Expert Interviews

National STD Curriculum Podcast

Monitoring and Interpretation of Syphilis Serologic Tests

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Dr. Khalil Ghanem, a Johns Hopkins University Professor of Medicine and a syphilis expert, reviews how to monitor and interpret syphilis serological tests in an interview with Dr. David Spach, the National STD Curriculum Editor-in-Chief.

Topics:

- Syphilis
- serology
- neurosyphilis
- STDs
- STIs

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Transcript

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[00:00] Introduction

Dr. Ramchandani
Hello everyone. My name is Meena Ramchandani. I'm an infectious disease physician at the University of Washington in Seattle. This podcast is dedicated to an STD [sexually transmitted disease] literature review for health care professionals who are interested in remaining up-to-date on the diagnosis, management, and prevention of STDs.

For this episode, we welcome my colleague, Dr. David Spach. Dr. Spach is a Professor of Medicine at the University of Washington and will be discussing the monitoring and interpretation of syphilis serologic tests with Dr. Kahlil Ghanem. David, take it away.

Dr. Spach
Meena, thank you. Well, it's my distinct pleasure to introduce Dr. Kahlil Ghanem, a Professor of Medicine at Johns Hopkins University and a national authority on syphilis and other sexually transmitted infections. Welcome, Khalil.

Dr. Ghanem
Thank you, David. It's a pleasure to be here.

[00:52] Why serological monitoring?

Dr. Spach
Great. Well, let's jump right in, and let's talk about one aspect of syphilis management that can be particularly confusing, and that is the monitoring of syphilis serologic tests after treatment. So, first question I have just to get us started is, so, why in the first place do we have to perform serologic monitoring after we treat people who have syphilis? With many other infectious diseases, you know, we just treat with antibiotics, call it good, clinically monitor. So, what's special about syphilis?

Dr. Ghanem
So one of the most challenging problems, David, with syphilis is that we don't have a simple diagnostic test to tell us if the infection is active or not. So think about, for example, gonorrhea, chlamydia, trichomoniasis, right? You have a nucleic acid amplification test. If it's reactive, it means the bug is there. And if it's not reactive, it means that the patient probably doesn't have this bug. The best way we have in syphilis to monitor responses are the antiphospholipid antibodies, the RPR [rapid plasma reagin], and the VDRL [Venereal Disease Research Laboratory], whose titers we follow to get a sense of whether the patient has responded appropriately to therapy or not.

And if the titers go down two dilutions or fourfold after treatment, we assume that it's a serological cure. If

the titers go up, then we take notice, and we think that maybe it's either reinfection or the possibility of treatment failure. So the problem is that we don't have great diagnostic tests that tell us whether the disease is active or not.

[02:24] Nontreponemal Serologic Test Options

Dr. Spach
Great. So you outline there, the nontreponemal tests that we're using, the RPR and the VDRL. Can you give us a little bit more information about these tests, and if there's any major differences between these two tests? Because those are the tests that we use to monitor.

Dr. Ghanem
That's right. So I'll just start by saying for somebody who's not very familiar with syphilis is that there are two different antibody tests that are available to diagnose syphilis. And you need to use both to diagnose syphilis. So, the treponemal antibodies are mainly used to confirm the diagnosis of syphilis. And, usually with these antibodies, once they're reactive, they're always reactive whether you treat the patient or not. But they're useful to confirm the diagnosis of syphilis. Once you've confirmed the diagnosis of syphilis, what you're basing most of your treatment and follow-up decisions on are the nontreponemal antiphospholipid antibodies, what we just talked about, the RPR mainly, and the VDRL mainly. There are other types of nontreponemal antibody tests, but we don't use them very frequently in this country.

And so, these antiphospholipid antibody tests are very useful because they provide a titer that allows us to follow the treatment response. Here, I just want to remind our listeners that these titers will usually decline over time, whether or not you treat a patient. So you don't necessarily have to treat the patient to observe those titers coming down. They will usually come down even in the absence of therapy. But they will come down more quickly when you treat somebody. So keep in mind that if you have somebody with a low titer, a low RPR titer, or a low VDRL titer, it doesn't necessarily mean that they were treated. It could be that they've had syphilis for a while, and those titers have gone down on their own, even without treatment.

So, usually, for follow-up of patients who have syphilis, once they're diagnosed and treated, the RPR or VDRL titers are what we monitor to help us decide whether the treatment has been effective or whether the patient has experienced either treatment failure or reinfection.

