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REVIEW

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VOLUME 2 – ISSUE 12: TRANSCRIPT

Featured Cases: Sexually Transmitted Infections

Our Guest Author is Khalil Ghanem, MD, Assistant Professor of Medicine Division of Infectious Diseases at the Johns Hopkins University School of Medicine.

After participating in this activity, the participant will demonstrate the ability to:

- Discuss the rationale and approach to extragenital testing for sexually transmitted infections
- Describe the management of treatment failures in patients diagnosed with *Trichomonas vaginalis* infection
- Discuss the management approaches for herpes in serodiscordant couples and for syphilis in HIV-infected persons

This discussion, offered as a downloadable audio file and companion transcript, covers the important issues related to Sexually Transmitted Infections in the format of case-study scenarios for the clinical practice. This program is a follow up to the Volume 2, Issue 11 eInfections Review newsletter—[Sexually Transmitted Infections](#).

MEET THE AUTHOR



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Unlabeled/Unapproved Uses: The author has indicated that this presentation WILL include off-label discussions of azithromycin (2g) to treat gonorrhea and nucleic acid amplification tests (NAATs) to test extragenital sites.

Faculty Disclosure

Khalil Ghanem, MD, has disclosed no relevant financial relationships with commercial supporters.

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MR. BOB BUSKER: Welcome to this *eInfections Review*[™] podcast.

eInfections Review[™] is presented by The Johns Hopkins University School of Medicine. This program is supported by an educational grant from AstraZeneca, Cubist Pharmaceuticals, and ViroPharma, Inc.

Today's program is a follow-up to our September 2010 newsletter topic: Sexually Transmitted Infections.

Our guest is Dr. Khalil Ghanem from Johns Hopkins University.

This activity has been developed for primary care physicians, internists, and infectious disease specialists caring for patients with infectious diseases. There are no fees or prerequisites for this activity.

The accreditation and credit designation statements can be found at the end of this podcast. For additional information about accreditation, Hopkins policies, expiration dates and to take the post-test to receive credit online, please go to our website newsletter archive, www.einfectionsreview.org, and click on the October 2010 podcast link.

Learning objectives for this program are that after participating in this activity, the participant will demonstrate the ability to:

- Discuss the rationale and approach to extragenital testing for sexually transmitted infections,
- Describe the management of treatment failures in patients diagnosed with *Trichomonas vaginalis* infection, and
- Discuss the management approaches for herpes in serodiscordant couples and for syphilis in HIV-infected persons.

I'm **BOB BUSKER**, managing editor of *eInfections Review*. On the line we have with us Dr. Khalil Ghanem, an Assistant Professor of Medicine in the Division of Infectious Disease at the Johns Hopkins University School of Medicine in Baltimore.

Dr. Ghanem has disclosed no relevant financial relationships with commercial supporters. His presentation today WILL include the off-label

discussion of azithromycin (2g) to treat gonorrhea and nucleic acid amplification tests (NAATs) to test extragenital sites.

Dr. Ghanem, welcome to this eInfections Review podcast.

DR. KHALIL GHANEM: It's great to be here, Bob, thank you.

MR. BUSKER: What we'd like to do today is illustrate how to bring some of the information presented in the newsletter into the exam room. So if you would, Dr. Ghanem, start us out with a case scenario, please.

DR. GHANEM: Our first case is that of a 22-year-old bisexual man who presents complaining of a 3-day history of dysuria. He denies any other symptoms. Seven days earlier he had unprotected receptive anal intercourse at a party that he had attended.

His vital signs are normal and his physical examination is unremarkable. There is no evidence of a penile discharge or any anogenital or pharyngeal lesions.

The urinalysis reveals 35 WBC/HPF and the urine is sent for nucleic acid amplification testing for both gonorrhea and chlamydia. His serum is also sent for HIV serological testing and for syphilis testing.

The patient is empirically treated with azithromycin, 1 gram orally, for chlamydia; and cefixime, 400 milligrams, for gonorrhea.

MR. BUSKER: Given that this patient has no other symptoms, what additional testing might be warranted here?

DR. GHANEM: Given his history of unprotected receptive anal intercourse, clearly rectal testing for gonorrhea and chlamydia is necessary. And additional information about pharyngeal exposure will be really important to ascertain, because testing in this situation may also be warranted.

