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STI EVALUATION AND TREATMENT

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STI Evaluation and Treatment
[video transcript]

[00:00:05] So I'm going to talk to you about STI evaluation and treatment. And the learning objective is simple, to implement currently recommended strategies for evaluation and management of STIs in HIV infected individuals. Just some disclosures and research support, should not affect what I'm presenting to you today.

[00:00:27] So I'm going to start with a case and this is a case of a 36 year old man who presents with urethral burning and tingling, discharge for three days. He reports one female partner in the past 12 months who ironically reported to him that she had been treated for an infection two days prior. His last contact with her was a week before. He reports oral and penile exposure through oral, vaginal, and penetrative anal sex. And a history of chlamydia is really his only STI history, he was 16 when that happened. Physical exam it's normal. And then he has a gram stain that is demonstrating inflammation or two or more polys high power field, no gram negative intracellular diplococci. And I put a picture there of a representative discharge that you would see in this situation.

[00:01:20] So he meets the criteria for non-gonococcal urethritis. So this is the first question that I have. What is the recommended treatment for NGU? Would it be doxycycline 100 milligrams BID for seven days, a gram of azithromycin, ceftriaxone 250 IM plus azithromycin a gram, or cefixime 400 milligrams once plus azithromycin 1 gram? So actually the first two of those answers doxycycline or azithromycin would be the correct answer for NGU. That is assuming you have the ability to rule out gonorrhea in your practice with a gram stain. So if you cant get to the point where you can characterize it as NGU, meaning you dont have that ability to look for gonorrhea on a gram stain, you just have a patient in front of you with urethritis, you should cover gonorrhea. Okay but specifically for NGU it would be doxi or azithromycin.

[00:02:20] So this patient was treated with azithromycin, all of his testing was negative. But he comes back in two weeks and he still has symptoms. So what would you do next? Would you take a sexual history and repeat his evaluation, would you go ahead and give him doxycycline for seven days plus the two grams of metronidazole to cover trichomonas, would you give him moxifloxacin for seven days, or would you do 1 and 3? Y'all go ahead and vote.

[00:03:14] And I'm going to make an argument here that you would go with number one first. And so you want to take a sexual history and you want to re-evaluate this patient. You want to know what's going on with them in the meantime. And that's because it's important to fully characterize this. First of all, is it really recurrent and persistent urethritis? And you want to know was this patient reinfected? So

in order to characterize it as recurrent or persistent urethritis, you need to document inflammation. So that would be in the form of either noting a mucoid, mucopurulent, or purulent discharge on the exam. If you have the staining capability, a gram of methylene blue or gentian violet stain to document the white cells in the absence of the gonorrhea. Positive leukocyte esterase on first void urine could be used or a first void urine that's spun down and evaluated for white cells. If this urethritis is confirmed, then if the person's been reexposed they can just be retreated really with the same regimen, because presumably they've been reinfected. However, if they do not give a history consistent with reinfection then we have to worry about another bacteria.

[00:04:36] And that in particular, one that is gathering our attention more and more these days is mycoplasma genitalium and I'm going to quickly just summarise this slide. This is a follow up, a secondary analysis of an NGU study that was performed several years ago and the punchline is that in the male patients who came back for follow up after treatment of NGU with azithromycin, the individuals who failed the most common organism isolated was M. gent. In those who just had clinical failure, most of the time no pathogen was isolated but those who had isolated pathogens it was M. gent.

[00:05:20] M. gent is very prevalent. This is a study that was published in The Journal of Clinical Micro in 2016 and it was a study performed in the context of performing a diagnostic performance study. So these were nucleic acid amplification based tests performed from seven sites in the United States. We had STD clinics, family planning clinics, an OB/GYN, and I think a family practice clinic if I remember correctly. And overall, women had a prevalence of about 16 percent and men 17 percent. And what's most concerning is of the women, a little over half had macrolide mutation of their M. gent, which means that the azithromycin would likely not work. In men it was close to half, 42 percent. And this resistance was not regional. It seemed to be widespread. So it's thought that this is an endemic process. Currently to make all of this more difficult, we don't have an FDA cleared test for Mycoplasma genitalium. There are tests available in large laboratories across the country, but to be honest we don't know what the test performance is of those tests. There are some tests on the horizon.

