Transcript Details
This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/change-story-preventing-missteps-invasive-fungal-infections/12501/

Released: 05/10/2021
Valid until: 05/09/2022
Time needed to complete: 60 minutes

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Change the Story: Preventing Missteps With Invasive Fungal Infections

Announcer:
Welcome to CME on ReachMD. This activity, entitled "*Change the Story: Preventing Missteps With Invasive Fungal Infections*" is sponsored by the Academy for Continued Healthcare Learning and is supported by an educational grant from Astellas.

Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the Learning Objectives.

DR. LEWIS:
Welcome to CME Activity on Invasive Fungal Infections. I'm Dr. Jim Lewis and I'm joined today by Dr. George Thompson. We're going to go forward and review a few cases and discuss wet - what went wrong and what could or should have occurred in some of these patients.

The first case surrounds invasive aspergillosis, and involves a patient by the name of Colin. Colin is a 68-year-old male who's a retired chemical plant worker who was recently diagnosed with AML. He received induction chemo which included cytarabine, daunorubicin, and gemtuzumab ozogamicin seven weeks ago. He has developed a fever and cough that had been slowly progressing over the last week despite levofloxacin therapy. Since his hem/onc provider has been away on vacation, he decides to present to the emergency department with his wife. Colin thinks that his symptoms are likely from a recent visit with his granddaughter. And after being examined in the emergency department, he receives therapy with fluconazole 400 milligrams daily from the emergency department and is instructed to continue levofloxacin, which had been prescribed by his hem/onc provider. Laboratory testing ordered in the emergency department reveals a white count of 1.3. But a differential is unfortunately not available, and a chest x-ray is ordered but no abnormalities are noted, and no other focal signs of infection are identified. The patient is discharged and returns home. He is, however, told to return if needed. And no follow-up is - on his workup is either recommended or documented in the chart. Over the next pursuing couple of days, Colin continues to feel a little bit better, and is able to resume some daily activities. But he complains of fatigue and feeling a little bit winded after short walks. Ten days after presentation to the emergency department, Colin's wife urges him to seek care because of this continuing and slowly worsening chest pain and shortness of breath. They've returned to the same emergency department and where a CT scan is ordered, and reveals a mass.

So, you know, George, when we look at cases like this, you know, what kind of pops out at you a little bit on, you know, maybe some of the things that are a little bit out of what we would like to see normally happen in patients like this?

DR. THOMPSON:
Yeah, I think that's a good question. I mean, I think our improvements in oncology care, have obviously im - improved outcomes, but they've also really extenuated the duration of risk for these patients. So we're able to keep these patients alive longer. But there are also a much larger population of patients walking around in the community that are leukopenic and neutropenic. So for better and worse, both, we are increasingly encountering these patients in different clinical settings. And this is a patient that sought care in the emergency room. And I think the emergency department was a little bit on the right track, they thought, 'Oh, he might have a fungal infection,' But really his major risks are not Candida, which fluconazole would cover. And in an invasive mold infection, fluconazole really doesn't have any activity. Again, so I think that was a little bit of a misstep here.

To back up just a bit though, I think rather than just jumping towards a mold infection, you know, these neutropenic patients, you have to really treat very aggressively from a diagnostic standpoint. So really trying to secure the diagnosis upfront. So admission was probably appropriate at that time, right, to - to bring them into the hospital, get a CAT scan early, of not only just the chest, but if there's any sinus complaints, that's certainly another location we really need to look at, see if they have an invasive sinus infection. And then once a mass lesion is found in the chest to not just assume that's a mold infection, really try to make a tissue or microbiologic diagnosis. You know, that can be still community-acquired pneumonia, despite the levofloxacin. It could be atypical pneumonia from a different bacterial pathogen. It certainly can be fungal. You know, we do see concurrent malignancy, unfortunately, on occasion. So I think really, a - attempts to - to diagnose that definitively was the biggest misstep. And then also, you know, not quite having a – a thorough understanding that fluconazole is not active against these different molds we see in these patients, would be sort of another, you know, error in this case.

DR. LEWIS: Yeah, you know, I think to the other thing that kind of jumped out at me a little bit in this case, is that you've got an individual who's running around with a white count of 1.3. And I'm a little bit unclear as to, you know, whether or not the levofloxacin was continued for kind of the entire duration, which I think would be a little bit unusual as well. You'd normally like to kind of see that stop after count recovery. So I - I was a little bit taken aback by, you know, some of the things that we saw there.

What do you think about, you know, the levofloxacin plus fluconazole and hold the whole QT interaction thing? You know, I - it's - it's one of those things where I feel like the literature kind of goes back and forth on the importance of quinolones and QTs, but I think that, you know, most of us would be a little bit tense about combining azoles with fluoroquinolones, especially not having an EKG kind of either ordered or at least described to us in some way. You know, how would you kind of look at or think about that?