Although most clinicians know that the majority of genital STDs are asymptomatic, a lot of clinicians may not be aware that up to 90% of cases of extragenital sexually transmitted infections may also be completely asymptomatic. So up to 65% of cases

of gonorrhea and up to 50% of cases of chlamydia among certain high-risk populations like, for example, men who have sex with men, may be missed if only genital testing were performed.

MR. BUSKER: Having said that, which tests can best detect extragenital gonorrhea and chlamydia?

DR. GHANEM: For gonorrhea, culture is cheap and relatively sensitive, and it detects rectal and pharyngeal gonorrhea pretty well. It is also readily available in most laboratories.

Although chlamydia culture is acceptable for extragenital testing, it is not very sensitive and most laboratories, even the large commercial labs, do not offer chlamydia culture testing.

So although not FDA cleared for that purpose, nucleic acid amplification tests have by far the highest sensitivity and excellent specificity when detecting extragenital chlamydia and gonorrhea. Here we mean both pharyngeal and rectal gonorrhea. Several studies have demonstrated significantly enhanced sensitivity as compared to culture for gonorrhea and culture for chlamydia.

MR. BUSKER: As you just said, NAATs testing for gonorrhea and chlamydia, that's not FDA-cleared. Are there any problems obtaining those tests?

DR. GHANEM: Many large laboratories conduct in-house validation assays that allow them to use non-FDA-cleared tests. That means they are sent specimens that are truly positive and some specimens that are truly negative, and they test those specimens using their own nucleic acid amplification tests. If they get good sensitivity and specificity on their tests, then they essentially have passed an in-house validation assay, so those laboratories can provide these tests for clinical specimens. The good news is, almost all large commercial laboratories today offer routine extragenital nucleic acid amplification testing for GC and chlamydia, as do many large hospital-based laboratories.

It's important for clinicians to know that they can obtain these tests on pharyngeal and rectal specimens from their patients, despite non-FDA clearance. I would recommend that clinicians call the laboratories that they normally use and inquire about extragenital nucleic acid amplification testing.

MR. BUSKER: There's a point of confusion here that we need to address, Dr. Ghanem. Now, if you are going to treat for urethral gonorrhea and chlamydia anyway, what's the point of extragenital testing in this case?

DR. GHANEM: The choice of antibiotic to treat gonorrhea and the duration of antibiotic therapy for challenge *Chlamydia trachomatis* varies depending on whether gonorrhea and chlamydia are found in the pharynx.

Let's start with gonorrhea. The choice of antibiotics to treat gonorrhea is dependent to a certain extent on the presence or absence of pharyngeal infection.

If ceftriaxone is going to be used or was used, ceftriaxone has excellent activity against pharyngeal gonorrhea infection. However, cefixime, which was used in this case, only is 90% effective in eradicating pharyngeal gonococcal infection. And spectinomycin, which is currently not available in the US, but which is a recommended alternate agent to treat gonorrhea, is only 70% effective in treating pharyngeal gonorrhea. So if cefixime or spectinomycin were used to treat pharyngeal gonorrhea, then clinicians might consider doing a test of cure 2 weeks after treating their patient to make sure that the gonococcal infection was eradicated from the pharynx. That's why it's important to know whether gonorrhea is present in the pharynx.

The duration of antibiotic therapy for *Chlamydia trachomatis* infections varies depending on the serotype of *Chlamydia trachomatis*. Remember, *Chlamydia trachomatis* has 2 different serotypes that cause rectal infection. The D through K serotypes are the common *Chlamydia trachomatis* serotypes that we see on a routine basis in the United States today.

Rectal infection with a D through K serotype requires only 1 week of doxycycline therapy or a single 1 gram dose of azithromycin. However, infection with the L1 through L3 serotypes, which cause lymphogranuloma venereum, require up to 3 weeks of antibiotic therapy with doxycycline or 3 doses of azithromycin, 1 gram, separated by 1 week.

It's important to know which serotype is causing rectal *Chlamydia trachomatis* disease because, again, the duration of antibiotic therapy changes. Remember that lymphogranuloma venereum strains L1 through

L3 of *Chlamydia trachomatis* will also be detected by routine rectal nucleic acid amplification screening. So if you are unable to distinguish between D through K and L1 through L3, the better part of valor is to treat patients with *Chlamydia trachomatis* in their rectums with 3 weeks of doxycycline 100 milligrams PO BID, or 3 doses of a single gram of azithromycin 1 week apart.

