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Case Discussions

National HIV Curriculum Podcast

Evaluation of Dyspnea in a Person with Advanced HIV

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Dyspnea in persons with advanced HIV has a broad differential diagnosis. National HIV Curriculum Podcast Editors Dr. Jehan Budak and Dr. Aley Kalapila discuss potential causes and diagnostic options with a specific focus on the wide array of diagnostics for *Pneumocystis pneumonia* (PCP), including blood tests, sputum stain types, DFA, and PCP PCR.

Topics:

- OIs and HIV
- Dyspnea
- PCP
- TB
- PCR
- LDH

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Disclosures

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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. 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 doing this episode.

Dr. Budak

So, on today's episode we will be talking about shortness of breath in someone with HIV, which is a very common situation that we see in clinical practice, so let's just get started.

case-intro**[00:39] Case Intro**

Dr. Budak

The patient is a 25-year-old man with no known prior medical problems and not taking any medications who presented to the ER with chest pain, shortness of breath with ambulation, and a nonproductive cough, which had been progressively worsening over the last 4-5 weeks. His O2 saturation was 90% on ambient air, and a chest radiograph showed opacities in the right upper lobe and in the lower lobes bilaterally. He was admitted to the hospital and the following morning, his plasma-based HIV antigen/antibody test resulted as positive.

So, before we talk more about this case, Aley, I'm going to ask your opinion on your differential diagnosis, and respiratory complaints in someone with HIV can have a very broad differential diagnosis. So, can you please break it down in to the organism buckets as you usually do and then also split that up based on whether the CD4 cell count is greater than or less than 200? And, for the listeners, at the moment we don't know the patient's CD4 cell count yet so it's really important to consider all the possibilities.

bacterial**[01:36] Bacterial?**

Dr. Kalapila

Yeah, sure. So, I agree it's a broad differential, so let's first tackle the bacterial bucket. Now, for a CD4 count greater than 200, the organisms I think about are your standard community-acquired pathogens, including atypical bacteria. So, bacterial pneumonia of course occurs frequently in people living with HIV and the common organisms that we would think about would be organisms like *Streptococcus pneumoniae* or *Haemophilus influenzae* or the atypical community-acquired bacteria would be *Mycoplasma pneumoniae* or

Chlamydia pneumoniae. Now, if an individual had a nosocomial exposure, so say for instance they were residing in a long-term care facility or if they had been recently hospitalized, then we would also need to think about nosocomial bacterial pathogens such as *Staph[ylococcus] aureus*or *Pseudomonas aeruginosa*. *Legionella* is also an atypical bacteria that can cause pneumonia; now, this has a classic-like epidemiologic association, which is manmade aquatic reservoirs and that too as we know can cause severe pneumonia in people with HIV.

Now, in general, in this bacterial category, the chest x-ray can be quite helpful actually especially if it shows us like a lobar consolidation, which would suggest a typical pathogen, for instance like pneumococcus, but that wasn't seen on this chest x-ray, right? So, we saw more patchy opacities, which are more suggestive of an atypical bacteria, and that could also be due to a virus or a fungal pathogen, as well. Now, remember that bacterial pneumonias tend to have a far more acute presentation, so you would have expected this patient to have worsening symptoms over a much shorter period of time, but based on the history that you've just given me, his symptoms had been going on for several weeks, suggesting that this is more of a subacute process.

Dr. Budak

And then what if someone had a CD4 count less than 200?

Dr. Kalapila

Right. So even with a CD4 count less than 200, people with HIV are more susceptible to community-acquired bacterial pathogens, including or especially pneumococcus. But other bacteria I think about for individuals with HIV would be tuberculosis \(TB\), which can happen in any CD4 cell count, but for people with advanced HIV there's a higher risk of pulmonary TB and also for disseminated TB. And these patients with the low CD4 count and TB can also present with diffuse opacities on a chest x-ray and also have a subacute to chronic duration of symptoms, which is what we see in this case. So, my question for you, Jehan, is did this patient have any epidemiologic history that would make TB a more likely diagnosis for him?