DR. THOMPSON:
Yeah, I think that's a really good point. I mean, these oncology patients, unfortunately, accumulate a lot of medications. The anti-nausea medications are going to cause QTC prolongation. He's an older patient, I think he was in his 60s. Yeah, you know, that's definitely a risk factor for QTC prolongation. And then adding these medications together, you know, if he was just on fluconazole, and – and levofloxacin, I probably would get a baseline EKG at the initiation of those. And there's - there's some nice data about that in the past, specifically in the oncology population. But I also think he's probably on more than just these two medications. And I think that's definitely going to be a risk that needs to be assessed in some fashion.

DR. LEWIS:
Yeah, you know, and I guess I'm a little bit surprised too, you know, that when you see hem malignancy patients, and I think you did a nice job of already kind of touching on this, this is not someone that, you know, I – I think we would have routinely thought of stopping at a chest x-ray and discharging. So I, you know, I think that this is a little bit, you know, different than - than how I would normally think of one of these patients being handled. And I think it, you know, again, brings up an important point that you touched on nicely with regards to the fact that, you know, when - when you bump into these for - folks more and more, and, you know, with all the various complications in therapy, and you and I were joking about this not too long ago that, you know, in the time that we've been talking, there probably been three new mabs, um, you know, approved, you know, for this disease state or some other malignancy. And so I think the complexity of these cases, is such in the complexity of these patients is such that - that certainly, I think, you know, even though his hem malignancy provider was out of town, I think it probably consultation with our - with our hem malignancy colleagues, would have certainly been warranted in a case like this. And, you know, I - it, fortunately, we – we don't tend to run across these cases that often. But, you know, occasionally, as you said, these folks are going further and further out from academic centers. And, you know, when - when we look at these patients in rural - Oregon is such a rural state, you know, and we routinely send these folks out, you know, all over the place. And so I think it is really important for emergency department providers and - and other primary care providers to be kind of thinking about some of these issues.

You know, I guess the other question, you know, that you touched on a little bit already is, you know, where do you go now, assuming that, you know, this looks like barks, like smells like, you know, an invasive mold infection and let - you know, let's - let's complicate it or pin it down a little bit, you know, coming back to your diagnosis point, let's say that this gentleman gets a BAL. And, you know, the GM is – the galactomannan, it's completely off the charts, um, when you get that result back. Where - where are you going? What are you thinking, um, you know, with regards to drug selection at this point?

DR. THOMPSON:
Yeah, those are - those are great questions. I mean, there's been several recent papers looking at, you know, other azoles in the management of invasive aspergillosis. So, you know, voriconazole was used for a long time after that seminal paper. Isavuconazole I think we're very comfortable with after the last few years. Um, you know, it's - it's been in the Aspergillus guidelines – 2016 Aspergillus guidelines recommend that as upfront therapy as well. And then posaconazole, sort of, you know, I think it's been used for a long time

for prophylaxis in high-risk patients. But now we do have treatment data from the new *Lancet* paper as well. I think each of these medications really offers a niche advantage, right? So we've talked about QTC prolongation. So, you know, voriconazole is going to have the same QTC issues. Posaconazole is a little bit different. I think that's kind of hard to weed through, you know, um, package insert still really cautions against QTC prolongation, even though it's one of the healthy volunteer studies, it really looks like there was no effect. Um, so I think that's a little bit difficult for people to know what to – to think about. Isavuconazole causes QTC shortenings. It does have a potential advantage, if that's a big concern in the treatment of these patients. And I think that is something that really comes up often, uh, in the treatment these oncology patients, and for all the issues we talked about earlier.

DR. LEWIS:
Yeah, you know, could not agree more. And, you know, I think we still reflex the vori. You know, I think we've all been trained that way. We think that way. It's been generic for a long time now. You know, and, you know, rightly or wrongly, we get a lot less push - pushback from third-party payers when we try to prescribe voriconazole than we do, you know, some of the more branded or more expensive formulations. But that being said, you know, to your point, I – I would really be getting fairly nervous about voriconazole with a fluoroquinolones from a QT standpoint. And, you know, I think increasingly - and I'm not sure if it's just because we look for it more, or if we just, you know, we under recognized that a lot, but it does seem like some of the mental status issues, with voriconazole are more prevalent than they used to be. And again, you know, that may just be recall bias, selection bias, what have you. Um, and so I think, you know, you put those two kind of com - combination things together, and vori is just finicky. You know, I'm a pharmacist, I'm a drug nerd, I - you - I want levels until the cows come home. Um, but you know, it - vori makes me batty. I mean, you know, the only thing you can predict about vori is its unpredictability. And so, you know, even if you - even if you dose it by weight, even if you, you know, stand on your head, and it's Tuesday, you still don't know what you're gonna get when that first vori level comes back. I mean, would you agree with that?

