Expert Interviews

National STD Curriculum Podcast

Antimicrobial Resistance in Neisseria Gonorrhoeae: Key Microbiologic Factors

June 24, 2025

Season 5, Episode 10

Microbiologist and Associate Professor at the University of Washington Dr. Olusegun Soge reviews six different ways that the microbiology of *Neisseria gonorrhoeae* contributes to its antimicrobrial resistance. Dr. Soge and National STD Curriculum Podcast Host Dr. Meena Ramchandani then explore how current overuse and misuse of antibiotics in the STI field might be part of the problem.

Topics:

- microbiology
- Gonorrhea
- biofilm

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Disclosures

Disclosures for Olusegun O. Soge, PhD
Grants to Institution: Hologic, Inc., Applied BioCode, Inc.

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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 STI [sexually transmitted infection] review for health care professionals who are interested in remaining up to date on the diagnosis, management, and prevention of STIs.

We are delighted to have back Dr. Olusegun Soge, who also goes by S.O., join us for this episode. Dr. Soge is a microbiologist with expertise in molecular diagnostics and antimicrobial resistance of sexually transmitted pathogens, and is an associate professor at the University of Washington. We are very excited to have him on this episode to talk about antimicrobial-resistant *Neisseria gonorrhoeae* and surveillance for this organism.

Dr. Soge

Well, thank you. Thank you so much for having me.

natural-competence**[00:51] Natural Competence**

Dr. Ramchandani

Tell us a little bit about some features about *Neisseria gonorrhoeae* that make antimicrobial resistance such a concern, like for example, is there anything about the specific microbiology that makes this pathogen *more* resistant to antibiotics?

Dr. Soge

Well, thank you. That's an excellent question. So, *Neisseria gonorrhoeae* has a very fascinating microbiology and probably explains why it's been able to sequentially, consistently, notoriously develop resistance to all antibiotics that have been recommended for treatment. First, there's the natural competence for transformation, which means *Neisseria gonorrhoeae* is naturally competent for transformation. It can take DNA readily from wherever it is in terms of the environment where you have it. In the pharynx where you have asymptomatic infection and the patient will not even know they have it, and then they can carry it for 16 weeks and not even know it's there unless they happen to go in for screening, and then the test.

So, during the time that *Neisseria gonorrhoeae* is there in the environment with all the commensal *Neisseria* species, all the bacteria, it provides a good opportunity for it to pick resistant DNA and then it can just incorporate it into its genome. And this is being used to explain the mechanism of reduced susceptibility to cephalosporins due to the PenA mosaic.. And when we talk about commensals, these are natural flora. These are bacteria that are there not causing infections. It's there in your pharynx. But *Neisseria gonorrhoeae* that is pathogenic interacts with it and is naturally competent and can pick DNA incorporated into its genome and then become resistant to the antibiotic.

genetic-mutation**[02:50] Genetic Mutation**

Also, aquisition of antibiotic resistance by genetic mutation is very common in Neisseria gonorrhoeae. For instance, mutations in 23S rRNA confers azithromycin resistance. And there you have two types of mutations that are very important, the C2611T mutation confers low-level azithromycin resistance and the A2059G mutation confers high-level resistance. So, *Neisseria gonorrhoeae* is having fun, and why is it having fun? Wherever it is, either in the rectum or in the pharynx, it's developing and acquiring mutations that will lead to resistance to the drug we're using for treatment.

Also, the selective pressure from antibiotic use. Some of our standard of care practices are contributing to selection of *Neisseria gonorrhoeae* antimicrobial resistance. For instance, someone comes back for a gonorrhea test-of-cure, and we use a very sensitive nucleic acid amplification test (NAAT), which, actually, guess what? Is so sentitive that it detects both viable and dead organisms. NAAT does not discriminate between viable and dead organism or just remnant nucleic acid material. And so if NAAT detects a dead *gonococcus*, the clinicians will still treat the patient because they must treat everyone that is positive for *Neisseria gonorrhoeae.*