[00:06:40] So this is a busy algorithm, but this is just in terms of an NGU. Once again this is in a situation where we've been able to sort out gonorrhea is not present. So first line would be azithromycin or doxycycline and then there's some alternatives of that does not work. If they resolve, great. If they don't resolve infection, then they have objective evidence of inflammation then you would ask about re-exposure. If they've been re-exposed then you can retreat with the same regimen. But if they've not been re-exposed, the recommendation would be if they were treated with azithromycin originally would be to go to the moxifloxacin for seven days, or if they were treated with doxycycline originally that you would go with the azithromycin at this point. And then if it's a man who has sex also with women, you would add trichomonas coverage onto that with either tinidazole or metronidazole 2 grams stat dose

and that would be also for areas of the country where trichomonas is prevalent. So in the south, it's quite prevalent.

[00:07:48] So in summary, M. gent appears to be an important pathogen specifically for male urethritis. We are still evaluating how significant it is for cervicities and upper tract disease in women. We don't have a reliable test currently, but there are some on the horizon. Unfortunately even though we don't have a test, the treatment we have seems to already be failing and the salvaged drugs that we don't have access to currently in the US that are being studied in other countries are not slamdunks unfortunately. They don't look great. So a screening program is not ready for prime time. It's not recommended that you screen for M. gent, but do consider this in men who fail therapy for urethritis.

[00:08:38] I wanted to just to bring up another phenomena we're appreciating more recently and it's manifested by this 18 year old who came into an STD clinic with a greenish drip. His gram stains showed the classic gram negative intracellular diplococci, but all of his NAAT-based tests were negative for gonorrhea. Any ideas what happened with this? Any shout outs?

[00:09:04] Neisseria meningitidis. So remember Neisseria meningitidis and gonorrhea actually can do the same things. They can flip flop. We don't see it that often but we are recognizing now that we're seeing more meningococcal urethritis and this was picked up through the gonococcal isolate surveillance program that CDC runs, where gonorrhea cultures are performed routinely in certain clinics to have resistance testing performed. And this specific note from the MMWR documented in some cases in Ohio and Michigan. Almost all of the individuals were heterosexual. It was almost all urethritis cases and almost all of them had reported fellatio. So it was picked up through these discordant results. The culture grew what looked to be a Neisseria gonorrhea, of course there's further testing that can be done to sort out meningococcus versus gonococcus. And then the negative NAATs. Fortunately, treatment for gonorrhea covers this and there was no increase in invasive Neisseria meningitidis over this time period. Just so you're aware, in case you have some discordant test results.

[00:10:24] All right. So this is another patient of mine and this is a picture of a lesion I ran across in my high resolution and anoscopy clinic. And I'll just give you a minute to soak that in. Okay. Yeah. And if you were to palpate it, it's kind of thickened. And I encourage you to always, with a glove, palpate the patient's lesions because you can get some hints there.

[00:10:54] And to back up, I did already have this information because even though HRA clinic's pretty targeted, I do take a sexual history and examine the genitals and the trunk. So he had actually reported three sexual partners, male partners, over the last six months. HIV positive and negative and this gentleman was HIV positive. He has a stable group of partners, he has for years. Though some of his

partners step out sometimes. And he had no contact to STDs recently that he was aware of and I had noticed on his scrotum, and this is a representative picture from another patient because this patient I'm talking about was Caucasian but I didn't get a picture of a scrotum that day, but he had the same lesions these papellous squamous lesions on his scrotum. They are very very subtle and I'm not sure if you can appreciate, they almost blend in to the rugae of the scrotum so it's almost as you have to step back and look and get the sense that there is a rash there. He had maybe, maybe three lesions on his flanks.

[00:11:59] So how would you manage him the day of the visit? Would you treat him for herpes and give them valacyclovir, would you give them bicillin 2.4 million units once, would you do both of those things? Would you give him both of those drugs and then also give him some ceftriaxone and doxycycline to cover gonorrhea and chlamydia for good measure? Or would you do none of those above and just kind of wait on your test results?

[00:12:42] All right. You guys, you're after my heart here.

[00:12:46] So I would definitely bicillin this guy before he left the clinic and you could also consider covering him for HSV. I see so much HSV in that area. That was at the gluteal clef. And when I do HRA almost always the men are not aware that, or the women, when I examined women they are not aware that was present. But for sure I would cover syphilis before letting that patient go.

[00:13:14] So that's what happened. His RPR came back at 1:256. All of his other testing was negative. So I tested him for all STIs because I suspected this one. I did perform HSV 1 and 2 PCR. And then inside he was actually pretty pristine that day so I did no biopsies, but I couldn't resist biopsying the lesion. And I sent it for testing and it did come back with T. pallidum positive. So it was syphilis.

