Expert Interviews

National STD Curriculum Podcast

Antimicrobial Resistance in STI Pathogens

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Dr. Johan Melendez, a Johns Hopkins School of Medicine Assistant Professor, discusses STI antimicrobial resistance (AMR) and why *Neisseria gonorrhoea* is resistant, AMR diagnostic options such as point-of-care assays, and his work on evaluating AMR in resource-limited settings with National STD Curriculum Podcast Editor Dr. Meena Ramchandani.

Topics:

- STI
- antimicrobials
- Gonorrhea
- Mgen
- Syphilis

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Disclosures

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References

Paper #1

Transcript

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introduction**[00:00] Introduction**

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] 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 back Dr. Johan Melendez, who is an assistant professor in infectious diseases at the Johns Hopkins School of Medicine. His research focuses on characterizing antimicrobial resistance (AMR) in sexually transmitted infections (STIs). Welcome back, Johan. It's great to talk to you again.

Dr. Melendez

Thank you, Meena. I'm happy to be here.

stis--amr-overview**[00:39] STIs & AMR Overview**

Gaydos CA, Manabe YC, Melendez JH. A narrative review of where we are with point-of-care sexually transmitted infection testing in the United States. Sex Transm Dis. 2021 Aug 1;48(8S):S71-S77. [**PubMed Abstract**]

Dr. Ramchandani

So I'd like to talk about antimicrobial resistance in STI pathogens, and I know that this is a topic you are very passionate about. And so, I'd like to hear more about your research and the research that's going on. So first, let's, for our audience, take a step back in an overview, what are the main STI pathogens affected by antimicrobial resistance and why are some STI pathogens more readily antimicrobial resistant and others are not?

Dr. Melendez

So, I'm going to start by talking about the pathogen that is very close and dear to my heart, *Neisseria gonorrhoeae* because that is one of the main challenges that we have right now. *Neisseria gonorrhoeae* has

acquired resistance to all of the antimicrobials that have been used for treatment in the past and even the ones that is being used right now, which is ceftriaxone, which is the one and only treatment that is recommended. And, the other challenge that we have with *Neisseria gonorrhoeae* right now is that we are seeing some strains that are becoming extensively drug-resistant, meaning that not only do they have high levels of resistance to azithromycin, but they also have resistance to ceftriaxone. And so, this is becoming quite a challenge because those strains are spreading globally, so that there's a concern that gonorrhea could become at some point untreatable with some of the antibiotics that we have.

The other challenge that we have in terms of antimicrobial resistance in STIs is *Mycoplasma genitalium*. Even though it's a newer STI, it has quickly acquired resistance to azithromycin, which is the primary antibiotic that is used for treatment. And then if somebody has *Mycoplasma* that is resistant to azithromycin, then you go to another antibiotic, a quinolone. And we have also started to see resistance to that quinolone very quickly. In terms of syphilis, penicillin is working very well, but we have to be cautious about resistance to doxycycline as we continue and we hear more about Doxy PrEP [preexposure prophylaxis] and PEP [postexposure prophylaxis] that is being introduced right now.

Dr. Ramchandani

That's a wonderful overview, Johan.

gonorrhea**[03:07] Gonorrhea**

Dr. Ramchandani

So, let's take *Neisseria gonorrhoeae*. Why do you think it's more readily antimicrobial resistant? What is it about this pathogen that it tends to become resistant to the antibiotics that we use?

Dr. Melendez

So, I think there are two factors that made *Neisseria gonorrhoeae* such a pathogen that is prone to develop AMR. The first one is that it is a naturally competent organism, meaning that it can acquire DNA from all the species very easily, including commensal *Neisseria* species. And so, if you have *Neisseria gonorrhoeae* that is in the same environment as another species that has antimicrobial-resistant markers that they can exchange DNA between the two of them. That is one of the mechanisms by which antimicrobial resistance emerges in *Neisseria gonorrhoeae*.

The other factor, and people laugh whenever I say this, I think *Neisseria gonorrhoeae* is a very smart bug because, over time, it has found a way to become resistant to each antimicrobial that it has been treated with. So, it has many surface proteins that allow for the antimicrobial to be expelled from the organism, and so it has many ways of not only developing resistance, but also of dealing with any antimicrobial that is being introduced for treatment.