We've shown in a study that we published in Seattle, that previous use of azithromycin, which is a macrolide, was actually significantly associated with azithromycin-resistant GC (*Neisseria gonorrhoeae)*. So a patient who has been previously treated with azithromycin either for chlamydia or other STIs like *Mgen* (*Mycoplasma genitalium*), for instance, and they come back when they have gonorrhea. We cultured the *Neisseria gonorrhoeae* and then we performed antimicrobial susceptibility testing on the isolates. What did we find? We found that those isolates have elevated minimum inhibitory concentrations to azithromycin. We found that the risk of azithromycin resistance increased with *more recent and more frequent* use of azithromycin.

role-biofilm**[05:28] Role of Biofilm**

So, I've talked about asymptomatic infection is a reservoir of infection and also of antimicrobial resistance in *Neisseria gonorrhoeae*, but something that is not always talked about is *Neisseria gonorrhoeae* actually can produce biofilm, and the biofilm is just like a protective layer that will protect the bacterium from antimicrobial agents. So, that also contributes to antimicrobial resistance.

immune-evasion**[05:57] Immune Evasion**

Another important one that I want to talk about is *Neisseria gonorrhoeae* is a master of immune evasion. It's a master of disguise. So, you can have gonorrhea over and over again, and the reason is because *Neisseria gonorrhoeae* can evade your immune response so easily because it has found a way to do that through phase variation as well as antigenic variation. So, it can change the structure, it can alter its surface protein to evade the immune response, so the target will not see it at all that it's there. So, these are all contributing not just to repeat infection, also contributing to antimicrobial resistance in *Neisseria gonorrhoeae*.

plasmid-mediated-resistance**[06:45] Plasmid-Mediated Resistance**

So, also acquisition of genes, acquisition of plasmid. We've talked about *tet*(M) gene, which actually the origin was streptococci. The origin of the high-level tetracycline resistance in *Neisseria gonorrhoeae* is a non-*Neisseria* species, *Streptococcus*, gram-positive bacteria. And, we just expect that over time, *Neisseria gonorrhoeae* will naturally because it's just a way of life; that's just normal to them to find a way to develop resistance to all antibiotics. So, the microbiology is very, very fascinating.

fitness-advantage-or-defect**[07:25] Fitness Advantage or Defect?**

And another thing I should talk about is the linkage between antibiotic resistance and fitness. Some of the resistant genes we're talking about, like the *gyrA*, you would think the acquiring resistance could either be a fitness advantage or be a fitness defect. Some of those genes actually confer fitness advantage, just make it

happy and just make that strain to continue to disseminate and to spread. It doesn't die out. Whereas some genes actually make *Neisseria gonorrhoeae*die, but some of those genes, even after we've withdrawn them, we are no longer recommending them, like cipro, the resistance will not go down completely. It's because they're there and they're stable. Some of those genes, resistant genes, do not confer fitness defect, but they actually confer fitness advantage, so they make *Neisseria gonorrhoeae* to continue to proliferate and just have fun and continue in the population.

Dr. Ramchandani

That's fascinating. So, it sounds like there's a number of different ways that the microbiology of *Neisseria gonorrhoeae*contributes to antimicrobial resistance, including snatching up DNA from other bacteria, the overuse of antibiotics, the biofilm formation that makes it difficult for antibiotics to penetrate, and then changing morphology of the surface so that the immune system really can't recognize the pathogen.

antibiotics-use-sti-field**[09:05] Antibiotics Use in STI Field**

Dr. Ramchandani

Has there been a concern among the scientific community of general antimicrobial use in the STI field? Why is that?

Dr. Soge

There has been a lot of concern, and there will still be a lot of concern. The infectious disease community, the STI field is particularly concerned. Why? Of all bacteria STI pathogens, *Neisseria gonorrhoeae* has actually done a great job for decades that we've never been able to keep one antibiotic for treatment of gonorrhea for decades. *Neisseria gonorrhoeae* has always found a way to develop resistance, and that I've actually brought up the question of what are we doing in terms of antimicrobial stewardship, what are we doing in terms of STI management that could be contributing to the selection of antibiotic resistance in *Neisseria gonorrhoeae*? The use of tetracycline for treatment of NGU [non-gonococcal urethritis], for treatment of chlamydia, for instance, we found in Seattle right now after the introduction of DoxyPEP, *Neisseria gonorrhoeae* tetracycline resistance, not just the chromosomally mediated but the high-level tetracycline resistance that is a plasmid, the *tet*(M) resistance, is the predominant resistance in Seattle right now.