[00:13:46] So just to remind you guys of the natural history of syphilis. We have exposure, once that organism enters either the mucosal surface or the skin, then we have a primary chancre that's painless that a patient will not recognize unless it's in their face, sometimes they will ignore it. But unless they can actually see it, they may not realize is there. And then if that's not treated the syphilis, the spirochete will disseminate. They may feel ill, they sometimes will have a rash. That rash can look all kinds of different ways. It may involve palms and soles, but not every single time necessarily. Could have condyloma lata as a manifestation, mucous patches, etc. And then if that's not treated people will go into latency, and then of those about a third will go on to form tertiary syphilis over time.

[00:14:41] Just a couple of things to remember that primary and secondary syphilis can overlap and I think that is what he was in between. Said that chancre, the reason it was patchy T. pallidum, was because that was a chancre that was resolving. And then I was seeing the papillo squamous lesions on the scrotum and the lesions on his flanks that was secondary rash beginning. Okay and this overlap is more common in HIV infected individuals. Also keep in mind neurosyphilis can occur at any stage of syphilis.

[00:15:17] So we all know, I'm sure you guys are aware, primary and secondary syphilis continues to increase in the United States. These are the most recent data from CDC up to 2016. So in all populations it's increasing. We still have a great disparity with MSM having higher rates than MSW and women. And HIV infected MSM are disproportionately represented in our early syphilis cases and just to make note, these are primary and secondary syphilis cases that are tracked separately than the others because these are the new cases, they are also the infectious cases. So you can see in MSW, men who have sex with women, and women, few of those individuals are HIV and coinfected as compared to the MSM.

[00:16:13] Treatment. Penicillin is the drug of choice and the amount of penicillin you give depends on the stage they are at. So that's why it's always important to thoroughly evaluate the patient. Mouth, skin, genitals, rectum regardless of sexual activity they were reported. I would look at all orifices because condyloma lata for instance is a manifestation of a disseminated infection and can be perianal even if they haven't had anal sex. So I would encourage that because that will dictate how you treat. So primary, secondary, and early latent, so that someone without symptoms who has acquired syphilis in the last year, the only way you'll know that is if you're systematically performing RPRs and you see that they convert or that they significantly raise a titer in that timeframe or if they have a connection, an epidemiologic connection, to an early case and sometimes a disease intervention specialists can help us out with knowing that information. Otherwise, it's unknown duration syphilis or late latent and they would need to have 3 rounds of the bicillin 2.4 million units a week for three weeks. And then neurosyphilis is treated differently and that would I.V. penicillin. Keep in mind that the treatment is the same whether an individual's HIV infected or not, so HIV infected individuals do not need extra penicillin.

[00:17:43] What if he had reported an allergy to penicillin? And anaphylactoid type of reaction. What would you have treated him with that day? Would you give him 2 grams azithromycin, 14 days of doxycycline, give him 10 to 14 days of ceftriaxone IM, or would you send him for desensitisation?

[00:18:15] All right. And so the majority say doxycycline and nothing. In this situation that's reasonable to do. And it would be a 14 day course for an early syphilis, an individual with early syphilis. We don't have a lot of data to back that up but except the tincture of time. If you actually go looking for data there's not much out there. Desensitisation could be considered. Of course it is going to get into sending

him potentially to the ICU for desensitisation depending on your Allergy/Immunology person. Of course if this individual been pregnant, we have to desensitize them. If it had been neurosyphilis we were concerned about, they have to have penicillin. Ceftriaxone could be considered but there's not as much data for that.

[00:19:02] So he was treated with the bicillin, he came back in 3 months. No sexual activity since then and his repeat titer at that point was 1:64 so he was a 1:256 the first day you saw him, and now has a 1:64 3 months later.

[00:19:18] So what would you do now? Would you check titers again in 3 months and let him ride? Would you retreat him again and give him another round of bicillin? Would you do an LP to rule out neurosyphilis? Would you double check that RPR just to really make sure it was a 1 to 64? Or would you do something else?

[00:19:48] Good good. So you're demonstrating patience with the titers. And titers are really problematic aren't they? I mean it's like the bane of venereologist. I mean it keeps us in business, but it's I think the most common question we get from the STD prevention training center point of view. It is because it's complicated.