DR. THOMPSON:
Yeah, I think that's a really good point. I mean, until we're in the era of true genomic medicine where we can, you know, look at their, CYP status with, you know, be it 3A4, 2C9, 2C19 all - all impact voriconazole metabolism, right? Um, we're just not going to be able to predict what their vori levels are. And – and furthermore, you know, there's a group of people that start to auto-metabolize voriconazole over time, and so you're pretty satisfied where you are right? And then you check in next month, and they're voriconazole levels are too low.

DR. LEWIS:
Yeah.

DR. THOMPSON:
Which is really frustrating. The problem for us is, you know, a lot of these patients, right, they're not on meds for just a few days or a few weeks, they're on these medications for, um, multiple weeks, at least six weeks. And then if they're going to get another course of chemotherapy, they're back on it as secondary prophylaxis. Right?

DR. LEWIS:
Yeah.

DR. THOMPSON:
So they're just accumulating, potential side effect days. And in Northern California with a lot of sunshine, you know, the photosensitizing effects of voriconazole are – are pretty difficult for them to deal with. We have a very high discontinuation rate. You know, if they have impaired renal function, there's this aspect of hyper fluorosis, right, they accumulate fluoride over time from the voriconazole drug, and then develop bone lesions. I think, you know, that's not as common, but that's pretty debilitating for those patients. So, and, you know, we know that head-to-head study, isavuconazole versus vori, there were 17 percent fewer side effects in the isa group. And those are primarily, you mentioned, mental status, certainly visual changes, skin changes, and then hepatobiliary. I mean, there's just some big advantages to using isavuconazole. And we haven't really talked about therapeutic drug monitoring for ica or posa.

But what's your all's practice sort of locally about, you know, TDM, for both of those drugs?

DR. LEWIS:
Yeah, you know, with - with regards to posaconazole, you know, we did some work with the tablets right after they came out. And, you know, we were still finding that about 10 percent of patients were, you know, in a range that we were not happy with. And so I think the posaconazole tablets are a light-year improvement, um, over where we were with that finically old liquid that you know, you had to give with olive oil, ice cream and a Big Mac to have, like, you know, any chance of getting good absorption. But –

DR. THOMPSON:

Which sounds great for a few days.

DR. LEWIS:
Yeah, and then patients get pretty grumpy about it. But we - we actually, there were - there were patients that we would mix it with ice cream, and we became very popular with the patients at those - at that point, but you know, the – the tablets – we - we've got an individual right now, the tablets aren't small, and you know, you're taking three of them at once. And so the size of the tablets can be an issue for some patients, you can't crush them. You know, we've tried that once or twice and really not gotten very good levels, despite it seeming to make sense, you know, that they should be crushable. It's not worked well in our hands. So even the package insert says not to do it. And we still stay away from that. You know, so I think we do therapeutic drug monitoring at least once on pretty much everybody on posaconazole, and I think it was the Michigan group, um, that had some good data, that looks like maybe there's a weight effect. But also, you know, patients with diarrhea, again, do not seem to necessarily absorb this stuff terribly well. So it's way, way, way, way, way better, than it was with the liquid. And this is really what we use kind of day in day out for all of our prophylaxis patients. But we still do check at least one level, I would say on the vast majority of patients. You know, for us, isavuconazole we've been very fortunate. When we have used that compound, we are really yet to see a level under two. You know, we - we checked a lot of levels with it early on, just because of some - I think we've all been burned by being told we don't need to do TDM. And then five years later, we're doing TDM on - on everybody. So you know, we came out of the gate with isavuconazole pretty skeptical about the lack of – of requirement for TDM. But I think that we become more comfortable with that over time. And that we really, you know, again, are fairly comfortable with that at this point in time. I think if something unusual is going on with a patient, they're having a lot of diarrhea, they have something else going on that makes – does make me think that absorption is a problem, we will still do - still do the - do TDM but, you know, I – I think we for the most part had been pleased isa. And, you know, to your point earlier with regards to QT, it's - it's really funny. Our providers have really kind of picked up on that. I mean, that is if you've got a prolonged QT, they're like, 'Well, we can use isa,' you know And it's - it's really funny, I don't think - we any of us really know what that shortened QT means or, you know, how reliable it is from patient to patient. But boy, in a lot of our patients where we have, you know, slightly prolonged QT, or you're talking about having a stack and on top of, say, a levofloxacin, there certainly seems to be a lot of pr - appeal with regards to providers kind of going in that direction.

And you know, love that you brought up the – the posa treatment paper in *Lancet*. You know, it's really kind of cool now to see that you basically got treatment data across all three. it - it'll be very interesting to see what that does to third-party payer coverage of – of treatment with posa. But I think, you know, as long as - it'll be interesting to see how the guidelines kind of adapt to that study in the next iteration. And, you know, as – as someone who was intimately involved with those guidelines on the last go around, you want to give us any preview on when we might see an update on those?