And so, we did an analysis where we looked at when did this start; it predated the introduction of DoxyPEP. And so that raises the question, the use of tetracycline for NGU, for chlamydia, that was around the time we started seeing the increase. However, the increase actually skyrocketed with the use of DoxyPEP and now we are 65% as of June of last year. By the end of last year, probably, we'll be above that. I'm talking of 65% of not just low-level tetracycline resistance but high-level resistance. So, the reason why there's concern in the STI community is because the overuse and misuse of antibiotics causes a selective pressure that leads to the development and spread of antimicrobial resistance in *Neisseria gonorrhoeae*.

treating-asymptomatic-infections**[11:30] Treating Asymptomatic Infections**

Dr. Soge

Some of our standard practices, like epidemiological treatment for STI, you treat contact to STI, at times you treat all the partners, you treat everyone even without the result. It's not automatic because you slept with someone, then you must get the gonorrhea. But because we do empirical treatment and then we do epidemiological treatment, than wait for the result. "Oh, okay, maybe you have chlamydia in addition to gonorrhea," but what happened if they come back negative? We already treated them. So, that is also causing selection of antimicrobial resistance in *Neisseria gonorrhoeae*, treatment of asymptomatic infections, we're not sure. Are they viable, are they not viable? But will patient be happy that when they have infection, you're not going to treat them? I don't think so. Some European countries are actually moving away from

treating asymptomatic infections, and then it's also causing some discussion in the U.S. Should we be doing that so as to reduce the selective pressure and control antimicrobial resistance in *Neisseria gonorrhoeae*?

Our test-of-cure is guided by nucleic acid amplification test (NAAT) positivity, so if someone comes back and they've not completely cured the infection or they've cured the infection, other is there is just dead organism or remnant nucleic acid? We still treat them. We think they have not been completely cured even though the culture will be negative, but the concern is culture is not very sensitive compared to the NAAT. So, we treat patient during test-of-cure if they're still positive, but we don't have a viability assay. And when I talk about viability, there's an assay that tells you, "Oh, *gonococcus* is still alive," and so they can transmit that *gonococcus* to another person, but the *gonococcus* is dead. If we have the viability, it tells us, "Oh, gonorrhea is dead, but it's completely dead; don't worry about it." We don't have any FDA approval to do that.

Excessive antimicrobial consumption in specific populations is a big problem, like MSM [men who have sex with men] that are on HIV PrEP. You test them so often. The more you test, the more you see, the more you detect, and then we'll treat.

global-surveillance-disparities**[13:50] Global Surveillance Disparities**

Dr. Soge

Then global disparities in GC surveillance. In the U.S., we've been monitoring antimicrobial resistance since 1986, and there are countries of the world where this resistance is emerging, and they don't have the resources to do that. Whereas, for us, I mean that's why the scientific community is concerned that the highly resourced countries have all the money to do the surveillance, but the low-resourced countries do not have the money to do the surveillance. But, when it comes to the emergence of resistance, history has taught us over and over again that it emerges in Asia… in Southeast Asia. And all the other countries not in the U.S., shouldn't we be monitoring the emergence of resistance in low-resource countries? I think that's what WHO [World Health Organization] and CDC have been trying to do, but that program, probably the future is uncertain right now in terms of the funding to continue that activity.

Also, the impact of the use of antimicrobials, not just on *Neisseria gonorrhoeae.* What happened to *Staph aureus*? What happened to other things? The excessive use of antimicrobials to treat dead gonorrhea. I'm not saying all of them are dead, but some of them are dead, but we don't have a way to know whether they're dead or they're not dead. And that includes DoxyPEP as well as asymptomatic treatment and other use of antimicrobials. So, antimicrobial stewardship is critical, which some European countries are actually doing a lot to address, but I think it's going to take time, and we need perspective of the patient as well. I think this needs to be a shared decision in terms of whether a patient will be willing to wait for you to actually get a test result back if they've contracted gonorrhea, if they'll feel okay to wait.