Dr. Ramchandani

So, it has this ability to constantly change and make it so that the antimicrobials are ineffective.

Dr. Melendez

That is correct. Yeah, that is a very simple and great way to put it.

Dr. Ramchandani

It's probably one of the reasons we also don't have a vaccine for it.

Dr. Melendez

It is mutating so quickly, and it changes very quickly. So, it's difficult to develop a vaccine that is going to work for all of the strains and that is going to continue to work for an extended period of time.

amr-surveillance**[05:12] AMR Surveillance**

Dr. Ramchandani

Johan, can you tell us about some of the surveillance strategies or programs, either nationally or internationally focused, to detect antimicrobial resistance for STI pathogens? And, we can start with *Neisseria gonorrhoeae*, especially since you mentioned that there are ceftriaxone-resistant strains or strains that theoretically would not have an antibiotic that would treat these types of infections.

Dr. Melendez

When you look at all the STIs, *Neisseria gonorrhoeae* is the one that has better surveillance data. And so, in the U.S., we have two programs. The first one is GISP, which is the Gonococcal Isolate Surveillance Project, and this was developed back in the 1980s. They collect isolates from throughout the U.S. and they analyze them for antimicrobial susceptibility profile. In 2016, that program was expanded by another program called SURRG, which is Strengthening the United States Respond to Resistant Gonorrhea. That program continues and it provides us with the ability to collect a few more isolates and do better surveillance.

On a global level, they also have EGAS, which is the Enhanced Gonococcal Antimicrobial Surveillance program, and this program does a lot of work in Europe, Australia, and also in Africa, trying to collect susceptibility data from gonococcal strains from different regions throughout the world. So, there is a lot of surveillance data out there. One of the challenges that we have, the data that is coming from this program only represents about 10% of all the gonococcal infections that we see, and the reason why that is, in order to be able to determine antimicrobial susceptibility profiles, we need viable organisms. And because the majority, 90-95% of the gonorrhea cases are being diagnosed right now using nucleic acid amplification tests, we do not have the ability to collect those viable organisms.

And so, it is great that we have programs that collect isolates and provide surveillance data, but the data that we have is limited. So, we only have a snapshot as to what is really going on in regards to AMR globally.

Dr. Ramchandani

That's really helpful, and that leads to my next question.

detecting-amr-options**[07:46] Detecting AMR Options**

Dr. Ramchandani

What are the ways can we diagnose antimicrobial susceptibility or resistance for these common STI pathogens? And you can pick either a *Neisseria gonorrhoeae* or *Mycoplasma genitalium*.

Dr. Melendez

So, as I said before, for *Neisseria gonorrhoeae*, we are looking at phenotypic antimicrobial susceptibility testing. We can do some molecular tests for detecting some of the markers associated with resistance. Some of that work very well. They have a high level of predictive value, such as gyrase for ciprofloxacin (cipro) susceptibility resistance. When we are looking at ceftriaxone resistance, it's a little bit more challenging because the mechanisms associated with ceftriaxone resistance tend to be very complex. So, it's difficult to do susceptibility testing for ceftriaxone using molecular approaches.

Mycoplasma, we are limited as to what we can do. We can only do molecular detection because *Mycoplasma genitalium* is a pathogen that is very difficult to grow. It can take a few weeks just to grow, so imagine trying to do antimicrobial susceptibility testing on a pathogen that is so difficult to grow. So, we are limited as to what we can do in terms of looking at antimicrobial susceptibility for both of these pathogens right now.

Dr. Ramchandani

So, there are certain genes that have been associated with antimicrobial resistance, but most of the testing is currently phenotypic testing, correct?

Dr. Melendez

That is correct. Most of the testing that we have from surveillance data is through phenotypic testing, but we are able to do more testing if we can target some of these resistant genes, but they only work for some drugs, not for others. So, the best information that we have right now for antimicrobials that are being used right now is to do phenotypic antimicrobial susceptibility testing.

