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Case Discussions

National HIV Curriculum Podcast

Management of Cryptococcal Meningitis

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After diagnosing cryptococcal meningitis in the last episode, National HIV Curriculum Podcast Editors Dr. Jehan Budak and Dr. Aley Kalapila review the complexities of managing a patient with HIV and cryptococcal meningitis.

Topics:

- HIV
- OIs and HIV
- Crypto
- cryptococcal
- meningitis

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Transcript

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introduction**[00:00] Introduction**

Hello, everyone. I'm Dr. Jehan Budak from the University of Washington in Seattle, and welcome to the National HIV Curriculum Podcast. This podcast is intended for health care professionals who are interested in learning more about the diagnosis, management, and prevention of HIV.

So in our last podcast, we discussed the evaluation of a patient with HIV who had a headache and was diagnosed with cryptococcal meningitis. Last time we focused on diagnosis. But in this episode, we're going to focus on the management of a patient with cryptococcal meningitis. And so I'm back with my colleague, Aley Kalapila, an infectious diseases physician at Emory University in Atlanta to talk about this. Hi, Aley.

Dr. Kalapila

Hi, Jehan. And hi everyone listening. Excited to be back to pick up where we left off.

background**[00:48] Background**

Dr. Budak

And to recap where we left off: In the last episode, we had discussed a 28-year-old man with a new diagnosis of HIV with a CD4 count that was 4 who presented with two weeks of headache, photophobia, blurry vision, and nausea, found to have cryptococcal meningitis, which we will refer to as crypto or crypto meningitis.

From a diagnostic perspective, he had an elevated opening pressure, an elevated serum and CSF [cerebrospinal fluid] cryptococcal antigen, which we refer to as a CrAg, positive CSF India ink stain and a CSF culture positive for *Cryptococcus*.

empiric-therapy**[01:22] Empiric Therapy**

So Aley, the first thing I wanted to ask for your opinion on is a question about empiric therapy. When someone comes in and we suspect crypto meningitis and we do an LP [lumbar puncture] and there's a high opening pressure, but we are still waiting for the cell count in the CrAg, what would you start empiric therapy?

Dr. Kalapila

Yeah, you know we always seem to be making this decision in the middle of the night. So fortunately in this specific case, we did get our results back pretty quickly and so we didn't have to wait too long. But if that were not the case, then I think you have to kind of weigh the clinical presentation and also your diagnostic information. So in this case, we know that this patient had a low CD4 count, which puts him at risk for cryptococcal meningitis. He also had a subacute headache, which is a presentation that was classic for cryptococcal meningitis. And then you did the LP and you've now documented an elevated opening pressure as well. So I think putting all this together, in my mind, this is crypto and so even if I did not have the CrAg result in front of me, I would 100% initiate empiric therapy for presumed cryptococcal meningitis.

Dr. Budak

Totally. This is a potentially life-threatening disease, which can lead to both morbidity and mortality, especially if untreated. And so, I too would start treatment empirically.

induction-phase**[02:38] Induction Phase**

Dr. Budak

Aley, what is it that you're starting with? Can you walk us through the basics of crypto meningitis treatment, which I know are a bit complex?

Dr. Kalapila

Yes, very complex. It's always fun trying to teach this to learners. So when I think about cryptococcal meningitis treatment, I think about it in three phases. So you have an induction phase, a consolidation phase, and a maintenance phase. Now, from a very big picture perspective, your induction phase, which is the first phase, is your most intensive. So this is where you're going to hit the person hard with aggressive therapy. And so, you're going to actually start with intravenous antifungal therapy. And this is typically for about two weeks. After that, the next phase is called consolidation, and that lasts for about eight weeks. And then finally you have maintenance therapy, which can be for a year or longer. Now, both consolidation and maintenance are a little bit less intensive, and so these would be with oral antifungal agents.

Dr. Budak

So all this to say this is quite an involved and lengthy treatment course.