Dr. Budak

No, he was born and raised in Atlanta, has not traveled recently, and has never been incarcerated. He also has no known exposure to anyone with active TB. And then to just round out the history, non- sort of epi-based, he has no sick contacts, does not smoke, and is up to date on his COVID vaccination.

Dr. Kalapila

Okay, so that makes me think that TB is much less likely right now. So, if he had an underlying lung disease, he may also be at risk for non-tuberculous mycobacteria, which also can have a subacute and chronic presentation, but for now, I think that's all I have in my bacterial bucket.

viral**[04:51] Viral?**

Dr. Budak

Okay, so then let's move to viruses.

Dr. Kalapila

So, very, very huge category. Many respiratory viruses that we think about right now can cause disease in individuals regardless of CD4 count. You'd probably expect a more acute presentation, which again doesn't fully fit with this patient's presentation. Obviously, you might see more severe disease in people who have a lower T cell count. The viruses that we think about obviously would be things like COVID, influenza, respiratory syncytial virus \(RSV\), adenovirus, and other common respiratory viruses. Now, there are some

less common viral etiologies for pneumonia that can affect patients with a low CD4 count, and the two main ones that I would think about would be cytomegalovirus, which we refer to as CMV, or varicella zoster virus, which we often say as VZV. And usually if we see pneumonia from that, it's because of reactivation of latent disease. But, typically, those two viruses, I see them as affecting individuals who are immunocompromised for other reasons, so these are the people that have had stem cell transplants or an organ transplant, and less so in people with HIV. So, in general, again, kind of given the subacute to chronic nature of his symptoms, I probably would move viral infections further down on my differential.

fungal-pathogens**[06:18] Fungal Pathogens?**

Dr. Budak

And then what about fungal pathogens?

Dr. Kalapila

Now, I don't typically think of fungal infections when a CD4 count is greater than 200. Of course, endemic fungi can cause pulmonary disease in individuals who have a T cell count greater than 200 if they've had the right epidemiologic history or exposures. So, for instance, if you told me that this patient lived in an area where coccidiomycosis was endemic, like in the southwestern USA, then maybe you could expect like an acute pulmonary cocci. But, in general, for someone with a CD4 count less than 200, I would expect a far more severe presentation with these endemic mycoses. So again, based on the history you just gave me, the patient didn't have any exposure history to put endemic mycoses super high on my differential. However, he does live in Atlanta, so the endemic fungi, or fungus, that I would think about would be histoplasmosis \(or histo\), and we can't completely rule that out. But again, if this person had a low CD4 count, that they had advanced HIV, the presentation of histo that we typically see in individuals with low CD4 counts is disseminated disease rather than a predominantly pulmonary presentation. But, given the diffuse nature of his chest x-ray, the subacute course, and of course because we are in histo territory, I think it's reasonable to keep histo on my differential, but it is definitely not at this point the top of my differential.

Dr. Budak

Totally.

Dr. Kalapila

And then of course, there's the possibility of pulmonary cryptococcus. Now, pulmonary crypto is a less common presentation of cryptococcal disease in people with HIV, and we typically see more of a meningitis presentation for people with a CD4 count typically less than 100. But, of course, the main fungus that can cause significant respiratory symptoms and pulmonary disease in individuals with advanced HIV when the CD4 count is less than 200 is actually *Pneumocystis* pneumonia, which we often abbreviate as PCP or PJP. Now, PCP is one of the most common opportunistic infections in people with HIV. Patients with this type of pneumonia typically have a T cell count less than 200 and they present with a subacute cough, dyspnea, fever, and hypoxia, some of which can be exertional. So, all of that, and especially the time for this patient's clinical symptoms, kind of fits with the presentation and with a PCP diagnosis.