Dr. Ramchandani

And even for molecular testing, if one was trying to detect a certain gene, do you have to have a certain number of, let's say, copies or specimen available?

Dr. Melendez

So, if you are able to detect *Neisseria gonorrhoeae* in a clinical specimen, you are likely to have the ability to detect the resistant gene. We have some concerns when you are dealing with asymptomatic patients who tend to have a lower bacterial load, and really, they have not been a lot of work looking at whether or not we can do molecular resistant testing from asymptomatic patients. So that's something else that needs to be done, but in the case of symptomatic patients, we don't have any concerns about being able to detect given resistant markers as long as that resistant marker is very predictive of the resistant phenotype.

poc-assays**[10:57] POC Assays**

Dr. Ramchandani

Are there any point-of-care (POC) assays that can detect *Neisseria gonorrhoeae* antimicrobial resistance or susceptibility that could potentially influence treatment, let's say, in the real-time or real-world settings?

Dr. Melendez

There are some developers that are working on that. There is an assay by SpeeDx in Australia that can detect the marker associated with cipro susceptibility, but that test takes between 90 minutes and two hours. So, it's really not at the point of care, but that can be used to help guide treatment in the sense that, if somebody comes into a clinic, they collect a specimen, which then tests positive for gonorrhea, then they can be a reflex testing to see if the *Neisseria gonorrhoeae* in that specimen is susceptible or resistant to cipro. In the case that the strain is susceptible to cipro, then that person can be treated with cipro instead of ceftriaxone, and in turn, that can help to reduce the level of ceftriaxone that we are using right now, so that we can hopefully extend the lifeline of ceftriaxone for a few more years.

Dr. Ramchandani

And what about *Mycoplasma genitalium*?

Dr. Melendez

So, *Mycoplasma genitalium* is another one that they're working on developing these assays, and in Australia and some places in Europe, they're actually using it right now to help guide treatment. And so, anyone who tests positive for *Mycoplasma genitalium* then is tested. And then, depending on the results of the test, they can be treated with antimicrobial X or Y depending on what results happen to be.

Dr. Ramchandani

That's great. Can you tell us a little bit more about how these point-of-care assays work?

Dr. Melendez

So, they're not really point of care. Those are not at the point of care. They cannot be done right away, but what they typically do is they detect the mutation associated with resistance to the given antimicrobial. And so, in some of the cases, you have to detect *Neisseria gonorrhoeae* first, and then those samples that test positive, then they get reflex testing for resistance testing. And then, you look for the presence or the absence of a given mutation in a given gene to determine whether that strain is susceptible or resistant to the antimicrobial. And then based on that, you can treat someone with the antimicrobial that was recommended by the resistance testing.

Dr. Ramchandani

When do you think they'll be ready for real-time and use in the clinical setting or even in the home-based setting?

Dr. Melendez

Well, in a clinical setting, I think hopefully soon. This is something that have been on the development for a few years. I will tell your audience that we have to be cautious about susceptibility testing at the point of care because it's not going to be able to be implemented everywhere. For example, when we're talking about the ability to do susceptibility testing for cipro at the point of care using a molecular assay, that could work in the U.S. when resistant levels for cipro are 35 to 40%. If you go to other places in the world, we have almost 100% resistant to cipro, and so, those tests will not be able to be implemented in that setting. So, they're coming and they're going to be able to be implemented in some settings. Another concern that we have about implementing this in the clinical setting is whether insurance will reimburse for resistance testing or not. And there's a lot of debate going on about it right now, not only for *Neisseria gonorrhoeae* but also for *Mycoplasma genitalium* because it's a bigger challenge because who's going to pay for the testing? That is the concern right now.

Dr. Ramchandani

Yeah, it makes sense from a clinical perspective and a patient perspective, but I guess insurance companies are not used to that and probably don't have the billing mechanism to even set that up.

Dr. Melendez

That is correct.

Dr. Ramchandani

How about syphilis or chlamydia? Any concerns about antimicrobial resistance? You mentioned doxycycline for syphilis. What about chlamydia infection?