DR. THOMPSON:
I think there's some conversations occurring about when to update those guidelines. Certainly, there's been a lot of changes, there's new risk factors for, invasive aspergillosis, you know, COVID, which I think we'll talk about later.

DR. LEWIS:
Yeah.

DR. THOMPSON:
Post influenza, post respiratory virus, lots and lots of new medications. Ibrutinib has emerged as a major risk factor for particularly, you know, CNS aspergillosis. But to more directly answer your question, I really think that these are all three going to be listed as alternative first-line therapy.

DR. LEWIS:
Yeah.

DR. THOMPSON:
And you're going to really consider an individualized approach these patients, which is what our patients really need, right, they need to sort of personalize look at what other medications they're on, how long are they expected to be on this, what's going to best sort of fit that particular patient?

DR. LEWIS:
Yeah, no, completely agree. And, you know, I think having - having more options, not less, in this space is always a good thing, because of the complexities that we're talking about. You know, and coming, you know, you brought up the – the purple elephant sitting in the room, right. COVID-19 has completely wrecked all of us for, you know, the last 12 months. And, you know, what are kind of your thoughts on, you know, COVID-19 and the risks that come along with this with invasive aspergillosis? You know, I saw a really nice kind of, opinion piece yesterday from, the MD Anderson group and JID, you know, on this and, you know, kind of talking about the strengths

and the weaknesses of the data that's out there, and - and how difficult of a diagnosis this is to make. And this is, you know, really been something that you and I talked about a couple of times, and - and we've seen this in several of our patients, especially some of our sicker COVID patients on ECMO, where you get this out of a tracheal aspirate, and it's like, oh, my gosh, what do we do with this now? And so, you know, as we - as we sit here in April, of 2021, you know, more than 12 months into this, kind of what - what are you thinking at this point, and how – how are you handling these patients who maybe have an Aspergillus in a sputum and they're really sick?

DR. THOMPSON:
Yeah, that's a great question. I think, you know, a year ago, we sort of convened as the mycoses study group and wrote sort of that early opinion piece that's in, OFID, to really talk about this and try to educate clinicians, we think this is going to happen. We saw it a lot with influenza, right? Particularly, swine flu, H1N1 is one that was really first recognized. And - and I mean, it's really a non-traditional host, right? This is not a leukemic patient. This is not a profoundly immunosuppressed patient, but they do have really a constellation of – of risk factors together. So you know, with - with a severe, lower respiratory infection with the virus that causes epithelial injury, and we breathe in Aspergillus conidia, you know, all day long. So these conidia that are - that are colonizing the lung then have access to deeper tissue, right, there's a breach and your epithelial barrier. Combined with, you know, critical care illness, you've got impaired ciliation, you can't clear these different pathogens out of your lung. And then if they've got severe lung disease with COVID, these patients are getting steroids, right? So they're going to be immunosuppressed, they might get tocilizumab. Not totally clear if that's a significant risk factor or not. Um, Jim always likes these fancy names, right? So, but I think all of these - these risk factors have definitely, you know, set these patients up to get bad fungal infections. And Aspergillus has been, you know, the brunt of these. But COVID patients also can be leukopenic or lymphopenic. So that's just another hit to their immune system. So there have been some with mucormycosis. We've certainly seen reactivation of old disease, reactivation of tuberculosis, reactivation of endemic fungal infections. I mean, these are really emerged as a significant problem in these ICU patients with COVID-19.

DR. LEWIS:
But, you know, to your point, right, and this - this is the same skirmish that I've had with - with, you know, several - several folks here, is 6 milligrams of dexamethasone for 10 days, and we're going to invoke that that's going to cause invasive aspergillosis in folks and a single dose of tocilizumab. You know, I'm like, really? You know.

DR. THOMPSON:
I agree with you. I think in some cases, it's just the final hit, right?

DR. LEWIS:
Yeah.

DR. THOMPSON:
They've already, you know, been leukopenic, lymphopenic, have impaired structural lung disease. Again that epithelial breach. I mean, I think all of these together, you know, definitely cause, you know, infection. And – and the rates are all over the board, you know –

DR. LEWIS:
Yeah.

DR. THOMPSON:
-they're 2 percent in the critical care unit, they're as high as 10 percent. You know, the Netherlands routinely has very high rates of – of Aspergillus in their ICU patients, which - so I think there's probably some ecologic phenomenon, you know, sort of, that's - that's been a nice paper in the CID a number of years ago comparing sort of Seattle's experience with a seasonal variability of aspergillosis to Houston's so and you know, they blame it on precipitation, right? So, with moisture is going to be mold in the environment. So Seattle is going to have a nice curve over time. Houston doesn't change much with precipitation. So it's going to be pretty steady. But I do think that this is much more complicated than we've tried to just blame it on a single thing.