Dr. Budak

I totally agree. And I'd actually like to take a quick aside to discuss abbreviations. So, *Pneumocystis* was originally called *Pneumocystis carinii*, hence the abbreviation PCP for *Pneumocystis carinii* pneumonia. They used to think that it was a protozoa but it was reclassified as an atypical fungus. And now, we think that *Pneumocystis carinii* refers to the *Pneumocystis* that infects rats, whereas *Pneumocystis jirovecii* is a species that infects humans. So, I think it's okay to refer to this as either PCP or PJP, and you'll hear us referring to it as both of those.

malignancies**[09:17] Malignancies?**

Dr. Budak

So, now back to those buckets, Aley. Are there any other ones that you want to include here when thinking through this case?

Dr. Kalapila

I think it's always good to keep malignancy on the differential diagnosis as well. Now, if this patient had a history of significant tobacco exposure, then of course he would be at risk for lung cancer, regardless of his CD4 count. And, if he had advanced HIV, then we would need to think about HIV-associated malignancies, and that would include lymphoma, as well as pulmonary Kaposi's Sarcoma \(KS\).

more-test-results**[09:54] More Test Results**

Dr. Budak

Okay. So, let me share some more information about the case. While he was still in the ER, he was started on ceftriaxone and azithromycin empirically for community-acquired pneumonia, and they also tested for COVID, flu, and RSV. And I think it is safe to assume here that in ER, he looked relatively well and, again, this was a young patient with no other medical comorbidities that anyone was aware of, including the fact that nobody was aware of his HIV status, patient included. His COVID, flu, and RSV PCR [polymerase chain reaction] testing all came back as negative. And then the day after his HIV antigen test came back as positive, a CD4 count was resulted and was 7 or 2%. So, with that information, what are you thinking about now?

Dr. Kalapila

So, that CD4 count is very low, so it's definitely well below 200 and then of course you've given me his clinical presentation with the subacute hypoxia, exertional dyspnea, and diffuse opacities, which we've seen on a chest x-ray. With all of that information, PCP moves to the top of my list. TB is still a possibility, but again, based on his epidemiologic history, it is lower on my differential.

Dr. Budak

And while you're trying to get more information about this case, would you start empiric PCP treatment on this patient?

Dr. Kalapila

Absolutely! Now that we have all this information, I think that all of that is congruent with a PCP diagnosis, and I would initiate empiric PCP treatment while we're waiting for additional diagnostic information to come back.

Dr. Budak

And we'll talk about treatment details later and in a subsequent episode, but in the meantime, getting back to the diagnostics. An induced sputum AFB [acid-fast bacilli] stain and MTB [*Mycobacterium tuberculosis*] PCR are obtained, both of which are negative, and of course you know the sputum AFB cultures are still in process, as they will be for a while.

Dr. Kalapila

Okay, so that then that makes TB even lower on my differential, since his AFB smear is negative. Now, of

course, the definitive test is AFB sputum culture and that is still pending, for sure, but again based on information that we have, I just think that TB is far less likely. Now, other things that I would be worried about, based on his clinical presentation information so far, we would need to think about the fungi again, not quite as high on my differential. But still, you've given me history that says there's no recent travel to cocci endemic territories, but of course we should think about cryptococcus and histoplasmosis. And fortunately for us, you know, we have some useful diagnostic tests that should hopefully result in the next couple of days that can help us rule out those two fungi.

Dr. Budak

And I know in real life that these may not come back as quickly as I'm sharing right now, but his serum cryptococcal antigen, urine histoplasma antigen, and urine legionella antigen were all negative.

Dr. Kalapila

In my mind, you know, with those test results, along with his clinical presentation, I am comfortable moving histo and crypto to the bottom of my differential diagnosis, and PCP is now at the top. And, fortunately, we have already started empiric therapy for this patient for PCP. And in this specific case, I would also consider actually doing a CT of his chest to better characterize those radiographic abnormalities that we saw on the chest x-ray, because a high-resolution CT scan is actually more sensitive than a chest x-ray. And maybe a few other tests, since I'm thinking that PCP is pretty much the diagnosis that this patient has.