[04:37] Testing Method Consistency

Dr. Spach
So how important is it to stick with the same type of test in the follow-up monitoring? So, you know, in other words, if you make a diagnosis with syphilis with an RPR, do you need to stick with the RPR? Or, can clinicians go back and forth and maybe use the VDRL if that's more convenient for the laboratory that they're working with now?

Dr. Ghanem
So really, you should stick with the test that you started with. So if you started following the patient with an RPR, then you should stick with the RPR. And if you started with the VDRL, then you should stick with the VDRL. And the reason why is because the titers are not necessarily comparable. When reviewing the literature, and we did that for the recent laboratory guidelines for the CDC [Centers for Disease Control and Prevention], when reviewing the literature, there is a suggestion that the RPR titers tend to be about one dilution higher than the equivalent VDRL titers in the patient. But that is not a reliable enough observation to manage patients clinically.

So, what I usually tell people is if you started with the RPR, stick with it. If you started with the VDRL, stick with it. In some cases, you don't have an option. A patient is referred to you from another institution, and you use RPR, but you don't use the VDRL at your institution. In those cases, I think that by using that one dilution rule, I think it's reasonable, but understand that it may not be accurate.

[06:08] Primary or Secondary Syphilis Post Treatment Monitoring

Dr. Spach
So let's take a look now from a practical standpoint and cover the post-treatment monitoring schedule and with the different stages of syphilis. So with these situations, let's assume a person has been diagnosed with syphilis. They've been appropriately treated. And for now, let's assume they don't have HIV. So walk us through. What do we do about the monitoring after treatment of primary or secondary syphilis?

Dr. Ghanem
Sure. So the CDC recommends that following treatment for primary or secondary syphilis, serological follow-up should be performed at six months and 12 months in persons who are HIV negative. But there are caveats to that recommendation. If you're uncertain that the patient's going to follow up, then you should probably monitor whenever you get a chance, right? Whenever you see that patient, even if it's not at six months, you should get that test. The other one that I think is very important is the possibility of reinfection. If you think that the patient still has the possibility of being reinfected, you should follow up more frequently. I have to be honest with you, David, that even amongst my patients who are HIV negative, I often get a three-month follow-up titer because I'm worried about reinfection.

[07:25] Latent Syphilis Post Treatment Monitoring

Dr. Spach
What about after treatment for latent syphilis?

Dr. Ghanem
Sure. So the CDC recommends that following treatment for latent syphilis, serological follow-up should be performed at six months, 12 months, and 24 months. And the reason why they go out to 24 months with latent syphilis is because sometimes the titers can decline more slowly with latent syphilis than with early syphilis. And so they don't want people to just keep retreating these patients unnecessarily. Again though, if you think that your patient is at risk for reinfection, then you can certainly follow more closely those patients. In fact, that's probably the right thing to do.

[8:11] Neurologic, Otic, or Ocular Syphilis Post Treatment Monitoring

Dr. Spach
Okay. Now, let's turn to the monitoring of neurosyphilis, ocular syphilis, or otosyphilis. What kind of monitoring do we need after that?

Dr. Ghanem
So again, the serological follow-up is the same as above. So if the patients had, let's say, early syphilis, you can serologically follow them as above. If they had late syphilis, you can follow for a more prolonged period of time, up to 24 months.

And right now, for most patients who are treated for neurosyphilis today, they do *not* require a follow-up CSF [cerebrospinal fluid] examination as long as they are responding clinically to therapy, as well as serologically to therapy. So those patients do not need a follow-up CSF exam unless they are living with HIV and they are not taking antiretroviral therapy. So the follow-up for patients with otosyphilis, ocular syphilis, and neurosyphilis is, now for most patients, serological follow-up and clinical follow-up to make sure that they are doing better after treatment.

[09:16] Titers and Responses Interpretation

Dr. Spach
That's great. I know there are a lot of clinicians and certainly a lot of patients that are happy not to have repeated lumbar punctures with CSF analysis. So I think a lot of people really welcome this new

recommendation for monitoring. But let me turn now to a different issue. So I think one thing that really confuses clinicians is, you know, how do you compare the different titers of these tests and judge whether or not a good serologic response has occurred?