LGV needs to be treated for a longer period of time compared to the non-LGV strains of *Chlamydia trachomatis*. Testing for LGV can be performed by some of the large laboratories and can be performed using blood tests.

In many instances, however, if clinicians don't have access to those tests, it's okay to treat empirically for LGV with a longer duration of therapy.

MR. BUSKER: Thank you, Dr. Ghanem, I think that clears things up. Let's move on now, if you would, and look at another case.

DR. GHANEM: Our second case is that of a 26-year-old woman who presents with recurrent vaginal discharge. Only one week earlier she had been diagnosed with *Trichomonas vaginalis* infection and she had been treated with a single 2 gram oral dose of metronidazole.

She says the symptoms initially improved, but within two days they recurred. Her urine 1 week earlier had been negative for *C. trachomatis* and *N. gonorrhoea*, and HIV and syphilis serological tests were also negative.

Today, the patient's exam is unremarkable except for a thin vaginal discharge. The vaginal pH is 5.5 and a wet mount reveals mobile trichomonads, no clue cells; the whiff test after adding KOH is negative.

MR. BUSKER: Based on what you've just described, what would you think is causing her discharge?

DR. GHANEM: So based on the data that we have, clearly this patient had *Trichomonas vaginalis* 1 week earlier and now, based on the wet mount, which is not very sensitive but is quite specific, the patient clearly has persistence of *Trichomonas vaginalis* infection.

Reinfection is the most common reason by far for failing therapy; that is, being exposed to a partner

who was not treated. So in this case, the first thing to do is to rule out reinfection from a partner who was not treated for *Trichomonas vaginalis* infection.

Remember, sexual partners of patients with *Trichomonas vaginalis* infections must also be treated in the same way that partners of patients with gonorrhea and chlamydia should be treated. All partners within the preceding 60 days should be treated for infection.

The second possibility why this patient presents again with a recurrent *Trichomonas vaginalis* infection is treatment failure because of drug resistance.

MR. BUSKER: Drug resistance in *T. vaginalis* strains – how common is that?

DR. GHANEM: In the United States, up to 10% of strains may exhibit decreased susceptibility to metronidazole. That doesn't necessarily mean that they will not respond to metronidazole, it just means that in some instances they may not respond.

Up to 1% of strains in the US may be completely resistant to metronidazole; in other words, these strains usually will not respond to the typical 2 gram single dose of metronidazole to treat *Trichomonas vaginalis* infection.

Although drug resistance testing can be performed through the Centers for Disease Control and Prevention by obtaining a culture for *Trichomonas vaginalis* and sending it to the CDC for testing, this is not routinely ordered, even in the setting of treatment failure.

If patients fail treatments several times, at that point drug resistance testing through the CDC can be considered.

MR. BUSKER: Aside from metronidazole, what other antibiotic options are available?

DR. GHANEM: Tinidazole, another nitroimidazole, was approved by the Food and Drug Administration for the treatment of *T. vaginalis* infections in 2004.

Tinidazole has been used in Europe for more than 20 years. Tinidazole is another nitroimidazole, so it's in the same family as metronidazole; however, compared to metronidazole, tinidazole has a much longer half

life, up to 72 hours, and it achieves higher tissue concentrations, particularly in the urogenital tissues.

What's more, the MICs of *T. vaginalis* tend to be lower to tinidazole compared to metronidazole. Because tinidazole has a longer half life than metronidazole, and because it's in the same family, patients should be cautioned about using alcohol when taking tinidazole. Unlike metronidazole, where patients should refrain from using alcohol for up to 24 hours after their last dose of metronidazole, tinidazole's half life is so much longer, so patients should avoid using alcohol for about 72 to 96 hours after their last dose of tinidazole, or they will have a disulfiram-like effect, which is essentially nausea and vomiting, if they were to consume alcohol earlier.

So again, tinidazole, approved in 2004, gives clinicians an alternate agent to use in the setting of treatment failure with metronidazole.

MR. BUSKER: So why not just go with tinidazole as the initial treatment?