Dr. Budak

Okay, so I'll give you some more info. He had an ambulatory O2 saturation that dropped from 92% to 90% with minimal ambulation. An arterial blood gas \(ABG\) was obtained on ambient air and had a PaO2 of 73. And a lactate dehydrogenase \(LDH\) was 475. As you mentioned, and/or suggested, the CT chest was obtained and showed patchy bronchocentric opacities in the lower lobes bilaterally and upper lobe and diffuse lower lobe ground glass opacities. So, what do you make of this information?

Dr. Kalapila

Well, so given the additional labs and imaging findings, this is again pointing more and more towards PCP, right? So, he had hypoxia, he has an elevated LDH, and bilateral ground glass opacities seen on the CT chest; all of this is very suggestive for PCP. Now, keep in mind that the LDH or the lactate dehydrogenase is an acute phase reactant so, of course, we can see it elevated in other acute processes like malignancy or other inflammatory processes. An LDH greater than 500 can often be seen in PCP, and a normal LDH usually makes PCP less likely. Now, this patient's LDHisn't quite 500, but it's elevated this again kind of points to PCP as the most likely diagnosis. Now if this *is* PCP, then the ABG will actually help us determine whether we give adjunctive steroids or not, so I'm glad that we have that information was obtained.

Dr. Budak

And the O2 sat in PCP can drop with ambulation and typically what we're looking for is a drop of 4% or more, but this finding is not always present and while an ambulatory desaturation *can* be seen with PCP, it is not specific to PCP. With regards to his CT findings, ground glass opacities can be seen with PCP. Other radiographic findings associated with PCP include pneumatoceles, cystic lesions, or pneumothoraces. Now, a beta-D glucan was sent but it takes a while for you to get that result at your hospital, right, Aley?

Dr. Kalapila

Unfortunately, yes. It takes over a week to result, and we're not really waiting for those results to come back to initiate treatment. What about for you? How long does it take for you to get those results?

Dr. Budak

Yeah, so we have it available, and the turnaround time is usually about 2 to 3 days, but it didn't used to be. It used to be more on the order of 5 days. And so, for the listeners, 1-3-beta-d-glucan \(or beta-d or BDG\) is a polysaccharide found in the cell walls of many organisms, including those of *Pneumocystis* cysts. It can be elevated in PCP, and the test has a high sensitivity, especially when combined with a normal LDH, so that can help rule out PCP. But the specificity of the beta-D-glucan is low. For example, other fungal diseases or even certain antibiotics can elevate a beta-d-glucan level.

respiratory-sample**[16:19] Respiratory Sample**

Dr. Budak

So, we talked a little bit about blood tests, but, Aley, what sputum specific studies would you want to make a diagnosis of PCP?

Dr. Kalapila

That's a great question. So, the first point I would want to make here is that the diagnosis of PCP is often presumptive, and we make it based on presentation, symptoms, chest imaging, oxygen desaturations, and the high LDH, and/or the high beta-D-glucan level. And the reason that this is a presumptive diagnosis, oftentimes, initially at least, is because the definitive diagnosis involves identifying the organism using histopathology or cytopathologic techniques on induced sputum, bronchoalveolar lavage, which we say BAL, and/or tissue. And, because these tests can often take a longer time to come back, or takes a long time to obtain those specimens, as I mentioned earlier, we're just not waiting to do these diagnostics to initiate empiric treatment since the patient is symptomatic and could actually get worse. Now, the way that you would make this diagnosis on an induced sputum is by doing a stain, and given the resource limitations to my specific hospital at that time, the only stain we had available was the methenamine silver stain, which basically stains the *Pneumocystis* cyst wall.

stains-dfa--pcr**[17:39] Stains, DFA, & PCR**

Dr. Budak

And regarding the stains for PCP, there are many different types. The DHHS [U.S. Department of Health and Human Services] Opportunistic Infection \(OI\) Guidelines state that some stains only stain the cyst wall and other stains detect the cystic and trophic forms, which I think can be confusing. Aley, I know you've looked into this before, so can you talk a little more about that?