Dr. Melendez

No concerns for chlamydia or syphilis; just to kind of keep an eye on doxy resistance for syphilis. So, we've been very lucky, knock on wood, that there are no concerns about resistance in chlamydia.

recent-amr-studies**[15:42] Recent AMR Studies**

Dr. Ramchandani

Some of your recent work has been evaluating STI antimicrobial resistance in resource-limited settings. I'd love to hear more about the work you are doing, for example, in Kampala, Uganda.

Dr. Melendez

Sure. So, my work in Uganda deals with two primary areas. The first one is surveillance of antimicrobial resistance in that setting, and the second one is something that I'm very interested in is epidemiology of pharyngeal gonorrhea in that setting and how that relates to antimicrobial resistance. And, the reason why I'm interested in looking at pharyngeal gonorrhea in that setting is because we know very little about the epidemiology of pharyngeal gonorrhea globally, but especially in Africa, we have limited data about that. And the other reason why I'm interested in pharyngeal gonorrhea is because it has been associated with the development of antimicrobial resistance in *Neisseria gonorrhoeae,* and this is associated with the fact that, in the pharynx, we have a lot of commensal *Neisseria* species, which can carry antimicrobial-resistant markers that can then pass those genes on to *Neisseria gonorrhoeae*.

So, it is a concern because pharyngeal gonorrhea tends to be asymptomatic, and it can then colonize the pharynx for an extended period of time and then it can exchange DNA with other commensal species and then lead to the development or emergence of antimicrobial resistance. So that's why I'm interested in exploring pharyngeal gonorrhea in antimicrobial resistance.

Dr. Ramchandani

A very smart bug. It uses what it has in the environment.

Dr. Melendez

And it uses their cousins to exchange DNA.

Dr. Ramchandani

Is there also concern about antimicrobial penetration in the pharynx, and if there's lower concentrations of an antibiotic then the pathogen could become resistant because there are lower levels of that antibiotic in that area?

Dr. Melendez

That is true, and there was a study done a few years ago that actually showed that cephalosporins, especially cefixime, does not penetrate the pharyngeal tissue very well, and so it's not ideal for the treatment of pharyngeal gonorrhea. And so, anyone who tests positive for pharyngeal gonorrhea now has to be treated with ceftriaxone, and in some cases, they have to be treated with even a higher dose of ceftriaxone to make sure that those patients clear the infection.

Dr. Ramchandani

Thank you for describing your work in Kampala. What are some of the findings you've recently discovered?

Dr. Melendez

A study that I'm just finishing up now, we looked at 250 men in Uganda who came into a clinic with symptomatic urethritis. I was interested in finding out if these men have symptomatic urethritis, how many of them are going to be positive for pharyngeal gonorrhea? And so, we collected pharyngeal samples and urogenital samples, and what we're finding is that, of those men who come into the clinic with symptoms, about 70 to 80% of them are positive for *Neisseria gonorrhoeae*. Of those men who are positive for *Neisseria gonorrhoeae*, penile *Neisseria gonorrhoeae*, about 10% of them also have pharyngeal gonorrhea. So, this is an ideal population to test for pharyngeal gonorrhea.

We found was that over 20% of these men have more than one curable STI. They had a combination of chlamydia, gonorrhea, and *Mycoplasma*. Some of them even had three STIs at the same time. In terms of antimicrobial resistance, we are finding out that over 95% of the isolates from Uganda are resistant to cipro, tetracycline, and penicillin. So, these are all antimicrobials that were used in the past. So, there's a lot of resistance in Uganda. And then something that I'm interested in is looking at how different pharyngeal *Neisseria gonorrhoeae* is from urogenital gonorrhea. We have isolates that were isolated from the pharynx and the penis of the same men. We have data to suggest that pharyngeal isolates have higher resistance levels than those are causing urethritis.

And so, a lot of more work to be done, but it's really exciting work, especially in that setting because we know so little about pharyngeal gonorrhea. We also know so little about what is going on there about antimicrobial resistance, and considering those, how high levels of resistance to those three antimicrobials that I mentioned, we are also keeping an eye on what's going to happen to cefixime and ceftriaxone resistance in that setting.