DR. GHANEM: That's a great question. Although tinidazole is readily available in all pharmacies, it is more expensive than metronidazole. Therefore, it is preferable to start with metronidazole, and if there is evidence of treatment failure, then consider tinidazole in that situation.

MR. BUSKER: The patient you described — in your clinical opinion, how should she be treated now?

DR. GHANEM: As mentioned previously, there is no need for resistance testing at this time, since this is the first time the patient has failed therapy. The first thing to be done is to make sure her partner was treated adequately. If the partner was not treated, go ahead and treat them now and re-treat our patient with 2 gram dose of oral metronidazole.

However, if the partner was treated appropriately, or if the patient denies having had any sexual exposures in the interim after her therapy, there are two options to treat drug resistant *Trichomonas vaginalis*.

The first is to use metronidazole but on a different regimen. In this case, metronidazole 500 milligrams twice a day for 7 days is a reasonable approach to treating a *Trichomonas vaginalis* infection that did not appear to respond to a single oral dose of metronidazole.

If, however, clinicians would rather use another agent, then in this case tinidazole, in a single dose of 2 grams, can be used.

If this patient receives either one of these regimens and fails this regimen yet again, you can consider using metronidazole, 2 grams daily for 5 days, or tinidazole 2 grams daily for 5 days. You can also consider treating the partner for drug-resistant *T. vaginalis* infection as the patient is treated. In this case, you can also consider sending the *Trichomonas vaginalis* culture to the CDC for testing.

If you choose not to test, that's fine, but go ahead and treat this patient and her partner for a drug-resistant organism.

MR. BUSKER: And we'll be back in a moment with Dr. Kahlil Ghanem from Johns Hopkins.

DR. PAUL AUWAERTER: Hello, I'm Dr. Paul Auwaerter, from the Division of Infectious Diseases at the Johns Hopkins University School of Medicine. I'm one of the program directors for eInfections Review.

eInfections Review is a combination newsletter and podcast program delivered by email to subscribers. Newsletters are published every other month. Each issue reviews current literature in areas of importance to infectious disease specialists, primary care physicians, and other clinicians caring for patients with infectious diseases.

These podcasts, which are also available as downloadable transcripts, provide case-based scenarios to help bring new information into practice in both the exam room and at the bedside.

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MR. BUSKER: Welcome back to our eInfections Review podcast. I'm Bob Busker, managing editor of the program. Our guest is Dr. Kahlil Ghanem from the Infectious Disease department at The Johns Hopkins University School of Medicine. We're discussing diagnostic and management approaches for a variety of STIs. Let's continue, if you would Dr. Ghanem, with our next case.

DR. GHANEM: Our third case is that of a 28-year-old woman who presents for a routine medical visit. She doesn't take any medications and she has no medical problems. She is accompanied, however, by her male partner. The patient has never been diagnosed with a sexually transmitted infection, but he does have occasional genital lesions that crop up spontaneously and then resolve.

He was told that he probably had herpes, but he was never formally tested. His syphilis screen at the time was also negative.

The patient wants to know what she can do to decrease her risk of acquiring genital herpes.

MR. BUSKER: Let me echo her question, doctor — what can be done to decrease her risk of herpes?

DR. GHANEM: Consistent condom users — that is, when condoms are used 100% of the time — have a 30% lower risk of acquiring HSV2 compared with those who don't use condoms or don't use condoms consistently.

Condoms are not more effective with HSV infection because HSV doesn't necessarily infect just the area that's covered with condoms. That's why the transmission probability using condoms is not reduced by almost 100%, as is the case with some other sexually transmitted infections.

Once-daily valacyclovir suppressive therapy in the infected partners can help decrease the risk of transmission to an uninfected partner by about 55%. In other words, the combination of consistent condom use and valacyclovir suppressive therapy, 500 mg a day in the infected partner, is probably the best approach to minimizing the risk of transmission to an uninfected partner.

MR. BUSKER: But now, at this point, we don't know that the partner actually has herpes. Should serological testing for herpes be considered in this case?

DR. GHANEM: You're right, the partner doesn't have a formal diagnosis of herpes, although in this country, in the US, the vast majority of cases of recurrent genital lesions in non-immunocompromised patients are related to a herpes simplex virus, either herpes simplex virus 1 or herpes simplex virus 2.