Dr. Kalapila

Absolutely, and I think we need to probably break that down a little bit further. So, for the first phase, the induction phase, the recommendation is to start with intravenous liposomal amphotericin B and flucytosine, which we often refer to as 5-FC, and that is an oral medication. Now, if liposomal amphotericin B is not available, then you can use a conventional form of ampho B, which is ampho B deoxycholate.

I think the main point that I do want the listeners to get across here is that you should ideally be ordering the liposomal formulation of amphotericin B, and this is to actually minimize the renal toxicity that is associated with ampho B in general. Obviously, if you're at a healthcare facility where you don't have access to the liposomal formulation, then I think at that point you can obviously use the conventional formulation of ampho B. Both the ampho B formulations are dosed by weight and you're going to give your induction therapy for about two weeks.

Dr. Budak

Okay. So a management point I'd like to ask for clarification, should the patient stay hospitalized for those two weeks?

Dr. Kalapila

Ideally, you do want the patient to be hospitalized because as we both know, ampho B can be associated with nephrotoxicity. You need frequent lab monitoring as well. And so, not to mention the fact that you would also need clinical monitoring for complications related to cryptococcal meningitis, specifically your elevated intracranial pressures (ICPs). You might have to have a patient have frequent LPs or maybe a lumbar drain. So, in order for all of these things to happen, it is much faster or much easier to be able to do this in the inpatient setting.

Dr. Budak

And Aley, you mentioned potentially needing multiple lumbar punctures, et cetera, can you expand a little bit upon that?

Dr. Kalapila

Yeah. You know, so if you remember from our previous podcast, our patient had elevated opening pressure. So initially we would tap the patient and drain his CSF down to an opening pressure less than 20 centimeters of water. So the goal is that with this aggressive induction antifungal therapy and serial lumbar punctures, your opening pressures will eventually normalize to a level that's less than 20.

Dr. Budak

You mentioned serial LPs. How many times are you doing an LP?

Dr. Kalapila

That really kind of depends on their symptoms. So if they're exhibiting signs and symptoms of elevated intracranial pressure, then you may need to tap the patient as frequently as every day. So there is no one size fits all. I really do titrate it to the patient. So I remember once I had a patient who had diplopia, which was his manifestation of elevated ICP, and whenever we tapped him and we were able to drain that CSF down to a normal opening pressure, the diplopia would resolve.

Other patients will say that their headache gets better once you've done that LP and normalized the opening pressure. So you really do have to titrate it to the patient. And in certain cases, depending on the severity of the opening pressure or the severity of the intracranial pressures, you might need to tap these patients every day. Now, if a patient is asymptomatic, but on that initial tap you've documented a high opening pressure, again, the frequency can vary, but you may even need to do it as frequently as every other day.

consolidation-phase**[06:49] Consolidation Phase**

Dr. Budak

Well, thanks for taking us through that. Let's say the patient is still on induction phase, when would you switch to consolidation therapy?

Dr. Kalapila

So, after your two weeks of induction therapy, the next phase, like you said, is consolidation and you would want to switch to consolidation after these two weeks *provided* that the patient is clinically stable. And what we would use for consolidation is high-dose oral fluconazole.

Dr. Budak

So Aley, the first key point that I think we should emphasize is that per DHHS [U.S. Department of Health and Human Services] of opportunistic infection (OI) guidelines, "The transition to consolidation therapy with oral fluconazole should occur *only if* the patient has clinically improved and is clinically stable. If patients are not improving or remain clinically unstable at that day 14 point, the induction therapy should be extended longer." So how do you determine that they've responded appropriately to the induction antifungals?

Dr. Kalapila

That's a really great question. So what you need to do is to repeat a lumbar puncture, which you're going to send off for CSF culture, so not CrAg, not India ink, at the end of your induction therapy on day 14. The important point that I want to emphasize here is that the response to therapy is based on sterilization of your

CSF culture. You are not basing it on your CrAg or India ink results. So I repeat, you do *not* want to send off a CrAg or an India ink again because these tests can actually remain positive for a prolonged period of time and they really don't indicate treatment. And so even if they stay positive, it's not indicative of treatment failure.