Dr. Ramchandani

That's really helpful, especially because it could impact treatment and patient care in those areas and thinking about the prevalence of antimicrobial resistance worldwide.

Dr. Melendez

That is true. And especially in low-resource settings where you don't do testing. These men get treated based on the symptoms that they have, and we need to make sure that we keep an eye on susceptibility data to see whether or not the treatment that they're using is going to continue to work.

Dr. Ramchandani

Another reason for point-of-care assays to detect antimicrobial resistance in resource-limited areas, right?

Dr. Melendez

That is true.

future-amr-research**[21:34] Future AMR Research**

Dr. Ramchandani

What are some next areas of research you plan on studying in this area? And if there are any that are being presented at the STI Prevention Conference in September of 2024 in Atlanta, please let us know.

Dr. Melendez

Sure. So, I'm really interested in looking at the pharyngeal microbiome and to see whether or not that can be protected. Again, somebody getting a pharyngeal infection and really to continue working and looking at the ability of *Neisseria gonorrhoeae* to acquire antimicrobial-resistant markers in this setting. The work that I'm

going to present at the STI Prevention Conference in September is not related to *Neisseria gonorrhoeae*. I actually presented some work at the last STI and HIV World Congress last year. So, the work that I'm presenting now at the STI Conference deals with looking at the ability of using dry blood spots (or DBS) for HIV and syphilis testing. We're doing this to see if a person can collect a DBS at home and then send it to the lab for HIV and syphilis testing. And so, by doing so, then patients don't have to come to a clinic to collect a blood sample, and then they can collect the samples at home and be tested for HIV and syphilis.

Dr. Ramchandani

When you're looking at the pharyngeal microbiome, are you looking just at other *Neisseria* species or pathogens?

Dr. Melendez

So, I think it will be important to look at other *Neisseria* species just to see what levels of colonization there is with commensal *Neisseria* species in people who have a pharyngeal gonorrhea infection. But it's also important to look at the total microbiome to see if some of the species are protective against somebody acquiring a pharyngeal infection. So, more work needs to be done in this setting, and it's also going to be very dependent on the population. We know that different populations have different microbiomes, so I think that this will be interesting work to do in different populations globally.

Dr. Ramchandani

I'm always curious about if there's an influence of the microbiome, especially in spontaneous clearance of STI pathogens, especially at the extragenital sites. It's almost like they're either competing for resources or influencing another pathogen's resources.

Dr. Melendez

That's a big question right now, and somebody that used to work with you in Seattle is actually somebody who pioneered some of the work looking at the natural history of pharyngeal gonorrhea infection and her data shows that there is a lot of spontaneous clearance, especially with pharyngeal gonorrhea. So, there is something about the pharynx that is very unique in the sense that pharyngeal gonorrhea infections are both asymptomatic and that they can be cleared without antimicrobial treatment. So, it is a great space to be working on. I think there's more questions than answers at this time, but it's great to do research in this area.

Dr. Ramchandani

Definitely.

most-common-amr-question**[24:57] Most Common AMR Question**

Dr. Ramchandani

What is the most common question you get about antimicrobial-resistant STI pathogens?

Dr. Melendez

So, my family says, "Have you been able to cure gonorrhea because you've been looking at this for so long?"

Dr. Ramchandani

"What have you been waiting for? What have you been doing?"

Dr. Melendez

Well, that's what they say. You know, it’s human behavior. There is the problem with antimicrobial resistance and so on, but at another level, a lot of people ask me about, "Why is *Neisseria gonorrhoeae* so resistant to antimicrobials?" And this is something that we talked about before because *Neisseria gonorrhoeae* is so competent to acquire DNA from all the species. It is a model organism for versions of antimicrobial resistance, and hopefully, learning a little bit more about how we can prevent this process from happening.

Dr. Ramchandani

Great answer. Thank you so much, Johan. This was so fabulous. I learned a ton from you. I really appreciate it. I hope you had fun, but I had a great time talking to you about these important topics.

Dr. Melendez

It was great talking to you. It was great to see you and talk about point-of-care testing and antimicrobial resistance, both topics that are very near and dear to my heart.

credits**[26:15] 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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