DR. LEWIS:
Yeah.

DR. THOMPSON:
So I agree with that.

So Jim, Francisca is a 58-year-old woman with uncontrolled diabetes that was first diagnosed three years ago, and she came into the ER with her husband with the chief complaints of weakness, nausea, vomiting, and confusion. And – and then per her husband really had been complaining of facial pain kind of over the right side of her face and noticed increased swelling, but really had blamed this on kind of a lack of sleep. Her husband said that he'd noticed this maybe two to three days ago, but really didn't think much about it. But he

did become more concerned when she seemed confused, and that's why he brought her in after they were at the bank together. When she was in the emergency room, they really thought she had diabetic ketoacidosis. She had a – a glucose 500s. Arterial pH was 7, serum bicarbonate of 16. And had ketones in both our blood and our urine. And on exam, what they had documented was really this affected skin was swollen, red, and painful and warm to the touch. They didn't look in her mouth or at her palate. Really didn't do a formal ocular exam at all. Ocular motion, really not a visual assessment. Didn't look in her ears. So that was sort of problematic when we looked through this chart, really not a lot of documentation. Again, no - no description of the ocular movements or – or palate exam. And they treated Francisca for bacterial cellulitis with I.V. vancomycin. And this dose, I'd sort of be interested in your opinion, about 500 milligrams q 6, and then they gave her fluid electrolytes, insulin, of course. It wasn't a DKA, but you know, really they did consult us to see, you know, this non-resolving bacterial cellulitis over her face and sort of our approach to this case. But I just wanted your thoughts kind of, what do you first think and when you see this?

DR. LEWIS:
Yeah, you know, any, you know, and it's probably the line of work we're in, right? But I think anytime I see a diabetic in DKA, with facial pain, especially around the eye, anything that involves nose, I mean, this just looks like, barks like, sounds like again, you know, invasive rhinocerebral mucormycosis. Which I think is, you know, one, to me is - is one of the most terrifying diagnoses that I've ever seen before, because the, you know, the residual devastation that is oftentimes left by the surgery, if the patient is lucky enough to survive, really is – is one of the most, disturbing things that I've been involved in my 20 years of doing this. And so, you know, when you describe to me a patient like this, that's immediately where my mind goes. And I think, you know, the only thing that would – would have driven my mind even more in that direction is if she - you told me that she had, you know, black discharge from her nose. That would have been just kind of the ultimate calling card here. You know, I mean, I – I certainly can understand why, you know, initially you would think, 'Oh, you know, cellulitis, diabetics get cellulitis,' but I think there are just - this is one of those disease states that I think just has to be on everybody's radar with - with the prevalence of, you know, diabetes in this country. You know, and, you know, as we talked about in the previous case, you know, we're – we're generating more and more immunocompromised patients who may or may not present like this, you know, but I think this just really - really rings as one of those cases that I would be jumping up and down about, we need to make sure this is not mucor. The other thing too, you pointed out, is the vancomycin 500 q 6 is - is certainly interesting. Someone went pediatric dosing on this woman with a – with a q 6 interval there. But you know, I - to their credit, right, it's an AUC dependent drug, and so it's basically the same as you know, a gram BID, it's just given in a slightly different fashion, if you will. So I - I certainly can't fault anyone for that. But again, I think, you know, going into a patient like this, I'm immediately thinking to your point, you know, we had a - we had an individual, like this last week who wasn't diabetic, but was otherwise immunosuppressed with a bunch of steroids. And, you know, had kind of this periorbital stuff going on, evidence of, you know, tissue invasion on some path, and everyone was, you know, jumping up and down and – and you know, yelling mucor.

And you know, I think, you know, you and I've talked about this, you and I were both for fortunate enough to have - have learned from Mike Rinaldi in San Antonio over the years, and I remember one of his quotes was that anyone who can identify a fungus, in tissue is either lying to you or has a direct connection to Jesus. And so I think, you know, when you - when you see fungus in tissue, you have to be very careful not to kind of overreact. And, you know, you kind of touched on a couple points in the - in this case that really, diagnosis is absolutely essential in a situation like this. And I, you know, I know, you've talked to me before, about, you know, cases where there are some mimickers there, and you want to talk about that a little bit?