Dr. Ghanem
Absolutely. So again, we're following here the RPR or the VDRL titers. And so first, I think what's critical is that you have to have a baseline titer on the day of treatment, or very close to the day of treatment, because it will help you monitor the response most appropriately. These titers can change significantly in a matter of days, particularly in primary and secondary syphilis. So knowing what the titer is on the day of treatment is of critical importance. So the definition of a serological cure is, in fact, a fourfold decline or two-dilution decline in titers. Fourfold decline, two-dilution decline, they're equivalent. So let's say you're at 1:64 on the day of treatment. A fourfold or two-dilution decline means that the titer has to drop to at least 1:16. So it goes from 1:64 to 1:32. That's a one-dilution or twofold decline. And then it goes to 1:16, that's a two-dilution or a fourfold decline.

Of course, the timing here of that decline is very important. So that decline, that fourfold decline, should occur within 12 months if you're treating early syphilis. And you have up to 24 months if you're treating late syphilis. So remember, 12 months for early syphilis, up to 24 months for latent syphilis, that's the timing. Again, the CDC did change those recommendations in the '21 guidelines because we were observing that a lot of clinicians were actually just waiting for six months. And then, if the titers didn't come down fourfold, they were retreating the patient immediately. And there are no data to suggest that that's the way to go. And so, honestly, right now, wait a good 12 months for someone whose titers, who was treated, I'm sorry, for primary or secondary syphilis. And wait up to 24 months for somebody who's treated with latent syphilis.

[11:43] Scenario #1: Monitoring after Serologic Cure

Dr. Spach
Okay, excellent. So that's a great overview. Now, let's just dive a little deeper, look at some specific scenarios, and have you guide us through what you would recommend. These kind of situations come up *all* the time in the clinic. So again, let's assume the person has received appropriate syphilis treatment and that they don't have HIV. Okay, so here's the first one. A person is diagnosed with secondary syphilis. They have a VDRL titer of 1:128. The six-month post-treatment titer is 1:8. And as you said, that would be a 16-fold decline. So with this nice response, do they still need any monitoring?

Dr. Ghanem
So really, what you're describing is a serological cure at six months. So let me tell you. I think that I would recheck at one year, but that's not an evidence-based recommendation. Also, keep in mind that based on their risk profile, you can decide how frequently to screen them for the possibility of reinfection. So what I'm really doing by screening them again at one year is really making sure that they're not getting reinfected during that timeframe. And to make sure that they, you know, on the off chance that they *could* experience treatment failure, you might catch it at one year following therapy. Remember, penicillin is about 95% effective in persons who are HIV-negative, and 5% of people may experience treatment failure with penicillin, and you don't want to miss those people. So again, I think that this individual has experienced serological cure at six months, but I would still get a test at 12 months for the two reasons that I mentioned.

[13:20] Scenario #2: Serologic Response with Persistent High Titer

Dr. Spach
Awesome. So now, let's look at another scenario. Again, with secondary syphilis and a person who has a really high RPR titer, let's say, 1:2,048, that titer right at the time of diagnosis or right at the time you're treating. So six months after treatment, the RPR has declined to 1:64, and after 12 months, it's 1:32. And I know in the clinic this often gives people a lot of angst because they go, "Oh, it's still really high." So overall, this is a 64-fold decline. But since it's still pretty high at 1:32, what would you recommend now?

Dr. Ghanem
So honestly, I am a believer in serological cures, no matter what the end titer is, because I'm not aware of any data in the antibiotic era, right? In the antibiotic era, I'm not aware of any data that suggests that after a person has achieved a fourfold decline—in other words, a serological cure, no matter if that titer is high—that they're going to have a worse outcome in the future. So as long as the titer has come down at least fourfold, I really don't do anything after that other than screening them periodically for the possibility of reinfection or treatment failure. Again, if the titers drop fourfold after therapy in the absence of reinfection, there are no data in the penicillin era to suggest that additional therapy is warranted in these patients.

[14:50] Scenario #3: Inadequate Serologic Response

Dr. Spach
Okay, great. Now, let's take a little bit different angle on this. So a little different scenario. A person is diagnosed with latent syphilis. They got a RPR titer that's 1:16. So post-treatment titers at 6, 12, 18, and 24 months really aren't changed a lot. Now they're 1:8, 1:16, 1:8, and 1:8 again. So at best, we got a twofold decline here. So clinically, they're doing great. They're asymptomatic. So, the question is, since this wasn't technically a fourfold decline, do they need further evaluation?