If you took 100 serodiscordant couples by history — in other words, one member of the couple seems to have lesions consistent with herpes simplex virus and the other doesn't — in about 25% of these cases where the clinical history suggests serodiscordance, these couples wind up being seroconcordant. And in most of these cases, the asymptomatic partner also has HSV2 or HSV1, but they are asymptomatic.

So HSV2 may be completely asymptomatic, as HSV1 can be. If suppressive therapy is being considered, serological testing may significantly change management. For example, in this setting, the partner is likely to be HSV2-positive, but if the patient is also HSV2-positive, suppressive therapy would not be warranted because both members of the couple are HSV2-infected.

Serological testing may be considered before instituting suppressive therapy if the sero status of one or both persons is not known. That's one situation where serological testing may be helpful.

MR. BUSKER: What about this specific case? In your opinion, from your experience, should serological testing be used?

DR. GHANEM: Yes. I think, given that about 25% of clinically serodiscordant couples in fact turn out to be seroconcordant, and given the fact that valacyclovir therapy is not without potential side effects, I think this is a situation where serological testing is warranted in both the partner and the patient.

MR. BUSKER: Other situations where serological testing for herpes might be warranted — what might those be?

DR. GHANEM: Let me first say that when we talk about serological testing, what we mean is glycoprotein G-based serological tests. A lot of manufacturers make these glycoprotein G-based tests, and I'm stressing these particular tests because the old tests that were used, the ELISAs, did not reliably distinguish between HSV1 and HSV2.

On the other hand, these glycoprotein G-based serological tests reliably distinguish between HSV1 and HSV2. Several manufacturers make them, and clinicians are urged to call their lab and make sure that when they are ordering serological tests for herpes, they are getting the glycoprotein G-based tests.

There are currently no universal screening recommendations for HSV testing. Clinicians can consider serological testing for HSV in:

- patients with recurrent genital symptoms or with atypical symptoms and negative HSV cultures
- patients who have been given a clinical diagnosis of genital herpes without laboratory confirmation, as in this case
- patients who have a partner with genital herpes
- patients who request testing for genital herpes

It's important to remember, however, that these glycoprotein G-based serological tests are both sensitive and specific, but the specificity of these tests is not 100%. In other words, false-positive test results can occur, particularly in a setting where the pretest probability for having HSV is low.

In other words, if you have a patient whose pretest probability for having HSV infection is very low, it is probably best not to get HSV serological testing, because a positive test result may be a false-positive, and there is no way at this time to check verify whether it is a true positive or a false positive.

So unless you have moderate to high suspicion for HSV infection, be careful when you interpret the test results from these tests.

MR. BUSKER: Thank you, Dr. Ghanem. I think we've got time for one more case, so if you would, please.

DR. GHANEM: Our fourth case is that of a 32-year-old HIV-infected man. His CD4 count is 175 and his HIV viral load is 65,000 copies. He is not taking any antiretroviral therapy.

He presents with a total body rash that also involves his palms and soles. His serum RPR is positive at a titer of 1 to 256, and his confirmatory MHATP test is also positive.

He had an unprotected sexual exposure one month earlier after his partner's condom broke. with the

diagnosis was secondary syphilis, and he was treated with 2.4 million units of intramuscular long-acting benzathine penicillin G.

MR. BUSKER: Because of this patient's HIV-positive status, should he be receiving additional doses of penicillin?

DR. GHANEM: This patient has secondary syphilis. HIV-positive patients are at higher risk of serological failure after therapy for syphilis. They are also at higher risk for developing earlier neurosyphilis; that is, neurosyphilis that occurs within the first year after infection.

However, the limited data that we have available suggest that additional doses of penicillin or alternate doses or regimens of penicillin are no more effective than a single dose of 2.4 million units of intramuscular benzathine penicillin G for early syphilis.

The recommendations that stand for HIV-negative patients are similar to those for HIV-positive patients. The patient does not need any additional antibiotics for syphilis at this time, but he does need close follow-up after therapy.

MR. BUSKER: This patient does not show any neurological symptoms, but since he is HIV positive, some clinicians might want a lumbar puncture. Your opinion, Dr. Ghanem — would you give this patient a lumbar puncture?