DR. THOMPSON:
Yeah, I think that's a really great point. Thanks for bringing that up. You know, the - the pathologists will routinely look at this on histopathology and say, this looks like mucormycosis or this looks like aspergillosis. And I think that's great. We – we definitely appreciate their help. But you know, Aspergillus, lots of things with like Aspergillus other hyaline molds. You know, Fusarium looks like Aspergillus, on histopathology, and - and even mucormycosis, despite what we're sort of taught in - in medical school, pharmacy school. You know, it is frequently misdiagnosed in – in - in both directions. So - so mucormycosis is actually aspergillosis and vice versa, on histopathology. So unless you – you have cultures, or you're able to do PCR in house on tissue, you know, I think you really have to weigh the patient's risk factors and – and sort of play the odds to some extent. But the – the big picture here is this patient needs aggressive antifungal therapy. We consider this a surgical disease. You know, we're going to call our ENT colleagues to come and do endoscopy in this patient immediately. You know, even with any kind of ocular cellulitis, but even bacterial, they really need an MRI of the orbit, right? For pre or post septal cellulitis. Or is this mucormycosis involvement? Is it already in the orbit and hopefully not in the brain? Um, you know, but this is something that really needs to be treated aggressively and as quickly as possible. This is not a situation where you can give people a trial of antibiotics for a few days, and then hope it goes well.

DR. LEWIS:
Yeah, I com - yeah, I completely agree.

DR. THOMPSON:
So, and then big picture wise, so you know, we'd approach this patient with surgical care. And in this case, we were very lucky, she didn't have ocular involvement. Um, you know, it was in the sinus just starting to erode through the bone. So ophthalmology was - was involved up front. But, you know, what's your kind of approach? What do you recommend to your team for antifungal therapy right out of the gate for these? Do you - are you sort of a standard amphotericin, dosing fan or you like the higher dose? Do you give combination therapy?

DR. LEWIS:
Well, first and foremost, you – you know that I would not go anywhere near conventional amphotericin ever. And – and I would remind our audience, you know, to be very careful, about how you talk about an order amphotericin products. We had an - you know, we had a near miss about 18 months ago, where there was confusion when someone was adamant that they wanted conventional amphotericin B, they didn't - they didn't know amphotericin B deoxycholate existed. And so to them, liposomal amphotericin B was conventional amphotericin. But it led to, you know, a huge mess. And so I think, you know, being precise, and kind of how we talk about that is - is step one. And conventional ampho, to my way of thinking has absolutely no role in a patient like this at all.

DR. THOMPSON:
Absolutely.

DR. LEWIS:
Now, that brings us to the lipids, right? And, you know, when you start to talk about the lipids, I think most of us would go with liposomal amphotericin B at this point in time. And, you know, they're, you know, the - the guidelines for this have 10 milligrams per kilogram per day as the starting dose recommended. And, you know, far be it for me to argue with Oliver Coronelli, on how he's dosing liposomal amphotericin B, that - that's not a fight I particularly want to have. But you know, I think that the data there, I think we would probably agree is, okay. You know, but again, we know that 10 milligrams per kilogram per day of liposomal amphotericin B is certainly associated with some nephrotoxicity. I think you'd go back to, you know, you're going to get into trouble with that dose. And you know, so I really have kind of stuck in that 5 to 7 milligrams per kilogram per day. And I am still routinely starting with lipid amphotericin B, and all of these patients. And truth be told, you know, even though the echinocandin data is very meh, the - the risk I think associated with a combination of liposomal amphotericin, B and an echinocandin, the addition of an echinocandin is - is such a safe addition for the patient, and the data looks like maybe it helps, you know, especially in patients like this where they're not neutropenic. But I – I still do it. Can I prove to you that it's right? No, but I can prove to you that this is an absolutely horrific infection. And so I'm kind of doing what I can, to hopefully optimize the care of the patient. I'm still not sure what the role of the azoles is as frontline therapy for these patients, and I think that the guidelines kind of reflect that as well. You know, so I - I'm still starting with liposomal amphotericin B. I'm usually adding an echinocandin to it, almost always adding an echinocandin to it. And then really, when they get to a point where they either can't tolerate the lipid ampho anymore, or they're ready for discharge is when I really - kind of when I start thinking about moving over to one of the azoles, either posaconazole or isavuconazole. And again, reminding the audience that you know, vori's got nothing against those molds. And so really, you're talking about having to use either posa or isa there. And, you know, I think that becomes, a little bit of a dealer's choice and a little bit of what can you get paid for more easily for the patient? Although I also happen to note that you've published a nice data lately, about some posaconazole toxicity issues that might be particularly pertinent in a patient like this.

