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Case Discussions

National HIV Curriculum Podcast

Pneumocystis Pneumonia: Management

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National HIV Curriculum Podcast Editors Dr. Jehan Budak and Dr. Aley Kalapila discuss their approach to treating Pneumocystis Pneumonia (PCP or PJP) in a person with advanced HIV, including the use of antimicrobials, adjunctive steroids, and when to start ART.

Topics:

- OIs and HIV
- pneumonia
- antimicrobials
- steroids
- ART

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Disclosures

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Transcript

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intro--case**[00:00] Intro & Case**

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.

I'm back with my colleague, Aley Kalapila, an ID physician at Emory University in Atlanta. Hi Aley!

Dr. Kalapila

Hi Jehan. Hi everyone. Looking forward to this episode.

Dr. Budak

So today, we will pick up where we left off, which was that a patient with progressive subacute dyspnea and nonproductive cough, newly diagnosed with advanced HIV with a CD4 count of 7, was found to have a pneumocystis pneumonia. During that prior episode, Aley took us through a differential diagnosis on a patient with HIV and dyspnea, and we discussed the approach to diagnosis of pneumocystis pneumonia, which we call PCP or PJP.

As a reminder, pneumocystis is a ubiquitous atypical fungus that causes pneumonia in persons with HIV, typically when the CD4 count is less than 200. Nondefinitive markers like lactate dehydrogenase (or LDH) and beta-D-glucan (or BDG) can be helpful, but definitive diagnosis requires pathologic identification of the organism on respiratory specimens, and an alternative diagnostic method is to use PCR [polymerase chain reaction]. Although, the diagnostics that one has access to is dependent on their health care institution. And, at the end of that episode, we talked briefly about how empiric treatment was begun, so I think that this is a good starting point for today's discussion.

pao2-vs-a-a-gradient**[01:30] PaO2 vs A-a Gradient**

Dr. Budak

Aley, can you tell me a little bit more about what treatment was used in your case?

Dr. Kalapila

Sure! So, you know, I think probably the best thing to do in this situation, or the first thing that we would need to do is to determine the appropriate treatment. And, the way that would do that is to look at whether or not the patient had mild-to-moderate or moderate-to-severe disease, which is how the DHHS Opportunistic Infection Guidelines (or OI guidelines) has this kind of demarcated. The main distinguishing factors between these two categories, of course, lies in the degree of hypoxemia that the patient has.

Dr. Budak

Yeah, let’s talk a little more about that.

Dr. Kalapila

Yes, so you know the degree of hypoxemia that the OI guidelines uses to delineate between severe and less severe disease uses either a room air PaO2, which is the partial pressure of oxygen, or an alveolar-arterial oxygen gradient, which we refer to as an A-a gradient. So, these are the two, sort of, labs that we would use in order to determine the degree of hypoxemia that a patient might have.

Dr. Budak

So, without getting too much into respiratory physiology, the A-a gradient is the difference between the oxygen levels in the alveoli and the oxygen levels in the blood. And, if the difference between the two is too big, then there’s a problem with how well the oxygen is moving from the alveoli into the blood. So, the A-a gradient helps us understand how the lungs are delivering oxygen to the blood and helps us determine the severity of PCP.

Dr. Kalapila

Yeah, thank you. That’s a great explanation, and I always sort of have to refresh my memory as well about the exact meaning of those two labs. But, you know, to be more specific, the OI guidelines define someone as having moderate-to-severe PCP if they have a PaO2, so this is the partial pressure of oxygen on room air, of less than 70 mmHg or an A-a gradient (or the alveolar-arterial gradient) greater than or equal 35 mmHg.

Dr. Budak

I don't know about you, Aley, but I really rely on the PaO2 instead of calculating an A-a gradient.

