talk about the who, what, where, and why of antifungal therapeutic drug monitoring (TDM). This is particularly important for patients that receive azole-based therapy for aspergillosis as well as antifungal prophylaxis. And it’s even more important for our special populations, and those are populations that have pharmacokinetic variability, such as the obese or ICU patient populations; those with fungal infections or suspected toxicity.

Typically, what we’re looking for in drug properties that require us to monitor serum drug levels is a number of characteristics. Does the drug have poor bioavailability? Is there inter-patient variability? Is exposure to that drug associated with some clinical outcome? Also, is exposure associated with toxicity of that drug? And then, are there drug-drug interactions? And really, when you consider these characteristics, there’s three agents that we should be monitoring, and those are itraconazole, voriconazole, and the posaconazole suspension.
Typically, you want to monitor these drugs once they reach steady-state, which is roughly a week but as soon as four days in some patients. Your goal trough concentration for prophylaxis is typically around 0.5, maybe up to 0.7 for voriconazole. And in response to our audience response question, the trough for treatment of invasive fungal infections is at least 1 for all of these agents. But the take-home message here is, we monitor trough concentrations once the drug has reached steady-state.

Typically, if levels are low, you increase the dose; if levels are high, you decrease to prevent toxicity. Therapeutic drug monitoring is also important for identifying patients who might require alternative therapies. There are genetic polymorphisms among patients that require them to metabolize voriconazole differently. So, maybe therapeutic drug monitoring helps us identify those patients as well.

The barriers to TDM – I think the most important barrier is that these assays are not regularly available at all of our hospitals. So, the idea of sending out a drug level may take a number of days at some of your facilities, and that does throw out certain barriers. There’s roles for TDM in long-term prophylaxis, but we don’t know what to do with some of those levels. And then finally, I’ll just leave you with this: in general, if you’re not going to do something with the level, don’t check it. Oftentimes we get this phone call: I have a level of “X;” I don’t know what to do. And they say, well, why did you check a level? And they don’t know. So, don’t check a level unless you intend to do something with it.
In summary, antifungal susceptibility testing is very important for optimizing antifungal therapy. We’ve talked about some of the roles for antifungal susceptibility testing. And similarly, I think we have an important role as clinical pharmacists to use therapeutic drug monitoring to optimize our use of these antifungal agents.

With that, I’ll turn it over to Dr. Slain for a few audience questions and some case scenarios.

I made two cases that come from patients that I have seen on my service recently, and my two fellow presenters here are good sports, because I didn’t give them details about these cases in advance.

I’m going to poll you, see what you have to say, and then we’ll turn to our experts here on the panel. These are cases that don’t have a lot of comprehensive information. And there may be more than one right answer.

This is a 34-year-old man with past medical history significant only for hypertension, Staph aureus endocarditis the previous year, and he’s a prior injectable drug user. He’s admitted to the cardiac surgery service for further evaluation for prosthetic valve endocarditis. He was diagnosed with infective endocarditis of the aortic valve with blood cultures of Candida parapsilosis in multiple blood cultures.

Labs

- Platelets: 52
- BUN: 40
- ALT: 27
- AST: 32
- Creatinine: 2.4
- Alkaline phosphatase: 500

I saw a number of labs there. Platelets are 52. You can see the BUN, creatinine, and also, I’ve included some LFTs. You can notice that some of those are not normal lab values. Based on this information, which of these regimens would you attempt to go with in this patient? You can see you have a number of options there. Let’s poll and see what we get.
We get a little bit all over the place there.

Panel: Would you like to comment as to which option you might pick, given that there’s limited information, and you’re allowed to, of course, expand if you had certain other diagnostic pieces?

Ryan Shields: This is an interesting case. Candida endocarditis is certainly a rare disease, but also one of those severe diseases. And I think when it comes to severe fungal infections, the first thing that crosses my mind is, is there enough benefit of using amphotericin B that outweighs the risks? Amphotericin B has really been the gold standard for endocarditis for a while, and I think that’s challenged most recently by new data with the echinocandins, suggesting that the echinocandins are also efficacious. So, when I’m looking at this case, I’m really debating in my mind between liposomal amphotericin B and a high-dose echinocandin. And the high-dose echinocandin is particularly important here because we have a Candida parapsilosis, which we know have higher MICs to the echinocandins, so there may be some discussion about, is an echinocandin really the best for this?

The other thing that I think is important about the pathogen here is you have Candida parapsilosis, which we know can cause biofilms. Biofilms are particularly important in endocarditis, and we know amphotericin B and the echinocandins are usually effective against biofilms; the azoles, less so. So, in my mind I’m weighing between amphotericin B and a high-dose echinocandin. So, answers “A” and “E.”