DR. THOMPSON:
Yeah, absolutely. So I – I agree, I think isavuconazole and posaconazole are your long-term choices. And the treatment duration for mucormycosis is a long time. You know, we can't really define that. It's until they're better, you know, clinically, and radiographically. So, you know, these patients are gonna be on drugs for a long, long time, measured in months or – or even a year in some cases, so you - you're going to really want to optimize their chance of not having adverse events on these drugs, right? And - and certainly, the, um, toxicity, the insurance companies may – may put on - on you bears a little bit of that out. But you know, posaconazole we found with long-term use, and you're going to push the dose for some of these sometimes from treatment mucormycosis. And if you've got a posaconazole level of four, you're probably going to give the patient hypertension through this sort of indirect endocrinologic mechanism where it inhibits some of the enzymes, in the sterile pathway, right? So you end up basically with what looks like hyperaldosteronism. And these patients are going to get hypertension, some get alkalotic, and some get hypokalemic. And we've seen that in about a fourth of our patients on long term posaconazole, so it is definitely, you know, it's there. It's frustrating for the patient, the hypertension is not always reversible. This is a diabetic patient. So they're going to have sort of that metabolic syndrome and may have some pre hypertension, even at baseline. So you may sort of just push them further down the road with posaconazole. And that said, it is a choice for some of those patients, right? Um, I think isavuconazole we've really seen is very safe for patients. The side effects we've seen are generally idiosyncratic. Um, you know, they're - they're non predictable. We do check, blood levels for a lot of these patients just to make sure it's a detectable level. You know, if it's above 1, we're pretty happy if they're almost all above 1.

So I think that those are both good options. Again, it's gonna be really a long course of therapy for these folks, keeping their diabetes under good control, you know, extensive counseling about, you know, recurrence and coming in right away. But these are still devastating infections.

The other thing I thought it'd be sort of - of interest is the audience is the incidence of mucormycosis in DKA patients has actually declined over time. And that's thought to be that these patients are on statin therapy, right? And statins are sort of subinhibitory prophylaxis against fungal infection. So even though it's in the textbooks, we actually are seeing less of this fortunately, and it may be just the baseline statin that they're on.

DR. LEWIS:
And you talk a little bit about pushing doses with the azoles. What are you doing? Are you doing that based off TDM? Or are you just starting higher doses because of the mold? Or what are you doing?

DR. THOMPSON:
Yeah, I think that's a great question. And – and you know, we do typically try to identify these organisms to species level. I think if that's needed is a whole nother conversation, right? There's not great data for doing that, getting susceptibility testing on mucormycoses. And then tailoring your therapy. We don't have data for that, right? I think it's just so driven by host factors.

DR. LEWIS:
Yeah.

DR. THOMPSON:
You know, getting the diabetes under control, stopping whatever immunosuppression, you can. I think that's why those studies haven't bore out really that there's a predictable, you know, drugged MIC, predictor of long-term, you know, improvement. That said, some of these mucormycosis have high MICs to one azole and not to another. We generally try to pick the one that's lower. Again, we don't have great data for that, but we do if the MIC is 1 or 2, and that's the lowest one we have, we will kind of push the dose and try to get it up in the 3,4 range. I do think that's a little bit controversial, but I think we're giving it our best shot to get these very sick patients better.

DR. LEWIS:
Yeah, completely agree.

DR. THOMPSON:
So Jim, we have another interesting case the other day I was going to kind of pick your brain about. This was a patient named Laura. She's a 70-year-old woman and had a CLL that was first diagnosed two years ago. And she had a stem cell transplant, been on prophylaxis with posaconazole for a significant amount of time. She's on a standard sort of 300 milligram daily dose of the delayed release tablets. But she started complaining to her daughter and her daughter's fortunately a nurse. The patient was having chest pain and shortness of breath over just a couple days. And her daughter lived out of state though but really encouraged her to come in right away and see us in clinic. So she when she came in, which was just a day later, she came in actually via the ER, had pleuritic chest pain, dyspnea, fever, a little bit of hemoptysis, and our - one of our infectious disease fellows was actually working that night in the emergency room and diagnosed her with what he thought was a breakthrough fungal infection. And based on that, was really switched from posaconazole very early fortunately to – to liposomal amp - amphotericin at 4 milligrams per kilo per day. But after a couple days of treatment, she's still getting worse, and was really presented to our multidisciplinary rounds, which is hematology, oncology, and infectious disease. So sort of what's your approach to this - this type of patient when you see them with – with sort of your team on rounds?

DR. LEWIS:
Yeah, you know, this is unfortunately, one of the kind of more common invasive fungal infections that we're seeing these days. You know, I think the - the advent of these newer generation azoles has just been such a game changer, in a lot of ways for the management of invasive aspergillosis for how we prophylax these patients. But man, does it create some challenging situations when, you know, someone breaks through on one of these.

DR. THOMPSON:
Yeah.