But regardless, you've now finished your induction therapy at day 14, you've done your LP and if your patient is clinically stable, you can go ahead and switch them to oral antifungals for consolidation therapy and you can go ahead and discharge your patient while waiting for your CSF culture results. And that is what is recommended by the DHHS OI guidelines.

Dr. Budak

And so they define successful induction therapy as a substantial clinical improvement and a negative CSF culture from that end of induction lumbar puncture. And as Aley's kind of intimating, these CSF culture results typically take about three weeks to incubate in the micro lab. So you will be, or most likely will be, discharging that clinically stable and improved patient before their CSF cultures have finalized, which can feel a little bit uncomfortable.

Dr. Kalapila

So, we've done that day 14 LP and while we are waiting for that end of induction CSF cultures to finalize, and remember, this can take about three to four weeks in a micro lab, the DHHS OI guidelines recommend that we can step down to consolidation therapy and consolidation therapy is with oral fluconazole dosed at 800 milligrams once a day.

Dr. Budak

Aley, wasn't that a change in the OI guidelines?

Dr. Kalapila

Yeah, this was changed in 2021. The previous recommended consolidation dose for fluconazole was actually 400 milligrams a day and it has now been upped to 800 milligrams a day. The guidelines recommend that once the CSF cultures have finalized and if they're sterile, you could consider downgrading the dose to 400 milligrams a day.

So, if you think about it in clinical practice, you've done your day 14 LP, you're waiting for the cultures to finalize, your patient is improved, you're going to discharge them first on 800 milligrams of fluconazole for consolidation. It takes about three to four weeks for the cultures to finalize. So your patient is going to remain on consolidation dosing for three to four weeks.

And then if those cultures are now negative, those day 14 cultures are negative, you have the option to downgrade to 400 milligrams if you'd like. Regardless of what dosing you use, if you choose to leave them on 800 or if you do 800 and then 400, the total duration of your consolidation therapy is going to be eight weeks from the time of your CSF cultures remaining negative.

Dr. Budak

And Aley, I don't know about you, but I think I usually, if a patient is tolerating that 800 milligrams, tend to just keep it at that until I'm going to make that transition.

Dr. Kalapila

Yeah, absolutely.

Dr. Budak

So now let's say that you are waiting for those cultures to finalize, what happens if it turns positive while you're waiting, while that patient is discharged and is on their fluconazole 800 milligrams a day?

Dr. Kalapila

That has also happened to me, not infrequently. So if the CSF culture does turn positive and we are again getting back to that day 14 CSF culture, but the patient is clinically improved, you've discharged them, you can actually increase your dose of fluconazole to 1200 milligrams a day. And this is actually recommended in DHHS OI guidelines.

They also recommend that you repeat your lumbar puncture with the caveat that the next LP that you do has to be two weeks from your most recent lumbar puncture. Now, in addition to the 1200 milligrams of fluconazole, the OI guidelines also give you the option of adding on oral 5-FC as well. But here's the problem. So fluconazole, as you and I both know is a 200 milligram tablet. Unfortunately, higher dose tablets are not available.

These patients are already taking six tablets of oral fluc[onazole] once a day. Now you're going to add on 5-FC as well. It's just a lot of pills. And so I'm just very hesitant to prescribe it for patients because in general I've just often worry that adherence is a big issue. But regardless of what you choose to do, again here, you would need to keep them on the 1200, repeat your LP, make sure the LP has sterilized, and then move back down to your 800 milligrams of consolidation dosing for eight weeks from your documented negative CSF culture.

Dr. Budak

Aley, I've got two clarifications. One, I think you had said that you're hesitant to add the 5-FC to the 1200 milligrams of fluconazole. For the listeners, Aley's not hesitant to increase to 1200 milligrams of fluc[onazole], she's just hesitant to add the 5-FC to the higher dose fluconazole. Is that right, Aley?