DR. GHANEM: I'll be honest, this is a very controversial topic. There are two situations where a lumbar puncture is recommended, and these recommendations are not controversial.

First, if a patient has serological evidence of syphilis and has neurological signs or symptoms. In that case, a lumbar puncture is warranted. Second, if a patient has serological evidence of syphilis, but no neurological symptoms, but the syphilis titers — that is, the RPR titers — do not decline appropriately after syphilis therapy, then those patients warrant a lumbar puncture.

Among HIV positive patients, those with a CD4 count that is ≤ 350 , or those whose RPR titers are greater than 1:32, appear to be at higher risk for asymptomatic neurosyphilis.

However, there have been no studies in the HIV era to show that these patients do better if you do a lumbar puncture. So at this time the recommendation is to consider doing a lumbar puncture in these patients, but it is up to each clinician to decide whether they want to do that.

The way I approach a patient is, if I think the patient is going to be reliable and will follow up with subsequent appointments, I may withhold doing a lumbar puncture if they have no neurological signs and symptoms, and I would just follow them.

If they develop any neurological symptoms such as headaches or visual changes, then I immediately do a lumbar puncture. If, however, the patient is not reliable and I don't think they will follow up closely, in those situations I would consider doing a lumbar puncture.

MR. BUSKER: Clinical follow-up — how long would you recommend a clinician follow the titers of a patient like this?

DR. GHANEM: Particularly among HIV-positive patients, but also among all patients with syphilis, it's important to follow titers because they give us an indication of response to therapy.

Among HIV-positive patients, the recommendation is to follow titers every 3 months for up to 2 years. In this case the patient has secondary syphilis; in other words, he has early syphilis. He should exhibit a 4-fold decline in titers by 1 year after therapy.

If his titers don't decline by that time or if they increase 4-fold any time after treatment, he will need immediate evaluation. In other words, he will probably need a lumbar puncture and he will need treatment if re-infection is ruled out.

However, if patient had a late latent syphilis; that is, syphilis that was >1 year in duration, he should exhibit a 4-fold decline in titers 2 years after appropriate therapy. Remember, treatment for late latent syphilis is usually 3 doses of 2.4 million units of intramuscular benzathine penicillin G over 2 weeks.

Remember also that serological titers for syphilis may decline more slowly among HIV-infected patients compared to patients without HIV. So in other words, in this patient I would wait up to 12 months before I

considered him a treatment failure, and if a patient had late latent syphilis, I would wait up to 24 months for his titers to decline 4-fold.

MR. BUSKER: For this specific patient — what else could the physician do to improve his clinical course?

DR. GHANEM: In addition to making sure that he has close serological follow-up of his titers, you should certainly make sure to counsel the patient that he should contact you immediately if he develops any neurological symptoms, even after appropriate therapy.

Several case reports document that patients with HIV and syphilis who are treated appropriately for their syphilis may, despite appropriate treatment, develop neurological symptoms that may be related to neurosyphilis.

Any patient who is treated for syphilis should be warned that, should they develop any neurological symptoms at any time after therapy, they should contact their clinician immediately.

Moreover, studies of HIV-infected patients who have syphilis have shown that highly active antiretroviral therapy (HAART) for HIV decreases the risk of serological failure and the risk of developing neurosyphilis.

Current DHHS guidelines, which recommend highly active antiretroviral therapy at or below a CD4 count of 500, indicate that this patient needs HAART. His HIV would benefit from HAART, as would his syphilis infection.

MR. BUSKER: Those neurological symptoms you mentioned — what would you tell this patient to be on the lookout for?

DR. GHANEM: Some of the common neurological symptoms that have been reported include headache, blurry vision, cranial nerve abnormalities, photophobia, stiff neck, and other typical symptoms of meningitis. Some rare symptoms include seizures, but they are not very common.

MR. BUSKER: Dr. Khalil Ghanem, from the Division of Infectious Diseases at the Johns Hopkins University School of Medicine — thank you for participating in this eInfections Review podcast.

DR. GHANEM: You're very welcome, Bob.

MR. BUSKER: This podcast is presented in conjunction with eInfections Review newsletter, a peer-reviewed CME accredited literature review emailed monthly to clinicians treating patients with infectious diseases.

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