DR. LEWIS:
You know, and I think that, you know, really, my – my pharmacy nerd side comes out, and the first thing I'm like, is what was her posaconazole level? You know, so I think the – the first thing I always do with one of these is – is run off and see if - if this person had - was having TDM done on their posaconazole. You know, we – we talked a little bit too earlier, you know, depending on how big she is, there's some weight effect perhaps posaconazole, you know, was she having diarrhea? Was there something that might have

negatively impacted her posaconazole absorption? You know, I think the other thing too, and you know, we kind of touched on this a little bit in both of the previous cases, diagnosis. Because, you know, I don't - I don't know about you, but the - one of the reasons that these things are absolutely horrific to try to deal with, is that the menu of potential organisms involved here is substantial. And really having to shoot in the dark, on a lot of these is - is really a challenge. I think, you know, we - we would have done exactly what your fellow did in the ER, which was basically switch off of the azole and go to the liposomal amphotericin B. But you know, then you just find yourself completely stuck, right? If you never get an organism back, you can never explain yourself that she had low posaconazole levels, it's like, oh, my gosh, if have I just sentenced this - this, you know, poor person to liposomal amphotericin B for the foreseeable future? You know, and so, you know, that's - that's kind of how we play them. Do you - I mean, what do you guys do with these folks, as far as, you know, really trying to establish a diagnosis? Because that's one of the places that I think we struggle the most with these folks.

DR. THOMPSON:
Yeah, yeah, I – I completely agree. The approach to this is switch them to amphotericin B while you're trying to let the dust settle. But the dust settle is assess compliance, right? I mean, you mentioned a posaconazole blood level, which is the first place to start but whether the patient's not taking it, they've got a drug-drug interaction to hypermetabolized posaconazole, which would probably be unlikely for this type of patient, but something worth doing. Making sure they're adequate levels. You know, about 10 percent of patients, even with the tablets still have, you know, subtherapeutic posaconazole levels. And at least at our center, it's not standard practice to check a level on posa prophylaxis patients. I think cost is an issue with that. But - but again, I think, like you said, that's really the first place to start. But you've got to make a diagnosis here for the reasons you said. You can't just put this patient on amphotericin B for the for see - foreseeable future. And then with improvement, just go back to an azole without understanding why that one failed. You know, they might have a Richter's transformation of leukemia, I mean, non-infectious causes still happen in this group, so you hate to put them on amphotericin B, you know, erroneously for that.

And, you know, the Duke data, from just a couple of years ago that Barb Alexander published, you know, showed with posa prophylaxis, this real change in what - what these patients are coming in with, they're coming in with more resistant organisms, you know, this is probably not aspergillosis. So mucormycosis, like the prior case, you know, Fusarium, Scedosporium, other resistant molds are more frequent in these patients on prophylaxis. We also note for some - from some recent literature by the MD Anderson group, you know, breakthrough infections do have a higher mortality.

So these are all the reasons you've really got to try to make a tissue diagnosis, you want to identify this organism to species level, really figure out if it's resistant in vitro to posaconazole so you can at least make an educated decision as you plan for their future. But these are very frustrating cases and becoming more and more common.

DR. LEWIS:
Yeah, you know, and it's - I'm glad to hear that it's a shared frustration. You know, because it's - it's one of the where, you know, a lot of times we end up kind of stepping back to your point and saying, okay, they - they're stable, they've been on, you know, lipid amphotericin B for some period of time, we're ready to send them home, but we don't really want to go back to the azole that they were on. You know, the issues - can you talk a little bit about, you know, the cross resistance within some of those molds that we talked about? Because I think, you know, there's – there's - we've run into some situations, right? Where we could try isa. Or we could try vori. And, you know, I just - I'm not a believer that unless you actually have your hands on the - that mold, and you have susceptibility results staring at you, that that's probably a particularly safe direction to go. How do you get - how do you handle a patient like that?

DR. THOMPSON:
Yeah, that's a - that's a great question. And again, that's really why we make such an emphatic attempt to make a tissue diagnosis here.

DR. LEWIS:
Yeah.

DR. THOMPSON:
Tissue and get cultures, do susceptibility testing, which admittedly does take time. That's frustrating for everybody taking care of the patient. It's frustrating for the patient to send out tests at almost every lab, you know, comes back in 10 days or so. So if you're able to do that, you're probably going to choose, you know, whichever one has the lowest MIC and - and sort of hope for the best because again, they can't stay on lipid amphotericin forever. My general approach is if they failed posaconazole, they're not going to go back on posaconazole –

DR. LEWIS:
Right.

DR. THOMPSON:
I'm really going to put them on isavuconazole. You know, if we're not able to make a diagnosis, I'm going to want to recover those resistant pathogens, so I'm going to be very hesitant to go to voriconazole. You know, Mucorales are going to be resistant. You know, Fusarium is probably going to be resistant even though that's what we have the best data for. So I think isavuconazole and sort of its spectrum of activity is probably where this patient is heading. If you're not able to – to get a – to really clinched the diagnosis here. But again, it's a little bit of a gamble.

DR. LEWIS:
Yeah.

DR. THOMPSON:
So that's why we make such an attempt to make a confirmed diagnosis upfront.

DR. LEWIS:
Thank you for participating in this CME activity.

Announcer:
You have been listening to CME on ReachMD. This activity is provided by the Academy for Continued Healthcare Learning and is supported by an educational grant from Astellas.

To receive your free CME credit, or to download this activity, go to ReachMD.com/CME. Thank you for listening.