[00:20:11] So just remember, so this patient had a 1:256, so he went down to 1:64 so that was a 2 dilution or four-fold change. He's actually already had an appropriate response in three months. And so we could even if he had not gotten down to 1:64 yet, we could have given him more time. Another example just to show you this will be a not-significant titer, that's a one dilution titer, even though it went up. There are a lot of questions that come up when patients, since we do serial RPRs, they sometimes bump back and forth within a titer and it stresses us out as providers. And we always want to take that history, see what's going on with their sexual activity, and whether they've had any contact. But this is not a significant change either. So no reason to really get concerned outside of some other history with the patient. If they had gone to a 1:8, that would be more concerning for a significant change.

[00:21:15] So just keep in mind in terms of response to syphilis therapy, we continue to learn more and more about this as time goes on. For primary and secondary syphilis we're looking for a fourfold or greater decline in the nontreponemal titer by about 6 to 12 months. We can give them up to 12 months follow up, but keeping in mind up to 20 percent of patients aren't going to even reach that goal. OK. So this is going to drive us nuts basically because we're going to have people that are not going to make that goal. Late latent syphilis it takes even longer, whether it's early latent or unknown duration, they have up to two years to make that fourfold drop if they've been greater than 1:32.

[00:22:04] And then in terms of seroreversion. I know in medical school, I feel like I was taught that people become non-reactive after treatment, it seems like very few people actually when you actually look at the data become non-reactive and this is a secondary analysis that Dr. Sena performed after an azithromycin trial for syphilis treatment. And these individuals had early syphilis, they all had at least a fourfold drop within 3 months of treatment of their early syphilis, and so she went on to look to see how many of them seroreverted or became non-reactive after therapy. And the bottom line is only 17 percent of them did. And these are all HIV negative individuals. So just I guess keep that in mind that we may see a lot of reactive RPRs in our patients in follow up.

[00:23:00] All right. So I'm going to move on to another case, this is a 51 year old individual who comes in for routine care. He's adherent to his therapy. He comes in reporting a rash on his chest for two days and he had just been, actually longer than two days, but two days before he had been at urgent care and been diagnosed with pityriasis rosea. What else do you want to know? Additional details about onset and accompanying signs and symptoms, grooming product history, is he on new medications, what's going on with the sex life, all of the above?

[00:23:43] All right. That was an easy win wasn't it. So that's true. I would go with all of the above. And what you find out, when I went back and this is a case where I went back and looked at the record after the fact, so he reported the rash for one week prior to presentation. No fever, night sweats or vision changes, he had no new products, no new medications. Sexual history was not obtained, RPR was drawn, but he was sent to dermatology and he was sent home. So what is missing besides a sexual history?

[00:24:18] His genital exam. There was no genital exam performed. Well so then he's sent a dermatology. He got worked in pretty quickly and the patient is kind of interesting in the note. He's concerned that he may have syphilis. He said he had syphilis in the 1980s and he's afraid he might have it again. The exams documented with multiple papules on the trunk and arms, but still no genital exam. They did a biopsy. Which demonstrated syphilis and his RPR had come back at 1:64, I think right after that biopsy who was performed. And then about a week later he's back with his HIV provider for treatment of syphilis.

[00:25:07] And this is how I feel when I get into the chart and see things like this. So when he presents for treatment, then we find out he's had four male partners in the past two months. He's had two painless ulcers on his penis that have nearly resolved, which would have been helpful history to have known. He has panorifice exposure through sex. He uses condoms intermittently and on his exam he does have small indurated ulcer on the lateral aspect of the tip of his penis, it almost had entirely

resolved but you could still tell what it was and it was still indurated. They appropriately screened him for other STIs at all sites of exposures and his rectal chlamydia came back positive.

[00:25:56] So just a couple of take points from this. If there's a rash, think about an RPR. I've seen so many very experienced, very excellent clinicians get fooled by the syphilis rash. RPR is easy, it's cheap, and we can verify. We can do you know confirmatory testing. The sexual history is important and the genital exam can inform patient management. Patients who have one STIs should be checked for other STIs at relevant sites. And if you have a high risk patient with you in clinic and you're concerned about early syphilis, go ahead and treat them before they leave the clinic. Because keep in mind that up to 30 percent of individuals who have the primary chancre, if it's real early on, will have a non-reactive RPR. So you can't totally hang your hat even on the RPR in that case.