And when it's negative, you don't need to treat them. But, I think they come back, we treat them, and then when we get negative results, I'm not sure whether we call them and say, "Hey, sorry, you actually didn't have gonorrhea, but we've already treated you anyway." So, these are some of the concerns in the field of STI, why some of the things we're doing—it's contributing to the problem of antimicrobial resistance in *Neisseria gonorrhoeae*, and we need to think about gonorrhea control and prevention from the lens of antimicrobial stewardship.

global-antimicrobial-stewardship**[16:20] Global Antimicrobial Stewardship**

Dr. Ramchandani

It really speaks to the importance of antimicrobial stewardship, and that's not only for STI pathogens because if *Neisseria gonorrhoeae* can grab resistance from other bacteria, it's antimicrobial stewardship, in general, for all infectious diseases. And I wonder if the lack of antimicrobial stewardship in some countries contributes to increased *Neisseria gonorrhoeae* resistance that we're seeing in some other countries that'll eventually,

most likely, come to the U.S. as well.

Dr. Soge

I totally agree with you. The use of antimicrobials are not regulated in many low-resource countries, and so you can just go to the pharmacy, and they call it "chemist," and all you just say is, you know, "I have this painful urination. I have these symptoms, and there's a tap running here. What can you give me to help me?" And then they tell you how much money you have, and based on how much money you give them, and that's what they sell you. So, when we talk about antimicrobial stewardship, there are places in the world where we don't have any program monitoring that. But also, we should talk about the U.S., where we have robust program, antimicrobial stewardship program, but our practices, standard of care practices, is also contributing to the problem. So, I think we all need a more coordinated approach to making sure our antimicrobial stewardship actually help in terms of reducing the excessive use.

The argument about DoxyPEP, for instance. Doxycycline is used for other things, acne, and all the rest. It's not just the little we're using to prevent STIs; it's not going to be causing the problem. So, I think overall, like you said, for all infectious diseases, having an holistic approach to look about how we can control and reduce our use of antibiotics. Like a report from CDC said, 30% of some of the prescriptions are unnecessary, even 70% we can reduce it. So, that's a lot of antibiotics we're using. And I agree with you. In low-resource country, where the resistance actually developed, we're not doing enough. And the little we're doing now with WHO, I'm concerned that we may not even be able to do it, which will put us in a very bad situation in terms of what's going to be the future of preventing the era of untreatable gonorrhea, which is what we really want to avoid. And what we do in the U.S. is not enough to stop what happened in Vietnam, in Cambodia; just investing into work over there. Working with folks all over the world in Africa and Europe, just to have global coordinated efforts to prevent the era of untreatable gonorrhea. That's what we should be doing.

Dr. Ramchandani

And from a pathogen perspective, it makes sense from *Neisseria gonorrhoeae's* perspective because if some resistance actually increases bacterial fitness, then it will just persist in that resistant form.

Dr. Soge

I agree. Yeah, from the pathogen perspective, it makes sense, but the pathogen doesn't want you to take any action to prevent that. And that's where we really need to face the reality that the pathogen is actually outsmarting us, and we need to actually outsmart the pathogen. And the way to do it is to actually invest to catching it where it develops and stop it before it spreads to other parts of the world.

Dr. Ramchandani

I can see why you study this disease. It's very fascinating.

Dr. Soge

Yes, I agree. It's my bug.

Dr. Ramchandani

I just want to say thank you, S.O. That was an incredible review of antimicrobial resistance in *Neisseria gonorrhoeae* and the surveillance that’s being done for this pathogen.

credits**[20:20] Credits**

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Training Center, and is funded by the Centers for Disease Control and Prevention. Transcripts and references for this podcast series can be found on our website, the National STD Curriculum at www.std.uw.edu. Thank you for listening, and have a wonderful day.

key-microbiologic-factors