Dr. Kalapila

Yes. Yes.

Dr. Budak

Okay, perfect.

maintenance-phase**[12:56] Maintenance Phase**

Dr. Budak

And then just for the listeners, I know that Aley repeated this, but again, induction therapy is a minimum of two weeks. Consolidation is typically eight weeks and then provided their CSF culture remains negative, then we can transition to maintenance. Right, Aley?

Dr. Kalapila

Yeah, that's right. So, at that point, once we transition to maintenance, the dose of fluconazole that we would want to use is just 200 milligrams once a day. Now, the duration for maintenance therapy is for at least a year from the time that you've initiated antifungal therapy for cryptococcal meningitis, as well as the patient should have no signs or symptoms of crypto infection, they must have a T-cell count that's greater than a hundred or a hundred or higher and they should have a viral load that is now suppressed in response to

antiretroviral therapy.

Dr. Budak

Which is *a lot of* stipulations. So effectively, individuals are on their maintenance dose of fluconazole, 200 milligrams daily for at least a year.

when-to-start-art**[13:56] When to start ART?**

Dr. Budak

And now that we've talked through the antifungal treatment phases, listeners may notice that we haven't mentioned starting ART yet. So Aley, when are you going to start ART for this patient?

Dr. Kalapila

So, you know, I base my approach to ART initiation on results from the COAT study, which I love and I know you love it too. So, I think that you should tell us a little bit about the COAT study, Jehan.

Dr. Budak

Okay, if you twist my arm, happy to. So the COAT study, which I think many of us know is from the *New England Journal of Medicine*, Boulware et al., and was published in 2014 and was a randomized controlled trial in Sub-Saharan Africa of individuals with HIV who had diagnosed cryptococcal meningitis. They were randomized to either start ART early, which they defined as one to two weeks after antifungal therapy was initiated versus starting ART later, which they defined as after five weeks after antifungal therapy was started.

Their findings were that there was higher mortality in the earlier ART-start group versus the deferred-start group. And the reason for this is that because when you start ART, patients will have immune reconstitution, which can lead to massive inflammation in a closed space, i.e., the brain and skull, increased intracranial pressures and potentially brain herniation.

Interestingly, in individuals who have a CSF white blood cell count less than five, mortality was even higher in the early-start versus deferred-start group. And Aley and I had actually talked about this in the first podcast where patients with a low CSF white blood cell count often have a worse prognosis and that's just because that they can reconstitute even worse than others.

Dr. Kalapila

That's a great summary, Jehan, thank you.

Dr. Budak

Thank you.

Dr. Kalapila

And, so based on the results of the COAT study, I would typically initiate antiretroviral therapy at the four-week mark. Provided of course, again, the patient has continued to clinically improve, and you have now documented negative CSF fungal cultures as well.

elevated-icps-during-induction**[15:54] Elevated ICPs During Induction**

Dr. Budak

And now, we've mentioned increased ICP both in regard to the disease process of cryptococcal meningitis and also with regards to fear of IRIS [immune reconstitution inflammatory syndrome]. When you're managing someone with crypto meningitis in the hospital during that induction period, what happens if despite repeat LPs, the patient remains symptomatic and has not achieved a normal opening pressure, or the patient is not able to tolerate having those serial lumbar punctures performed?

Dr. Kalapila

This too is a scenario that I have encountered several times. So, as I mentioned previously, we would need to repeat this LP based on opening pressure and clinical symptoms. Now, if after three to four LPs, the patient, like you said, is unable to tolerate the repeat lumbar puncture or they still have elevated ICPs and are still symptomatic from it, then this is the time when I would get neurosurgery involved.

Now, I'm not a neurosurgeon, but in my experience, typically the neurosurgeons start with a lumbar drain. And the hope here is that as your patient completes induction therapy, their CSF intracranial pressures will normalize. But, of course, if they don't have symptomatic improvement or you have persistently elevated ICPs, then you will need to internalize that drain into a VP shunt.