Dr. Kalapila

Sure. So, I don't want to get too in the weeds, so I'm going to majorly simplify the life cycle of PCP and say that there are two predominant forms that exist within the PCP life cycle. There's the cyst form and then there's the trophozoite form. Now, the trophozoite is the more metabolically active form and is more predominant during active infection, and some of the stains that we have available to us will identify both the cyst and the trophozoite form. But there are other stains that can only identify the cystic form, like the silver stain.

Dr. Budak

And so that probably explains why the DHHS OI guidelines say that the sensitivity and specificity of respiratory samples for PCP depend on the stain being used, the experience of the microbiologist or pathologist, the pathogen load \(or really how much PCP burden there is\), and the specimen quality.

Dr. Kalapila

Exactly. So, we're both agreeing on this: that the staining the cysts and trophozoites may not always be the best test to diagnose PCP. So, what stains do you have at your institution to diagnose PCP?

Dr. Budak

We can get a DFA or a direct fluorescent antibody stain, a type of immunofluorescence staining that uses monoclonal antibodies to detect the *Pneumocystis* antigen, and the DFA is more sensitive than direct staining methods.

Dr. Kalapila

Unfortunately, we don't have the DFA, and as I previously mentioned with this case, whereas we used to only have a silver stain available, more recently we have also access to an additional diagnostic test, which is the PCP PCR, which we can run on induced sputum, BAL, or tissue but should definitely not be run on expectorated sputum.

Dr. Budak

And, so I think it's important to note per the DHHS OI guidelines that histologic or cytopathologic identification of organisms on tissue, BAL, or induced sputum is the preferred method for diagnosis. So, this would be either biopsy or staining, which includes direct immunofluorescence. And, of course, biopsy is usually reserved for unusual cases where the diagnosis has not been made already using less invasive methods. So, most often in life, the diagnosis of PCP is made using an induced sputum sample or a sample collected from the BAL.

Dr. Kalapila

Yeah, you're absolutely right, Jehan! So, the PCP PCR is an alternative diagnostic method per the OI guidelines, but it is the alternative that I had available to me at my institution. And, of course, as you and I both know, different institutions just have different access to variable diagnostics based on their resources.

Dr. Budak

Fortunately, where I work, we have DFA and PCP PCR, and when I try to make a diagnosis of PCP, I send both the DFA and the PCR. The PCR is actually the most sensitive and specific but, unfortunately, cannot reliably distinguish colonization from active disease.

Dr. Kalapila

Since you mentioned colonization vs. active disease, I should comment that *Pneumocystis* is an environmentally ubiquitous organism, meaning that it is found everywhere, and so we are all exposed all the time. We cannot avoid it, and we're typically exposed by breathing it in, so by inhalational routes. Now, some of us may be colonized with *Pneumocystis*, but that doesn't mean that we actually have a *Pneumocystis* pneumonia. The PCR test, of course, will pick up any genetic material from our respiratory tract from the *Pneumocystis* organism, and so we would have to take a positive test result and put it into the appropriate clinical context in order to determine if a patient has *Pneumocystis*pneumonia or not.

Dr. Budak

Yeah, totally agree. The PCR we have access to is qualitative, meaning it just tells us if the *Pneumocystis* is there or not; we do not have a quantitative PCR. So, the qualitative PCR could give a positive result, which could represent low levels and colonization or high levels and a rip-roaring infection. And it's really up to us to use our diagnostic reasoning to interpret those results. So, all this to say, that the diagnostics you send are

dependent on your institution and/or laboratory, and there can be a lot of variability in this.