Dr. Kalapila

Oh yeah, definitely! I mean, I think the PaO2 is easily accessible because it’s the information that we receive when we get our results from an arterial blood gas (or the ABG), whereas the A-a gradient requires us having to do this additional step of actually going to an online calculator so that we can calculate it. So, can you just remind me what his ABG showed?

Dr. Budak

Yeah, his ABG on ambient air had a PaO2 of 65.

Dr. Kalapila

Okay, so that PaO2 is less than 70, so that to me puts him squarely into the moderate-to-severe PCP category range.

treatment**[04:18] Treatment**

Dr. Kalapila

So, getting back to our treatment discussion. So, the preferred regimen for treatment of moderate-to-severe PCP then is to use IV trimethoprim-sulfamethoxazole, which we can often refer to as trim-sulfa. So, we would start with an IV formulation of trim-sulfa and then we would switch to an oral trim-sulfa formulation after there’s some clinical improvement.

Dr. Budak

And the dosing of that isn't always straightforward. And, in fact, just over the weekend, I was in a team room with a bunch of residents, we all had our phone calculators out trying to calculate this. And so, we won't get into the details of dosing of trim-sulfa for pneumocystis pneumonia, but in short, it is weight-based, primarily based on the trimethoprim component of the combination pill. And, this is definitely a time to liaise with a clinical pharmacist for assistance in dosing. The dosing for not only the trimethoprim component has to be accurate but also the sulfamethoxazole component.

Dr. Kalapila

So, here's a leading question, Aley. Is there anything additional you would give this patient?

Dr. Kalapila

Because this patient has moderate-to-severe pneumocystis pneumonia, he qualifies for an adjunctive treatment and that is adjunctive corticosteroids. Now, these need to be initiated as soon as possible, and, ideally, you want to be able to start that at the same time as your first dose of antimicrobial treatment but no later than 72 hours after you have made your diagnosis of moderate-to-severe PCP. The choices that you have would be either to give the patient IV methylprednisolone (or methylpred as we often abbreviate it as) or oral prednisone if the patient can tolerate the oral dosing. The specific dosing of the steroids, I would say it's probably better to just refer to the OI guidelines for that.

Dr. Budak

And the sentinel study for use of steroids in pneumocystic pneumonia was from Bozzette et al. from the *New England Journal of Medicine* in 1990. And, actually, that paper looked at about 300 patients with AIDS and PCP, and they were randomized to receive either standard PCP treatment, mostly with trim-sulfa in the study, or standard treatment with adjunctive steroids. And the conclusion was that early adjunctive steroids reduced the risk of respiratory failure and death in those who had moderate-to-severe PCP. So, Aley, back to the treatment for this. It sounds like you started steroids for the patient. How long do you treat the patient for?

Dr. Kalapila

So, you know, the duration for the antibiotics and the adjunctive corticosteroids is 21 days, and the steroids would then need to be tapered over those 21 days.

Dr. Budak

And that dosing, again, is in the OI guidelines, as you had mentioned, Aley.

Dr. Kalapila

Yes.

trim-sulfa-alternatives**[07:05] Trim-sulfa Alternatives**

Dr. Budak

So, what if you have someone who is unable to tolerate trim-sulfa either due to an allergy, side effects that develop while on therapy, or perhaps some baseline renal dysfunction that may preclude use or dosing of trimethoprim-sulfamethoxazole?

Dr. Kalapila

So, yeah, that's a great question. It's a pretty common scenario that we see. So then, you know, your second-

line treatment that I would use for moderate-to-severe PCP is to use oral primaquine plus clindamycin. The clindamycin can be administered either intravenously or orally. Now, because primaquine can cause increased oxidative stress, you do need to check a G6PD level prior to administration of primaquine because if a patient has G6PD deficiency they can develop a hemolytic anemia. So, I think it is always a good idea, quite frankly, to obtain the G6PD level as soon as someone has that diagnosis of PCP because, I don't know about you, but for us in our hospital system, it takes several days for us to get that test result back. And so, if we do need to change therapy, then we have to like wait because of the G6PD level that's pending. So, regardless, check a G6PD level when you first admit a patient for PCP pneumonia, if you don't have it already and then, as long as the patient does not have G6PD deficiency, you can use oral primaquine and IV or oral clindamycin as your second-line treatment if someone is unable to tolerate trim-sulfa.