[00:26:49] And now thinking about this guy's rectal chlamydia, this is another area of concern in STI management. So there's concerns currently about azithromycin for rectal chlamydia. And I've got a graph here just demonstrating a variety of different studies over time that demonstrate the efficacy of azithromycin for rectal chlamydia ranging from 79 up to 94 percent in one study, compared to very high rates of efficacy for doxycycline. And then some more recent studies back Kong and Gratrix, they also have documented poor efficacy of azithromycin. However all of these studies are retrospective. And so they all have potential flaws with them, but an area that is on the radar right now.

[00:27:41] So the bottom line right now for rectal chlamydia is that the treatment guidelines have not changed as of now in the United States. So if it's an asymptomatic person we're talking about a gram of azithromycin or seven days of doxycycline BID. If you have an individual in front of you that has proctitis symptoms then they would need 21 days of doxycycline to cover the possibility of LGV, if it's an HIV infected MSM in particular or a very severe case of proctitis in particular. But don't forget to cover gonorrhea in that situation and also you may want to cover syphilis and HSV depending on the physical exam findings. There is a randomised controlled trial that is getting started in the United States and I know the Australians are planning one too, but in the meantime just I guess be vigilant about that.

[00:28:36] OK so what is the recommended treatment for gonorrhea? I'm hoping you guys know this. Is it cefixime one dose plus a gram of azithromycin, two grams of azithromycin, ceftriazone 250 plus a gram of azithromycin, or a one time does of ciprofloxacin, or is it something else?

[00:29:03] Excellent. You got it. So gonorrhea is increasing in the United States and the Midwest is trying to outstrip the South in this. I mean we are always leading in STIs unfortunately, but the Midwest is catching up. And we have concerns about resistance and the media is getting a hold of this. It's been kind of interesting to see this play out in the media. This most recently last month, we had a report now

from the U.K. of a man who failed treatment with what was four times our does of what we use of ceftriaxone. And he had very high level azithromycin resistance, so he would not have really responded to cotreatment of azithromycin, which he didn't get he just had the gram of ceftriaxone.

[00:29:59] So this is very concerning and we have a signal here in the United States that we're on our way to seeing this play out here. We've not had a treatment failure in the United States yet but this is a cluster of seven individuals in Hawaii who had extremely high azithromycin MICs and compromised ceftriaxone MICs. And this was in an Epi-X, that documented this. None of these patients failed treatment. The ceftriaxone azithromycin combination, they all cleared everybody. And they were all heterosexual individuals.

[00:30:38] So keep in mind, you guys got the correct answer the majority of you, the only recommended treatment for gonorrhea currently in the United States is the ceftriaxone 250 IM plus a gram of azithromycin. The doxi was demoted the last round of the guidelines because the azithromycin it's not really so much to treat chlamydia but to cotreat gonorrhea, and most of the gonorrhea in this country is resistant to doxycycline. If you have to give an alternative, cefixime plus azithromycin one gram would be one of the alternatives. But keep in mind that cefixime really does not clear the throat well. So they would need a test of cure. And then if someone had an allergy, severe allergy, and once again our allergy history is very important. We want to make sure that we are dealing with a true allergy, then our only choices would be either gentamicin 240 IM times one plus two grams of azithromycin. Not a fun regimen. That's a big load of gentamicin in the buttox. And two grams of azithromycin is not fun on the G.I. tract. Gemifloxacin plus azithromycin is another alternative but gemifloxacin is very difficult to get a hold of right now.

[00:31:55] Now if you think you have a treatment failure on your hands, what do you need to do? Well one thing is please try to get a culture and if you don't have it in your clinic talk with your laboratory or your health department to see if you can obtain one. You will need to retreat with either that gentamicin plus azithromycin or gemifloxacin plus azithromycin regimen. You want to let the health department know about this because they need to do amped up partner notification and treat the partners the same as the patient. And then this is an individual that will need a test of cure and a test to cure with both a NAAT test and a culture. Obviously if the patient has been re-exposed then you would treat them the same. So once again that sexual history, sitting down understanding what's going on with the patient is going to be important. Otherwise the only person who needs a test to cure outside of a concern for treatment failure would be someone with for pharyngeal gonorrhea that received an alternative regimen. That would be the recommendation right now and that would be a NAAT-based test or a culture 14 days, around 14 days, after treatment.

[00:33:08] And my last slide and Dr. Vail made this point beautifully is just that my plug again for extragenital testing. We've had it around for a while, it's still not FDA cleared, we're hoping maybe in the not too distant future to have it cleared. But in the meantime all the large labs perform this and many public health laboratories. And we're really missing the boat if we don't do extragenital testing in our men who have sex with men.

[End]