Dr. Kalapila

Yeah, that's an understatement. Like, at our hospital, as I said, we still don't have the silver stain but we actually don't really send it off anymore. Again, because of the issues we had mentioned previously, and so primarily we use PCP PCR in order to make the diagnosis and we can send that off either from the induced sputum or from a bronchoscopy with BAL.

use-bronchoscopy**[22:20] Use of Bronchoscopy**

Dr. Kalapila

So, that gets me to a question for you, Jehan, which is, would you want to request bronchoscopy for this patient?

Dr. Budak

I mean, if I can get a positive result on an induced sputum, I would prefer that, since its less invasive. But I also want to be cognizant in recognizing that can be hard to obtain, since oftentimes with PCP the patient has a dry cough and/or it can even be hard to expectorate even after someone has done the induction. So, if I cannot diagnose PCP on an induced sputum, then I will request a bronchoscopy, and, luckily, even a few days into empiric treatment, the tests will stay positive. Interestingly, I've also worked at places that don't even allow an induced sputum and you have to directly go to a bronchoscopy with BAL. So, again, back to what we're saying, that it kind of all depends on the context in which you work.

Dr. Kalapila

It's also worth mentioning that even if we wanted a bronchoscopy, the clinical scenario may preclude that, right? So, if the patient had hypoxia that was so severe and/or if the patient were presenting with a pneumothorax related to their PCP, which can be seen with severe PCP, then of course in these instances a bronchoscopy would actually not be feasible.

empiric-treatment**[23:33] Empiric Treatment**

Dr. Budak

So, Aley, that kind of just goes back to your point before that in those cases or in many cases, you're really reliant on the clinical presentation, the studies you can send from the blood, and the imaging.

Dr. Kalapila

Yeah, exactly! So, just like we've discussed so far, so much variability in how patients present with PCP, what testing is available at varying health care facilities, and of course, the timelines for all of these tests results to come back. So again, going back to what we talked about earlier, PCP is often a presumptive diagnosis early on, which we make based on indirect markers rather than a microbiologic diagnosis, which often comes later.

Dr. Budak

I think it's actually quite difficult to obtain a diagnosis of PCP, which is why I end up sending lots of things if I'm suspecting it: the blood tests, LDH and beta-D-glucan and sputum tests, both the DFA and PCR, if able. And, as you mentioned, because several days might elapse while we're waiting for results, sometimes the patient feels better with empiric treatment and is actually discharged before we have even made a definitive diagnosis.

But anyway, back to the case. The last we had left off discussing was the elevated LDH level. A beta-D-glucan results had not come back yet, and you had sent a PCP PCR, that eventually resulted as positive along with an elevated beta-D-glucan. But at that point you had already started empiric treatment.

Dr. Kalapila

Yes, so while we were waiting for all of those results, he was receiving empiric treatment, he actually started to get better clinically, and we ended up discharging him on day 4 of his hospitalization.

summary**[25:06] Summary**

Dr. Budak

So, we will talk about treatment and management in a future episode, including when we recommend adding corticosteroids, but for now, let's wrap up with some summary points about the diagnosis of PCP, which we can all agree can be tough to make. So, PCP is a ubiquitous atypical fungus that typically causes pneumonia in persons with HIV with a CD4 of less than 200. Non-invasive markers like LDH and beta-D-glucan can be helpful, but definitive diagnosis requires pathologic identification of the organisms on respiratory specimens. An alternative diagnostic method is to use PCR, and PCP treatment can be initiated presumptively based on presentation and imaging while awaiting a definitive diagnosis.

So, we'll return to pick up right where we left off to discuss treatment and management of PCP. Aley, thank you so much for today.

Dr. Kalapila

Thanks Jehan. Looking forward to the future episode.

credits**[26:00] Credits**

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