Dr. Budak

And then, Aley, what if someone with moderate-to-severe PCP had a G6PD deficiency precluding primaquine use and they couldn't receive trim-sulfa?

Dr. Kalapila

So, in that case, the alternative then is to use intravenous pentamidine.

side-effects**[08:56] Side Effects**

Dr. Budak

Oof! Ah, so I think actually that would be a good time to talk about some side effects of these antibiotics. You just mentioned IV pentamidine, and this one can have a lot of side effects, and I feel like whenever we even mention IV pentamidine there's a groan. I guess we just did one too. So, a big one I worry about is hypotension during the infusion. It can also cause leukopenias, renal dysfunction, severe hypoglycemia, and hepatitis, to name just a few. Going to the other antimicrobials that we use. You already mentioned the big thing we worry about when using clindamycin and primaquine is that the primaquine can cause hemolytic anemia if the patient has a G6PD deficiency. Clinda and really any antibiotic can cause antibiotic-associated diarrhea, as well as *C. diff* [*Clostridioides difficile*] diarrhea. And though, you know, I think a lot of us talk about clinda a lot when it comes to *C. diff.* And last, we have the most experience with trim-sulfa, I think it's worth mentioning again to everyone that it can cause renal dysfunction, hyperkalemia, leukopenia, hepatitis, and rash.

Dr. Kalapila

Once again, to reiterate the duration of treatment for PCP is typically 21 days, no matter what medication you use, and of course your adjunctive corticosteroids if you're giving it to a patient who has moderate-to-severe PCP should also be tapered over those 21 days.

treatment-mild-pcp**[10:16] Treatment of Mild PCP**

Dr. Budak

And, Aley, what about if the patient did *not* have moderate-to-severe PCP. I know your patient did, but let's say that their ABG had a PaO2 of 75. How would you treat the patient in this scenario?

Dr. Kalapila

Now in that case, the patient would be classified as having mild-to-moderate disease, so once again, the preferred regimen is to use trim-sulfa, but this time we can go straight to oral rather than using IV in the beginning like we did for the moderate-to-severe case. And, if we were unable to use trim-sulfa for whatever

reason, then the alternative regimens that are recommended by the DHHS OI guidelines would be oral primaquine and clindamycin, and that is usually my first go-to as an alternative regimen. Now again, as we mentioned earlier, you know, in order to use primaquine you need to make sure that the individual does not have G6PD deficiency. If they do have G6PD deficiency, and/or you're just unable to use the primaquine and clindamycin for other reasons, then the next alternative is to use atovaquone. The last alternative is to use dapsone plus oral trimethoprim. Dapsone, of course, has the same problem that primaquine does in that you cannot use that in individuals who have G6PD deficiency because of the risk of hemolytic anemia.

Dr. Budak

I don't know about you, Aley, but I've never had to use the dapsone plus trimethoprim combination. I've always been able to use one of the other alternatives to trim-sulfa that you had mentioned.

Dr. Kalapila

Yeah, the same. So, most of my patients who need an alternative regimen can tolerate either atovaquone or primaquine with clindamycin.