Now, this procedure will be deferred of course until the CSF is formally sterilized because you're not going to put in a VP shunt into contaminated or nonsterile CSF. More importantly, the standard medications that we would use for elevated ICPs, things like steroids or acetazolamide or mannitol are actually not recommended for the management of intracranial pressure, elevated intracranial pressure secondary to cryptococcal meningitis.

medication-side-effects**[17:41] Medication Side Effects**

Dr. Budak

So now we've talked about management of elevated OPs [opening pressures]. Can we touch a little bit about medication side effects? I feel like renal insufficiency with liposomal ampho B is probably the issue I see the most of. Specifically, Aley, what do you do or how you manage the patient when you are getting into trouble or having medication side effects with the induction meds?

Dr. Kalapila

That too can happen pretty frequently as well. So, the first thing that I would do is I would first look at the med recon list and I would try to take away any nephrotoxic medications. I would like to see if I could push forward as much as I can safely with induction therapy with liposomal ampho B and 5-FC. Other things I could do is also give them extra hydration with the renal toxicity as well.

But obviously, if you're pushed against a corner and your renal function is continuing to decline, then yes, you absolutely have to stop the amphotericin, and at this point your option would be to switch to high-dose fluconazole 1200 milligrams. And this is actually based on data or studies that have shown that the antifungal activity of fluconazole in CSF of patients with crypto meningitis increases as the dosing of the drug increases as well.

Dr. Budak

And so Aley, just to clarify for the listeners, if you're having to stop the amphotericin and switch to high-dose fluconazole, you are still combining that with the 5-FC?

Dr. Kalapila

Yes. You would continue the high-dose fluconazole with 5-FC.

Dr. Budak

And then aside from renal insufficiency, what are some other toxicities or side effects that you may see from induction therapy?

Dr. Kalapila

With ampho B, you can see electrolyte abnormalities such as magnesium or potassium wasting, which is why a lot of the order sets, because of the nephrotoxicity as well as the electrolyte derangements, the order sets often include pretreatment fluids. You can see rigors actually with ampho B. And so some order sets will come with administration of diphenhydramine or meperidine for the rigors. And then with 5-FC you can see cytopenias as well as hepatic and or GI toxicities as well.

Dr. Budak

Wonderful. So it is not a straightforward regimen, that's for sure.

Dr. Kalapila

Not at all.

Dr. Budak

So Aley, thanks for taking us through all of that.

teaching-points**[19:54] Teaching Points**

Dr. Budak

I'd like to wrap up with some teaching points. So first, treatment of crypto meningitis has three phases. We've got induction, consolidation, and maintenance. Induction therapy typically entails at least a minimum of two weeks of therapy with IV liposomal amphotericin B and oral 5-FC. After those two weeks, you should get a repeat LP, typically around 14 days, which we will call the end of induction therapy LP.

And then provided the patient is clinically improving, crypto meningitis treatment can be transitioned to consolidation therapy, and that is while you're waiting for that CSF culture to come back. And that is usually 800 milligrams of oral fluconazole. And that phase should last a minimum of eight weeks. Then, you go to maintenance therapy with oral fluconazole 200 milligrams daily, and this is typically continued for about a year, maybe even longer, and really can be stopped once that patient is on ART, has viral suppression and their CD4 count is greater than a hundred.

And then last, ART initiation should be deferred for some period of time after starting antifungals, and that's to minimize complications related to CNS [central nervous system] crypto IRIS. And the DHHS OI guidelines recommend waiting four to six weeks after antifungal initiation. But in clinical practice, as we've mentioned, Aley and I tend to start around week four. So, I think unless I've forgotten anything, we can call it a wrap. And Aley, thank you so much again for sharing your expertise with us today.

Dr. Kalapila

Thank you. Thanks, Jehan. Looking forward to the next one.

Dr. Budak

Bye everybody.

credits**[21:31] Credits**

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