Dr. Ghanem
So yeah, that's the dilemma of the inadequate serological response. And that's just probably the most common question that I get about syphilis serologies—when these serologies are not behaving the way that they're supposed to behave. So the first question that I always ask is, did they get reinfected, right? Because you're only checking at, let's say, six months and 12 months. And during these six months, those titers could have gone down fourfold, the patient could have gotten reinfected, and the titers went back up. And so you wouldn't document that, you wouldn't be able to document that.

So it's always really important, whenever you're managing a patient with syphilis, is to make sure that they didn't get or they didn't have the possibility of reinfection. And that's always tough to know. And you have to be able to have a reasonable relationship with that patient, so they can trust you and they can give you the information that you need. That's the art of medicine and not the science of medicine. So did they get reinfected? If you think that it's possible that they got reinfected, then just treat them. There's no reason to sort of hem and haw about it. Go ahead and treat them if the possibility of reinfection is there.

If the likelihood of reinfection is low, I think you have three options. And I'll quickly go over each one of these. The first option is do nothing and continue to follow, right? That's the first option. You can certainly do something else. And that is, you can decide to retreat using three doses of 2.4 million units of benzathine penicillin G because you've waited over a year since their last treatment, and their titer hasn't come down. That's certainly on the table. Or you can consider performing a CSF examination. And then, based on the CSF exam, you can act accordingly. Let me just mention that there are at least five observational studies to date that suggest that at least in the short- and intermediate-term, meaning up to about two years, it doesn't seem to make a difference whether you follow the patient without treating them, or whether you treat them with additional doses of benzathine penicillin G.

We don't know whether, in the long-term, after five years, after ten years, whether treating or not treating makes a difference in these outcomes. So in the short- and intermediate-term, it doesn't make a difference whether you follow them or you treat them. Ultimately, their titers are going to come down.

It's a long-winded answer, I know, David, but it's a complicated question. And, so what I do normally with these patients is—first, I rule out reinfection. If they got reinfection, I treat them. Otherwise, if the titer is less than 1:64, I will usually follow the patient unless the patient is pregnant. If the patient is pregnant, I retreat automatically because I don't want to take any risks in the setting of pregnancy. If the patient is not pregnant, I just follow them and continue to monitor their titers. And ultimately, for these patients, the titers will come down.

I don't think that I would dissuade somebody if they said, "I want to retreat this patient." It's fine. If you feel strongly about retreating the patient, give them three doses of benzathine penicillin G. But, then, if the titers don't come down after that, please stop. It's no use to keep treating patients with benzathine penicillin G for titers that don't come down, assuming no reinfection and assuming they don't have any neurological, ocular, or otic signs and symptoms.

[19:01] Scenario #4: Rising Titer after Treatment

Dr. Spach
Great. So let's take a look at the scenario where the titer goes up post-treatment. So the example I have is, let's say, a person has latent syphilis. They've been diagnosed with an RPR titer of 1:16. They come in for their three-month post-treatment titer, and it's 1:8. But let's say, at six months, their RPR titer is 1:64. So give us an idea of what to do here.

Dr. Ghanem
So David, just to summarize, just to make sure that people don't get confused because I'm worried that I'm going to confuse people. So when titers come down fourfold, even if the titer is high, I don't worry about it. If the titer came down fourfold, I call it a serological cure, barring the possibility of reinfection. When titers don't come down fourfold, but titers don't go up either, right? They don't go up fourfold, but they don't come down fourfold—that was the previous question. And with those patients, if I've ruled out reinfection, I will just follow them over time, unless the titer is very high, and then I might consider a lumbar puncture. But I usually don't treat them.

But, now we're talking about patients whose titers actually go up fourfold. And I think that's different because, for me, when the titers go up fourfold, what I'm thinking about are two possibilities, right? Two major possibilities. The first possibility is that the patient got reinfected. The second possibility is that the patient has experienced treatment failure. And I think those possibilities are very different in terms of the approach that I take, right? If I think that the patient has experienced reinfection, I'm just going to go ahead and treat them again, right? No problem, I just treat them again and watch those titers. If I don't think that the patient got reinfected, but the patient experienced treatment failure, then I usually worry about those patients. And I have a strong desire to perform a lumbar puncture to make sure that I have not missed asymptomatic neurosyphilis in these patients. And so it's a very different scenario.