Dr. Budak

Great.

mild-pcp-tx-side-effects**[11:51] Mild PCP Tx Side Effects**

Dr. Budak

So, let's just quickly review the side effects of the alternative options in mild-to-moderate PCP. We already discussed clindamycin and primaquine side effects. You already had touched on the fact that dapsone can cause a hemolytic anemia if used in individuals with a G6PD deficiency. And, you can also rarely see a methemoglobinemia with dapsone. It's worth remembering that dapsone has a sulfa moiety, so it's not a contraindication to use in individuals with a sulfa intolerance, but it is contraindicated for individuals who have a severe sulfa allergy. So, for instance, if someone had nausea or leukopenia to sulfa antibiotics, you should still be able to use dapsone. But if someone had a severe sulfa allergy, like anaphylaxis or Stevens-Johnson syndrome, then dapsone should not be used. And last, atovaquone is a liquid, and the main issue we hear about that is that it tastes pretty gross.

treatment-failure**[12:43] Treatment Failure**

Dr. Budak

What if, in your case, you've started steroids, you've started the trim-sulfa. What if your patient wasn't improving?

Dr. Kalapila

Yeah, also a very good question. So, of course, the OI guidelines actually have described this. They talk about this in terms of treatment failure, and so now treatment failure, as defined by the OI guidelines, is a lack of improvement or worsening of respiratory function after 4-8 days of treatment initiation. So, if this were to happen, I would ask myself if there is an alternative diagnosis driving the patient's symptoms. And so, we would need to evaluate for a concomitant infection, ideally with using bronchoscopy with a bronchoalveolar lavage (or BAL) because, again, remember that this is a patient who is profoundly immunocompromised and could be at risk for multiple things happening at the same time. Now, if no additional cause is found, then I think it's useful to sort of get an expert involved. This is the time when I usually go and involve pulmonary, as well, because it's not really clear what the best strategy is going to be. Now, the options, of course, are to

stay the course or switch to another regimen, and really all of that kind of depends on many different factors, like if there's a second process, if you're unable to find what the second process is, if it's a medication effect. Lots of different things you can think about in a differential diagnosis here. And so, it really just has to be assessed in a case-by-base fashion.

starting-art**[14:10] Starting ART**

Dr. Budak

And in his case, he had improved, and there was never concern for treatment failure. So, what about when to start ART [antiretroviral therapy] in this patient, who has a new diagnosis of HIV and is otherwise ART naïve?

Dr. Kalapila

So, I started ART immediately in this patient. And, in general, antiretroviral therapy can be started as soon as possible and within two weeks of the PCP diagnosis.

when-to-discharge**[14:33] When to Discharge?**

Dr. Budak

And, in general, when do you consider discharging patients with PCP?

Dr. Kalapila

So, with discharge, I would think about discharging the patient once they are clinically stable and they are able to tolerate a totally oral PCP treatment regimen. So, oftentimes, you'll probably be discharging them on sort of a sequence of oral meds that they need to complete for 21 days. So, once they've completed the 21 days of treatment, they should be transitioned to their secondary PCP prophylaxis to prevent further episodes of pneumocystis pneumonia. And the plan would be to continue that prophylaxis until they have sustained immune reconstitution on antiretroviral therapy.

summary**[15:01] Summary**

Dr. Budak

So, with all that in mind, let's wrap up this episode with summary points about the treatment of PCP, which often is initiated presumptively based on presentation and imaging while awaiting a definitive diagnosis. So, once diagnosed or even, really, considered, the clinician should determine if the patient has mild-to-moderate or moderate-to-severe PCP to guide management. And, moderate-to-severe PCP is defined as a room air PaO_2 < 70 mmHg or an A-a gradient greater than or equal to 35 mmHg, though as Aley and I discussed, we are predominantly using the PaO_2. The preferred drug for PCP treatment is trimethoprim-sulfamethoxazole, regardless of disease severity, and adjunctive corticosteroids should be used for moderate-to-severe PCP. The treatment course is 21 days in duration, and if adjunctive steroids are used, they should be tapered over that 21-day treatment course, and that dosing for that taper can be obtained on the DHHS OI guidelines. And last, ART can be initiated as soon as possible or at the very least within 2 weeks of the PCP diagnosis.

So, I look forward to next time. Aley, thank you again so much

Dr. Kalapila

Thanks, Jehan. See you soon.

credits**[16:31] Credits**

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