And I see the patient has an elevated serum creatinine, so it may make you a little bit wary of liposomal amphotericin B; but also, the Candida parapsilosis may make you a little wary of using an echinocandin. So, those are my two choices that I’m debating between. I think, for me, it depends on the severity of illness, how aggressive I would be here. Again, in a small case, there’s limited things. I think if the patient was really sick, I’d probably start amphotericin B and then try to get them to an echinocandin as soon as I could.

Melissa Johnson: I tend to agree. The IDSA guidelines here actually say liposomal amphotericin B plus 5-FC is first as combination therapy, or high-dose echinocandin if you can’t use amphotericin. I wondered if you were trying to suck us into the fluconazole with the Candida parapsilosis. And I could see some attraction to that, given the renal issues that the patient’s experiencing, as well as the concerns about MICs with parapsilosis and candins. But I think a static agent like fluconazole would be ill-advised here, and we should try to go with a cidal agent if we can. Hard-core, I would favor amphotericin B plus 5-FC, but looking at that creatinine of 2.4, you would have to say, where’s the patient on the continuum of that? Is that 2.4 and rising, or is that 2.4 and stable? You know, could you manage it or not? And certainly, there are data for high-dose echinocandins here. So, you could maybe do that temporarily while you sort things out with the patient. I was glad to see he was admitted to the surgery service, because the highest recommendation is to consider surgical removal of the valve.

Douglas Slain: Those are two great answers. Surgery is really curative, along with the antifungal agent. What we actually did was initiate the high dose of caspofungin. But what we noticed is those LFTs and those liver toxicity indicators started to increase, so we backed down on the caspofungin. We stabilized
the patient eventually and then the surgeons took over from there. So, that’s what happened there. Great answers, though.

Here is some additional information. It turns out this is what the MICs were. But based on these MICs, would you change what you would pick? Now, all of these are technically within the susceptibility breakpoint range. Two and less is for fluconazole and caspofungin for this, and 0.12 would be the breakpoint, or less, for voriconazole. So, would it change your vote?

Just what we did, doesn’t mean it was right, so I’m curious to see if anyone changed their vote based on that. So, what do you think, panel? The audience is kind of all over the board too. Would you have stuck with that caspofungin here?

Yes. I think a caspofungin of 0.25 is pretty good for Candida parapsilosis. Typically, these cluster around 1 and 2, and that’s due to a kind of natural FKS mutation in Candida parapsilosis. So, the MIC looks good, and I think only strengthens the encouragement for an echinocandin to me.

I agree. And I think it is nice, though, that you do have a susceptible strain with fluconazole since, eventually, these patients often have to transition to something orally for long, long courses of therapy, and that would at least open up the door for fluconazole as well, if you have to do that in the long term.
How about the second case – a 54-year-old female with AML develops a fever while neutropenic at day 12. She receives posaconazole prophylaxis. Her fever has not abated despite receiving piperacillin-tazobactam and vancomycin. You can see the lab value of the serum creatinine. LFTs are within normal limits. The team has given a presumed diagnosis of probable pulmonary aspergillosis based on galactomannan and nodules on chest CT. This is something we commonly see, especially if you’re in a center that is a bone marrow center or treats a lot of AML patients.

So, these are your options. Give it a vote here and tell us what you might pick for a patient like this. A little bit of spread here. Panel, would you like to address maybe what approach you would take?

Again, you have limited information, of course.

Melissa Johnson: Yes, I agree.

Douglas Slain: But you know what agent was used for prophylaxis.

Melissa Johnson: With this information, I’ve got a million things running through my head and I would ask about 80 questions of the team before deciding. Certainly, it’s concerning that she was on posaconazole prophylaxis when this happened, and raises the question of, what formulation was she on; did she have therapeutic levels; did she have malabsorption? Is this really Aspergillus or is it something else? And because of that question, we often start broadly with lipid amphotericin B until we really have histopath and sort things out. But if it is Aspergillus, you’ve got to start with voriconazole, based on the data. So, I think those would be the two I’d be thinking about. Isavuconazole, I might consider, if she has some QT prolongation issues or we’re worried about toxicities. That would also be in the back of my mind too, because you do have broader mold coverage with isavuconazole as well.

Ryan Shields: Yes, I agree. You have a breakthrough case here and somebody on azole prophylaxis, so I think I’d be inclined to start with lipid amphotericin B.
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