[21:00] Distinguishing Reinfection versus Treatment Failure

Dr. Ghanem
But how do I approach patients? Because remember, you need to get a really good history to be able to distinguish between infection, reinfection, or treatment failure. The patient has to trust you to give you a good history. And I found that my approach actually works pretty well. Rather than ask the patient immediately whether they had exposures that could have put them at the risk of reinfection, what I usually do with that patient is I will sit down and say, "Mr. Smith, since the last time I saw you, your titers have gone up fourfold. There are two major possibilities as to why this happened. The first possibility is you got reinfected. And this could also mean, you know, having oral sex with somebody because syphilis can be transmitted with oral sex."

"The second possibility is different. If it's the first possibility, if you think you could have gotten reinfected, then it's easy enough. I can just re-treat you, and we can follow you over time. If you don't think you got reinfected, then the other possibility is more serious. And the possibility is what we call *treatment failure*. And, sometimes this infection can reactivate, and it can sometimes reactivate in or around the brain. And we need to make sure that that hasn't happened. If that's the case, then we need to perform a lumbar puncture." And, then I explain what the lumbar puncture is. And then I say, "Listen, Mr. Smith, tell me, which do you think is the more likely scenario. You got reinfected, or you didn't?"

That, I think, helps to minimize the bias that patients always have. Remember, patients want to tell you the

truth. I really believe that patients always want to tell you the truth. But, patients also want to tell you what they think you want to hear, social desirability bias. And as a result of that, they'll sometimes lie to you. And so I think to minimize the impact of social desirability bias, I think by giving them both options, then the patients can decide which is the more likely option when they know what the approach is going to be for the management of that option.

And in the last ten years, I can tell you that I've had maybe six patients tell me that they could not have been reinfected. And they said, "No, doc, I did not have any sex since the last time I saw you." I sent every one of those patients for a CSF examination, and five out of the six patients had abnormalities consistent with neurosyphilis. So I think that that approach minimizes social desirability bias and gets you at the answer that you need to get at.

[23:34] Persons with HIV Post Treatment Monitoring

Dr. Spach
Fabulous! Fabulous! I love that perspective. So let's last take a look at people with HIV. So we've clearly been focused on situations, and I've tried to outline them to simplify this, to think about situations when people don't have HIV. So now, can you give us an idea about how the monitoring schedule or time for treatment response—how we might think about that a little bit differently for people with HIV?

Dr. Ghanem
Sure. So the CDC recommends more frequent post-treatment syphilis monitoring for people living with HIV. So namely, you're monitoring them at three months, six months, 12 months, and 24 months. They also suggest that people with HIV who are diagnosed with early syphilis may be allowed a full 24 months for the titers to decline fourfold. Remember, if you're HIV negative, the CDC says usually wait 12 months for the titers to come down for primary and secondary syphilis. What this tells you, and this is really based on some data that we have, first, we know that titers tend to decline more slowly among persons with HIV. And also, what else do we know? We know that persons with HIV are at slightly higher risk to experience treatment failure. So more frequent monitoring would help us detect both scenarios, right?

The possibility that the titers did not come down, the titers took a little longer to come down, and the possibility that the patient has experienced treatment failure. The syndemic of HIV and syphilis makes it such that reinfection risk is high among coinfected patients, right? So the pretest probability that reinfection would occur given that these individuals who have already come in with syphilis exist in a sexual network that probably has a high prevalence of syphilis so that the rate or the risk of reinfection is very high.

And so, for all of these reasons, the fact that the risk for reinfection may be particularly high amongst coinfected persons, for the fact that the titers may decline more slowly, and for the fact that they may experience higher rates of treatment failure, it makes perfect sense to monitor these patients a bit more aggressively, meaning at three months, six months, 12 months, 24 months, and even, you know, you can even do 18 months. I tend to do 18 months as well, again, because the risk of reinfection and the possibility of treatment failure are higher than in persons who are HIV negative.

Dr. Spach
Fantastic! Well, Khalil, that was quite a tour de force of serologic monitoring after people are treated with syphilis. So thank you again for joining us today and for that excellent overview.

Dr. Ghanem
It was my pleasure, David. Thank you for inviting me.

[26:25] Credits

This podcast is brought to you by the National STD Curriculum, the University of Washington STD Prevention Training Center, and is funded by the Centers for Disease Control and Prevention.

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